



Hot Topic



The HPV Vaccination: Is the Glass Half Empty or Half Full?

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Part I. HPV Vaccines

Much has been displayed in the media about vaccination against cervical cancer. Many issues surrounding the science, policy, and implementation of the vaccines have received less scrutiny. This issue delves into many of the concepts critical to HPV vaccination and their impact on future cervical cancer screening.

Age of Administration

Twelve was picked specifically as the age to administer the HPV vaccine because it coincided with the Society for Adolescent Medicine's (SAM) recommendation for the first well-adolescent visit, not because age 12 happens to be the optimal time to vaccinate for HPV. This "target age group" decision was a compromise for the wider context of public health. There are many vaccines recommended for adolescents, and age 12 happens to fit the timeline for implementation of all recommended vaccines, including the HPV vaccine.

SAM's recommendation is to administer the HPV vaccine with many other vaccines, including the meningitis vaccine and a booster for acellular pertussis. In addition, the MMR and Varicella boosters have been recommended for this age range. Although public health plans include the co-administration of several adolescent-based vaccines, there is very little evidence to date about the safety of co-administering Gardasil® with the other vaccines. This information is critical to future HPV vaccine implementation. At present, both companies are evaluating the safety of their HPV vaccines when co-administered with the meningitis and acellular pertussis vaccines.

Vaccine Endpoints

The endpoints of the vaccine trials are: (1) safety, (2) efficacy, and (3) immunogenicity.

Safety

The vaccines are safe. There is injection-site tenderness, redness, and swelling that dissipate within two to three days post injection. Long-term surveillance will continue post marketing.

Vaccine Efficacy

How to Measure Vaccine Efficacy in Populations

The definitions of the populations and outcomes of interest in the trials determine how vaccine efficacy is measured. When considering the population to be vaccinated, the determining criterion for maximal vaccine efficacy is whether or not the woman is currently infected with the vaccine-associated HPV types (e.g., type 6, 11, 16, and 18 for Gardasil® ; types 16 and 18 for Cervarix™). No other factors are

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HPV testing in routine cervical screening: cross-sectional data from the ARTISTIC trial.

Kitchener HC, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, Sargent A, Peto J; ARTISTIC Trial Study Group.

Br J Cancer. July 3, 2006;95(1):56-61. Epub June 13, 2006.

To evaluate the effectiveness of human papillomavirus (HPV) testing in primary cervical screening. This was a cross-sectional study from the recruitment phase of a prospective randomized trial. Women were screened for HPV in addition to routine cervical cytology testing. Greater Manchester, attendees at routine

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as important in vaccine efficacy—not sexual activity, not age, not number of sexual partners, not menses status, and not past HPV infection. The critical question is: Does she currently have a vaccine type-specific HPV infection? Not how old is she. In some circles, the HPV vaccine has been mistakenly labeled the “virgin vaccine,” as in it should only be given to virgins, or virgins are the only possible people who are HPV naive. This is absolutely untrue. The evidence shows that the only factor that matters is whether or not the woman has an HPV infection at the time she gets her first shot; not all three shots, but the first shot. HPV naivety means no current type-specific HPV infections at the time of vaccination, not virginal status. The age of the women in the HPV vaccine trials for which efficacy has been measured ranges from 15 to 26 years.

Another issue central to a discussion of vaccine efficacy is clinical trial outcomes, or endpoints, and how they are measured. Endpoints include multiple infection and disease manifestations, all of which are generally categorized by the HPV types that cause them. Most commonly, efficacy endpoints are either related to the vaccine-associated HPV types (or those phylogenetically related) or by any type of HPV that can cause the endpoint.

The multiple infection and disease manifestations include incident infection, persistent infection as defined by repeatedly positive samples at either a six-month interval or at a year interval, abnormal cytology, or lesion development categorized as CIN 1, 2, 3, or cancers. In these clinical trials, it is not feasible to measure cancer as a primary endpoint due to the time delay from infection to cancer development. CIN 2/3 histology is a cervical cancer precursor that can be measured in trials over a relatively short time span. CIN 2/3 is the primary endpoint used in the vaccine trials. CIN 2/3 as an outcome is further categorized as CIN 2/3 associated with HPV 16 or 18 infections, or CIN 2/3 occurring regardless of causative HPV type.

