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An Interview with Dr. Diane M. Harper, HPV Expert

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Throughout my examination of the Gardasil vaccine, there has been a steady flow of information, disinformation, and new developments. In my opening article, I wrote about the mandatory ruling in July of 2008 by the U.S. Citizenship and Immigration Services (USCIS) that would require all female green card applicants and immigrants between the ages of 11-26 to receive the Gardasil vaccine. As of December 14, 2009, that ruling was reversed.

In the larger conversation, perhaps no one professional has been quoted, and misquoted, more frequently than Dr. Diane Harper. The recipient of a Masters Degree in Public Health, Dr. Harper is a Professor and Vice-Chair of Research at the University of Missouri-Kansas City School of Medicine, specializing in Community and Family Medicine, Obstetrics and Gynecology, Bioinformatics and Personalized Medicine.

Dr. Diane M. Harper

I first contacted Dr. Harper in September 2009 to get a primer on the Gardasil vaccine, and to gain insight into the issues that were being raised about the marketing and the safety of the vaccine. In addition to the questions that I raised this month with Dr. Harper, I asked her to contribute a statement that would clearly elucidate her point of view in her own words. She sent me what follows via e-mail.

Statement:

"The most important point that I have always said from day one, is that the use of this vaccine must be done with informed consent and complete disclosure of the benefits and harms of Pap screening and HPV vaccines. The decision to be vaccinated must be the woman's (or parent's if it is for a young child), and not the physician's or any board of health, as the vaccination contains personal risk that only the person can value.

As all of the information in the United States concerned Gardasil, since that was the only vaccine approved in the U.S. from June 2006 until this past October 2009, my comments have been focused on Gardasil.

My points are as follows:

The Benefits of Pap Screening:
• Individual benefit to detect early precancers.
• Public health benefit: Only when 70% of the population has been screened will the population incidence of cervical cancer drop.
• Pap tests do not kill or handicap.

The Harms of Pap Screening:
• Screening must be repeated throughout a woman's life. One screen is not sufficient to protect her from cervical cancer.
• False negative rate of cytology screening: Among the women who develop cervical cancer in the U.S., 30% are women who have been routinely screened, and all their Paps have been normal.
• False positive rate of cytology screening: Women who screen abnormal are psychologically upset, anxious and left doubting the medical process (i.e. Her Pap was abnormal, but her colposcopy and biopsy were normal, with no explanation why *her* Pap was abnormal).
• Quality of life harms: Women with abnormal Paps have anxiety as high as women diagnosed with cervical cancer undergoing their surgical treatment. The stress of going to colposcopy and biopsy can be high for many women. The contemplation of a cervical biopsy and a scraping of the endocervical canal can lead to fear of pain.

• Relationship harms: Once women are told they have an abnormal Pap and that the Pap is abnormal because of a STD called HPV, most relationships are stressed as the partners attempt to understand who brought the infection to the relationship.
• Excisional treatments for detected precancerous lesions cause preterm deliveries in subsequent pregnancies, with concomitant low birth weight infants (which puts the infant at risk for life). In addition, scarring from the treatments lead to an increased cesarean section delivery method (as the cervix does not dilate normally due to scarring from prior excisions). These reproductive morbidities occur between 70%-300% more often in women with excisions.
• Recurrence of HPV associated cervical/vaginal/anal cancers at a rate of 3-12 times higher than those women who never had a cervical cancer precursor or cancer. These recurrences happen around ten years after treatment with peak recurrences between ten and twenty years from the initial treatment.

The Benefits of HPV vaccination:
• Cervarix protects against five cancer-causing types of HPV, which lead to CIN 2+ (precancers and cancers).
• Gardasil protects against three cancer-causing types of HPV, which lead to CIN 2+ (precancers and cancers).
• Cervarix induces antibody titers for HPV 16 and 18 that are at least ten fold higher than natural infection titers; the antibody titers for the other three cancer causing types (HPV 31, 45, 33) are also significantly higher than natural infection titers, *and* the titers stay high for at least 7.4 years - lasting the longer of either vaccines.
• Gardasil only maintains antibody titers for HPV 16 (*not* 18, *not* 11, *not* 6) at five years, making the true long lasting (five years) coverage of Gardasil only for one type of cancer causing HPV.
• If vaccination occurs within *one* year of the onset of sexual activity, there will be 57/1000 cases of all CIN 2+ types and persistent HPV 16/18 infections prevented, as compared to only 17/1000 cases prevented if virgins are vaccinated.