Reviewing the vaccine trial results by population, by infection status, and by endpoint of certain viral causation requires looking at four different conditions. The first population evaluated was those who do not currently have HPV 16 or 18 infections. This is the most straightforward of designs. Will the vaccine prevent HPV 16/18 naive women from getting CIN 2/3 caused by HPV 16 and 18? If the vaccine worked in this group, it would offer protection for many people. Both vaccines work exceedingly well. The vaccines prevent CIN 2/3 caused by HPV 16 and 18 100% of the time in women not currently infected with HPV 16 or 18.

The second population evaluated was women not currently infected with HPV 16 or 18. The studies looked at the protection against CIN 2/3 caused by any HPV type provided by the vaccine. After 2 years with Gardasil®, 39% of naive women are protected from all CIN 2/3 lesions, and after 3 years, 46% of naive women are protected from all CIN 2/3 lesions. It is expected that the protection against all CIN 2/3 lesions for Gardasil® will maximize at about 50% after 5 years for this naive population of women 15 to 26 years old. For Cervarix™, the bivalent vaccine, after 4.5 years, 73% of naive women are protected from all CIN 2/3 lesions; and after 5.5 years, 68% of naive women are protected from all CIN 2/3 lesions. It is expected that the protection against all CIN 2/3 lesions will remain close to 70% after 10 years for this naive population of women 15 to 23 years old because of cross-protection with other oncogenic HPV types. The general conclusion that can be drawn from these data is that women who are not currently infected with HPV 16 or 18 have a reduction somewhere between 50 and 70% of all CIN 2/3 caused by any HPV type.

The third population evaluated was women infected with HPV 16 or 18 at the time of first vaccination. Vaccine efficacy was the primary endpoint. Results show that the vaccines have no efficacy at preventing CIN 2/3 lesion development caused by the current HPV 16 or 18 infections. The vaccines are not therapeutic. Neither vaccine will cure her. The data clearly show this based on a study duration of three years. Beyond three years, we do not know whether vaccines will offer prophylactic protection against autoinoculation from past HPV 16/18 infections.

The fourth population evaluated was the whole population of 15- to 26-year-olds, some of whom have HPV 16/18 infections at first vaccination, most of whom do not. The primary endpoint was vaccine efficacy for all CIN 2/3+ prevention. Two years after vaccination, Gardasil® protects 12% of the

NHS Cervical Screening Programme. In all, 24,510 women aged 20 to 64 screened with liquid-based cytology (LBC) and HPV testing at entry. HPV testing in primary cervical screening. Type-specific HPV prevalence rates are presented in relation to age as well as cytological and histological findings at entry. In all, 24,510 women had adequate cytology and HPV results. Cytology results at entry were: 87% normal, 11% borderline or mild, 1.1% moderate, and 0.6% severe dyskaryosis or worse. Prevalence of HPV decreased sharply with age, from 40% at age 20 to 24 to 12% at 35 to 39 and 7% or less above age 50. It increased with cytological grade, from 10% of normal cytology and 31% of borderline to 70% mild, 86% moderate, and 96% of severe dyskaryosis or worse. HPV 16 or HPV 18 accounted for 64% of infections in women with severe or worse cytology, and one or both were found in 61% of women with severe dyskaryosis but in only 2.2% of those with normal cytology. The majority of young women in Greater Manchester have been infected with a high-risk HPV by the age of 30. HPV testing is practicable as a primary routine screening test, but in women aged under 30 years, this would lead to a substantial increase in retesting and referral rates. HPV 16 and HPV 18 are more predictive of underlying disease, but other HPV types account for 30% of high-grade disease.

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general population of 15- to 26-year-olds from CIN 2/3+ caused by any type of HPV. After 3 years, according to the Future 2 trial, Gardasil® protects 17% of the general population of 15- to 26-year-olds from CIN 2/3+ caused by any type of HPV. In other words, if we vaccinate the whole population of 15- to 26-year-olds, we can expect about a 14% reduction in CIN 2/3 at three years, which is really small. Many public health departments are not going to be excited about it. They expect a higher return on their investment.

In summary, the vaccines work well in women who are not currently infected with HPV 16 or 18. The vaccines have a more limited value if women are currently infected with the vaccine-associated types at the time of first vaccination.

Immunogenicity

The primary endpoint of immunogenicity measures how well the vaccine induces antibody levels to the L1 proteins of specific HPV types. This is different from efficacy, which measures the prevention of infection or lesions. The most important thing to remember about HPV is that it is an intraepithelial virus, and as such, it does not have ready access to the immune system. It is very hard for the body to understand that it has been infected with HPV. Less than half of the people who are infected with HPV actually have a memory response, meaning that few infected women produce antibodies. Producing an antibody response is an important tool in fighting future viral infections of that type. Vaccine-induced antibody responses are orders of magnitude higher than natural antibody responses.

Natural antibody titers are poor at preventing future infections. Dr. Viscidi and colleagues studied the role of naturally induced antibodies to HPV 16, 18, and 31 in over 10,000 women being followed in Guanacaste, Costa Rica, by the NCI. Both serostatus and HPV DNA status for HPV 16, 18, and 31 were measured at enrollment. Over the next five years, all new type-specific HPV infections were recorded. The number of HPV 16, 18, and 31 infections detected in women with and without prior seropositivity for HPV 16, 18, and 31, respectively, was compared. The frequency of new HPV infections did not differ by serostatus at enrollment for any HPV type. Women who were seropositive to HPV 16 at enrollment developed the same number of HPV 16 infections as did the women who were seronegative to HPV 16 at enrollment. In other words, women who had had prior infections with a specific HPV type got those same types of infection again regardless of the antibody titers generated from the past natural infection. This result was true for HPV 18 and 31 as well. If a woman had a natural antibody titer, it did not protect her from getting future same-type-specific infections. This study has challenged the concept that natural immunity gives lifetime protection. Their data suggest the contrary: antibody levels from natural infection are insufficient to protect against new HPV infections of the same type. This is a critical concept.

Vaccine-induced antibody titers are orders of magnitude greater than natural infection titers after all three doses of initial vaccination for both the bivalent and quadrivalent vaccines. For the bivalent vaccine, the high levels of antibodies remain sustained for at least 4.5 years for both HPV 16 and 18. For the quadrivalent vaccine, antibody titers peak immediately after complete vaccination. HPV 16 titers remain above natural infection titers through 5 years of follow up, but HPV 18 titers drop such that one-third of women lose their seropositivity 2 years.

Adjuvants boost a vaccine's immunogenicity. The HPV 16 /18 VLPs adjuvanted with AS04 induce twofold higher antibody levels than the HPV 16/18 VLPs adjuvanted with the traditional aluminum salts over at least four years. The five-year efficacy follow-up in the phase II Gardasil® trial¹ shows a drop in efficacy against HPV 18-related infection and disease to 91%. Whether this drop is artificial is unknown until large follow-up studies are conducted.

After vaccination with either vaccine, there is 100% initial seroconversion. At five years of follow-up, there is 100% efficacy for both vaccines for preventing HPV 16/18-related CIN 2/3 in women who were currently negative for 16 and 18 at first vaccination. We do not know the correlative titers, and we do not know what kind of boosting is going to be necessary. However, it is clear that some type of boosting regimen will be necessary, especially for Gardasil®.

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Dr. Harper has received numerous awards over the past 15 years for her teaching, research, and clinical abilities. She has been honored as one of the top clinicians in her field in the United States and Physician of the Year in New Hampshire in 2006.

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In summary, the HPV vaccines have both benefits and limitations. The vaccines are safe and well tolerated. VLPs produce a good antibody response. Women who are not infected with HPV 16/18 at the time of first vaccination receive complete protection that lasts for at least five years. However, there is no protection for women who are currently infected at the time of vaccination. The vaccines are not therapeutic and do not “cure” HPV-related disease. Vaccination does not cover all types of HPV, and thus, does not replace routine cervical screening or Pap testing.

Part II. Cervical Screening Impact

In developing countries, cervical cancer is the most important outcome attributed to HPV, as it is in developed countries. The rate of cervical cancer is five times lower in developed countries than developing countries, though, due to the Pap screening programs, which catch and treat cervical disease earlier, lowering the overall disease burden. One way to appreciate the contribution of Pap screening programs is to consider the number of cases of vulvar and vaginal disease. In developed and developing countries, the number of vulvar and vaginal cancers is similar. The five-fold observed difference in cervical disease between developing and developed countries is because of the Pap test and Pap screening programs. Because overall, worldwide, there are about 300 times as many cervical cancers as there are vulvar and vaginal cancers, the main goal of the HPV vaccines is to reduce cervical cancer.

In the general U.S. population of women 14 to 59 years of age, the rates of HPV infection are relatively small. About 2.3% of the female population has HPV 16 or 18 infections and 1.3% of the female population has HPV 6 or 11 infections at any one point in time. The high-risk HPV types other than HPV 16 and 18 account for about 20% of HPV infections in the general population of women in the United States. In European women 14 to 59 years of age, the HPV incidence rates are comparable to U.S. women. Of the 6.7% of women with high-risk HPV infections, 26% are HPV types 16 or 18. The next most common cancer-causing HPV types, HPV 45 and 31, add about 1%. Overall, in the general population, HPV 16 and 18 infection rates are low.

From the oncologist's perspective, on the other hand, infection with HPV types 16 and 18 cause the majority of cervical cancers, both squamous and glandular. HPV types 45 and 31 are the next most common cancer-causing HPV types. They happen to be phylogenetically related to HPV 16 and 18 and are partially prevented by the bivalent HPV vaccine. In general, only two high-risk types are completely prevented, leaving a population that is not protected from cervical cancer caused by the remaining high-risk HPV types. For example, a young girl receives Gardasil® today, and both she and her parents think she is protected from cervical cancer. The reality is that she may still develop cervical cancer from a non-16/18 HPV type. She has to start and continue routine screening despite vaccination.

Data from Edgren and Sparen² show that women with a history of CIN 3 have an increased risk, up to 10 times higher than the general population, for cancer of the vagina, vulva, and anus. The increased risk is age dependent with highest risk at early follow-up, with the increased risk continuing for at least 10 years. Data from Kalliala et al.³ show that the increased cancer risk post-treatment is independent of the initial grade of CIN. What these studies do not show is whether the repeat lesions are caused by the same HPV type as the initial treated lesions were.

The necessary long number of years that the HPV vaccine must provide protection against cervical cancer is illustrated by the high prevalence rate of HPV in all ages of women. In the United States, the percentage of the population that has any HPV infection of any type varies according to age group: 25% in 14- to 19-year-olds; almost 45% in the 20- to 24-year-olds; and 20% in 50- to 59-year-old women. Across the age ranges, the largest prevalence peak occurs just as young women and men ages 16 to 20 are beginning sexual activity. This group comprises the largest peak of HPV prevalence, which is why the vaccine studies were done in this age group. The prevalence data also show that women of all ages have high-risk HPV types. This is not an infectious agent limited only to adolescence. HPV is an infection that affects women of all ages, a fact that carries important implications for necessary duration of vaccine efficacy and continued screening.

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As with adults, the high-risk types of HPV infections that occur in the general population of adolescents are most often the 50s types, followed in decreasing order of prevalence by type 16, 18, 31, and 45. If all adolescents were vaccinated, vaccination would prevent fewer than 20% of the HPV infections in this age group. Vaccinating adolescents prevents very little immediate disease caused by HPV 16 and 18. Without decades of duration of protection from the vaccine and continued cervical screening, we gain little public health benefit in the first few decades from vaccinating adolescents.

The prevalence of HPV across age ranges has another important potential implication for vaccine implementation. Is there a use for any pretesting for HPV infection prior to vaccination? Regardless of age, there is no value to serotesting prior to vaccination. Drawing blood and testing for antibodies to a past exposure is not helpful for two reasons: (1) vaccine efficacy is only dependent on current infection status, not past exposures; and (2) serologic testing is not clinically validated for widespread use.

HPV DNA type-specific testing prior to vaccination seems a possible method to prevent wasting vaccination on women of any age currently infected with the vaccine-specific types. However, this strategy is not helpful because (1) only a small percentage of females are positive for HPV 16 or 18 at any one time, and (2) the currently available HPV DNA test is not type-specific. Digene's Hybrid Capture 2® (HC2) tests for a combination of 13 high-risk HPV types, which are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The HC2 test can be positive for 11 other high-risk types in addition to 16 and 18. Most of the time women who are HC2 positive are so because of some other type that is not 16 or 18.

HPV Plus Pap

Women in the United States have been taught and expect to receive cervical cancer screening every year. A few years ago, the American College of Obstetricians and Gynecologists (ACOG) recommended the use of HPV testing in addition to cytology for primary cervical screening in women over the age of 30. This improved the quality of care but also raised concerns about cost. Additional research supported lengthening the screening interval to every two or three years in order to decrease cost without compromising care. In fact, the normal Pap test combined with a negative HR HPV HC2 test provided assurances that there were no cancer precursors present and that the woman could safely be rescreened in three years. Despite the cost savings, some providers and patients remain concerned that longer screening intervals decrease quality of care. As long as providers continue to recommend annual screening, it does not make sense to add HPV testing to cytology because the ability to gain any cost benefit is completely lost with a yearly screening interval. It is important for providers, who screen patients annually and not every two or three years, to avoid adding HPV testing. Annual HPV testing does not improve patient care and only adds unnecessary cost.

Is There an HPV Test to Use?

There are a variety of HPV tests. Just as cytology comes in several forms, including the conventional Pap smear or a liquid-based test such as SurePath® or the ThinPrep®, HPV tests come in several forms. Laboratories commonly create their own tests, often using PCR techniques to perform typing and quantification of viral loads without benefit of standardization or external laboratory verification. In the United States, the only FDA-approved HPV test is HC2.

Some have asked if p16 could replace Hybrid Capture. This seems unlikely because, even though the data look good for being able to detect CIN 2/3, there is a significant false-positive rate seen in metaplastic transformation zone cells that makes p16 unsuitable as a primary screen test. This high false-positive rate was one reason why the ARTISTIC trial is not including p16 markers.

There are no societal or organizational recommendations based on clinical trial evidence for how to follow women who are generically HPV positive, cytologically normal. The ARTISTIC trial offers tremendous insight into this clinical dilemma (see sidebar). Thus, cervical cancer screening is still necessary.

Why Is Cervical Screening Still Necessary?

There are two reasons: (1) time and (2) all the other cancer-causing HPV types not covered by vaccination.

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1. Time.

A 12-year-old girl receives Gardasil®. We know that Gardasil® is an alum-based vaccine; we assume its efficacy will last for about 10 years because (1) HPV 18 antibody titers drop after 2 years, with a small decrease in efficacy for HPV 18-specific disease at 5 years, and (2) we know that most alum-based vaccines need boosters within 10 years. At 22 years old, she is in the age group where the peak incidence of HPV infections occurs. She is potentially no longer protected by the vaccine she received as a child and yet is at the most vulnerable time for exposure. She needs to have a booster and screening tests now. She will continue to need boosters and screening throughout her life in order to remain protected. This involves systems engineering to coordinate her screening exams with the need for boosters at the appropriate intervals.

There are two embedded concepts in the issue of time: duration of efficacy and low amount of immediate disease prevention from vaccination.

a. Duration of efficacy.

The first concept is that we don't know how long the current vaccines will remain protective, but the duration of efficacy of the vaccines is critically important for public health implementation policies. Implementation policies must include plans for continued boosters with explicit expectations that cervical cancer screening must continue to detect and treat those precancers and cancers that cannot be prevented by vaccination alone. We have to expectantly manage the misconception that vaccinating a child at 12 years of age exempts her from future Pap testing. In my opinion, this misconception of no further need for Pap testing could lead to an increase in cervical cancers in a short time frame thus wasting all the investments made in early childhood HPV vaccination.

b. Low amount of immediate disease prevention from vaccination.

The second concept of immediate benefit from the HPV vaccine needs to be explored. All other vaccines are designed to prevent an immediate bout of a lethal infectious disease (e.g., rotavirus, measles, or polio). The initial protection is praised despite no sense of duration of protection because at least the pandemic was aborted. The HPV vaccine doesn't give you that immediate return. The cancer prevention happens years later.

2. The importance of other high-risk HPV types in precancers and cancers.

Assuming an instantaneous complete population vaccine coverage, a lifelong duration of vaccine efficacy without need for boosters, an HPV-naïve state at the time of vaccination, as well as HPV type distributions for abnormal cytology states as reported by IARC, the maximum benefit seen with the HPV vaccines does depend on which primary screening test is used: liquid cytology or Hybrid Capture 2 HR HPV testing. Assuming that Gardasil® offers complete protection against HPV 6, 11, 16, and 18 as has been reported, and that Cervarix™ offers complete protection against HPV 16 and 18 and partial protection against 45 and 31 as has been reported, the degree of prevention of abnormal primary screening tests differs.

For primary screening with the HC2 high-risk HPV type probe, IARC and other epidemiologic studies indicate that HPV 16 and HPV 18 infections comprise about 30% of all HR HPV-positive tests; and HPV 45 and 31 infections comprise about 10% of all HR HPV-positive tests. Gardasil® would then prevent about 30% of abnormal primary screens; and Cervarix™ would prevent about 35% of all abnormal primary screens if HC2 HR probe was the primary screening tool. There is no economical programmatic value for HPV 6 and 11 protection, as the primary screening tool only identifies high-risk HPV types.

Cytology is the traditional primary screening tool. ASCUS Pap results come from a variety of causes. In the United States, HPV 16 and 18 cause about 19% of ASCUS Paps, about 28% of LSIL Paps, about 55% of HSIL Paps, and about 76% of cancers. HPV 6 and 11 cause about 12% of ASCUS and LSIL Pap results. HPV 31 and 45 cause about 15% of ASCUS and LSIL Pap results, 11% of HSIL Pap results, and 8% of cancers. In terms of real numbers, not just percentages, regardless of HPV type, about 5 million women per year have cervical abnormalities: about 3 million ASCUS Paps; 1.5 million LSIL Paps, 550,000 SIL Paps, and about 11,000 cancers. Gardasil® is estimated to prevent about 35% of the

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abnormal cervical cytology reports and Cervarix® is estimated to prevent about 44% of the abnormal cervical cytology reports, a significant reduction in the burden of all cervical disease. Even with these reductions about 55 to 65% of the women in the United States will continue to have abnormal Paps and will continue to need care and follow-up within the system.

a. CIN 2/3.

Returning to the real world where time is an economic parameter, the return on investment for prophylactic vaccination becomes important, modeling exercises illustrate differences in disease reduction by age of cohort vaccinated and duration of vaccine efficacy. As noted above, 60% of CIN 2/3 is caused by infection with HPV 16 or 18. Somewhere between 30 and 50% of CIN 2/3 lesions are not vaccine-preventable, meaning that young girls who are vaccinated may still develop high-grade disease and need treatment and follow-up.

Using this information, it is possible to model the reduction of CIN 2/3 incidence caused specifically by HPV 16 and 18. The baseline for this model is routine cervical screening with Pap testing. There is no additional decrease in the incidence of CIN 2/3 by continuing the current practices of the Pap screening program.

Now consider a 12-year-old girl who is vaccinated today. Assume she returns for all three shots in the series and all of her boosters, when they become indicated throughout her lifetime. Assume some 12-year-olds are not vaccinated on the day they turn 12 years, but instead are vaccinated over a few years, until the entire cohort is protected. If we just vaccinate 12-year-olds and no one else, the result is that it takes over 20 years to reduce the incidence of CIN 2/3 by half. In my opinion, most public health departments will not be willing to wait 20 years to see a return on investment that still has hundreds of thousands of women with cancer precursors from both 16/18 non-coverage and from other HR HPV types.

Now, consider vaccinating all females ages 12 to 26 years. Using the same model assumptions, a 50% reduction in CIN 2/3 occurs after more than 10 years, accelerating the decrease in women with CIN 2/3 by almost 10 years. The benefit seen by public health officials occurs more quickly when older women are also vaccinated. If males are included in the 12- through 26-year-old cohort, the 50% reduction of CIN 2/3 incidence happens in a little less than 10 years. There is some improvement, but a small amount, potentially not enough to justify the additional incremental cost of vaccinating all men 12 to 26 years old.

b. Cancer.

Using the same model assumptions for cancer reduction as used for reduction of CIN 2/3, it is possible to see the time necessary for disease reduction when the population has maintained all boosters necessary for lifetime protection against HPV 16/18. The curves for cervical cancer are more disturbing than for CIN 2/3. The baseline is our "no vaccine" scenario, which represents our ability to reduce cervical cancer rates with screening alone. Consider the scenario in which every single 12-year-old female is vaccinated. It will take almost 40 years to realize a 50% reduction in cervical cancer incidence. By vaccinating all 12- through 26-year-old females, the cervical cancer rate decreases by 50% in about 25 years, a much-accelerated time frame for public health benefit. Likewise with CIN 2/3, if all males ages 12 through 26 are added to the vaccine cohort, the cervical cancer rate does not decrease that much more quickly. The reduction of both CIN 2/3 and cervical cancer are long-term public health goals that require an investment in boosters and continued screening.

Consider what happens to the 12-year-old girl if the vaccine only lasts 10 years; she is still receiving her Pap testing regularly. However, she does not come back for boosting and loses coverage for HPV 16/18. In this situation, the reduction of CIN 2/3 follows a different model that over 20 years maximally reaches a 20% reduction in CIN 2/3. If all 12- to 26-year-old women are vaccinated as was seen to be the quickest economically rewarding scenario above, but the vaccine duration is limited to 10 years, the number of CIN 2/3 cases drops by about 40% in the first 10 years of vaccine coverage. Over the next 10 years, though, with no further vaccine protection, the rate of CIN 2/3 increases rapidly

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returning to the maximal reduction of 20%. The duration of the vaccine efficacy has a huge impact on what will really happen to cervical disease incidence rates.

Policy Issues Raised in the United States

Mandating the HPV vaccine for middle-school entry in the United States has been a huge political fiasco. Because there are insufficient funds in the United States to make the vaccine available publicly, mandates place a huge burden on families. There has been backlash from a lot of different political and religious groups. Part of the problem is that information around the vaccine has not been presented to the public in a forthright manner. Instead, what has been presented to the public is a misleading message that this vaccine is 100% effective and will cure cervical cancer, which is simply not true. This vaccine represents a significant advance in women's health care, but the limitations should be adequately exposed and described.

Other countries are using the vaccine as well. Outside the United States, two countries have started vaccinating 12-year-old girls. Australia started a program, but it is not mandatory. The government provides free vaccination in schools. Canada has a similar program

Conclusion

With regard to HPV vaccination, the glass may be half full: HPV vaccination will indeed largely reduce cervical cancer throughout the world. Possibly the glass is half empty: HPV vaccination may have a moderate impact on a screened woman's overall health. In reality, the glass may be twice as big as is necessary. There is going to be a 20- to 30-year return on public health investment, and we do not know how often a booster will be needed to maintain protection. We also do not know whether the intervals of cervical cancer cytology will change, or how the cervical cancer cytology programs for screening will change. What is clear, though, is that cervical cancer screening programs should not be abandoned. Those programs are going to help detect the other cancers that are not caused by HPV 16 or 18.

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