The Harms of HPV Vaccination:
• Duration of efficacy is key to the entire question. If duration is at least fifteen years, then vaccinating 11-year-old girls will protect them until they are 26 and will prevent some precancers, but postpone most cancers. If duration of efficacy is less than fifteen years, then *no* cancers are prevented, only postponed.
• Safety: There is at least one verified case of auto-immune initiated motor neuron disease declared triggered by Gardasil [presented by neurologists at the 2009 American Neurological Association meeting in Baltimore, Maryland). There are serious adverse events, including death, associated with Gardasil use.
• *No* population benefit in reduction of cervical cancer incidence in the United States with HPV vaccination as long as screening continues.
• Incidence rate of cervical cancer in the United States based on screening is 7/100,000 women per year.
• Incidence rate of cervical cancer if women are only vaccinated with Gardasil is 14/100,000 per year (twice the rate of cervical cancer if young women vaccinated with Gardasil do not seek Pap testing at 21 years and the rest of their life).
• Incidence rate of cervical cancer with Cervarix vaccination is 9/100,000 per year– better than with Gardasil, but still more than with screening alone.
• Incidence of cervical cancer without screening and without vaccination is nearly 90/100,000 per year. The combination of HPV vaccine and screening in the U.S. will not decrease the incidence of cervical cancer to any measurable degree at the population level. Those women who do not participate in Pap screening, and who are vaccinated, will have some personal benefit for five years for Gardasil and 7.4 years for Cervarix (maybe longer), but they will not affect the population rates.

Boosters for Gardasil after antibodies wane makes the cost of vaccination escalate significantly, and cause implementation challenges to reach those women who might want to be revaccinated."

Questions:

Can you explain what your role as a "principal investigator (PI) for clinical vaccine trials" for Merck (Gardasil) and GlaxoSmithKline (Cervarix) entailed?

"Principal investigator means that I was responsible for assembling a research team to recruit participants, deliver the health care during the study, collect biological specimens at the correct time, and retain subjects over the entire time frame of the study. After the data collection is complete, I have a professional/medical/clinical obligation to review the data for interpretation, comment and publication. There are instances when industry will exclude a PI from participating in the data publication process. In total, for Merck and GSK, our team enrolled and followed nearly 3000 women in these studies. We have been participating in these trials as early as1997 when the first protocols were written."

Some reports state that you received no compensation; others qualify you as a "paid consultant." What was your relationship with these companies?

"The institutions at which I conducted the clinical trials were reimbursed for the costs of conducting the trials. I received no direct money for conducting the trials. I was a consultant for both GSK and MERCK, for which I was paid."

The public has identified you as a doctor knowledgeable about HPV and the vaccines, potentially without an agenda. Can you explain what you support about the Gardasil vaccine and what you see as its faults?

"I am an international expert in HPV science, its vaccines, its clinical disease and treatment. I have personally seen tens of thousands of women with abnormal Pap smears and have a referral clinic/office that includes women coming from all continents of the world to consult for my opinion on their personal care.

Gardasil offers sexually active women, who do not currently have HPV 6, 11, 16, or 18 infections, protection from genital warts and CIN 2+ disease for five years. If the vaccinated person is not sexually active during the five years of its efficacy, then the vaccine has

not protected her from disease (as we do not have evidence that Gardasil offers efficacy any longer than five years). Its faults include tiny antibody titers for all HPV types other than HPV 16; limited protection; limited duration of efficacy; and safety concerns (as outlined in my opening statement)."

Can you comment on the disconnect between the fact that efficacy was proven only in the 16-26 year old demographic, yet Gardasil is being approved for those in the 9-26 year old demographic.

"Immunologically, the disconnect is explained by two studies. One study in the 16-26 year old women showed both antibody titers and efficacy. The second study in 9-15 year olds showed similar antibody titers to those induced in 16-26 year olds where efficacy was seen. Hence, the inference is that efficacy must exist in 9-15 year olds. The fault in this logic is that 9-15 year olds may not be exposed to the virus until after the vaccine has waned."

Do you believe that the Gardasil vaccine, as it currently stands, could present more risks to a young girl or woman than the possibility of cervical cancer?

"Pap smears have never killed anyone. Pap smears are an effective screening tool to prevent cervical cancer. Pap smears alone prevent more cervical cancers than can the vaccines alone.
Gardasil is associated with serious adverse events, including death. If Gardasil is given to 11 year olds, and the vaccine does not last at least fifteen years, then there is no benefit - and only risk - for the young girl. Vaccinating will not reduce the population incidence of cervical cancer if the woman continues to get Pap screening throughout her life.

If a woman is never going to get Pap screening, then a HPV vaccine could offer her a better chance of not developing cervical cancer, and this protection may be valued by the woman as worth the small but real risks of serious adverse events. On the other hand, the woman may not value the protection from Gardasil as being worth the risk knowing that 1) she is at low risk for a persistent HPV infection and 2) most precancers can be detected and treated successfully. It is entirely a personal value judgment."

Has the original Gardasil marketing campaign of "one less" muddied the waters and misinformed the public, who heretofore believed that a Pap smear was sufficient to protect them from cervical cancer?

"If women were participating in Pap screening, or if as a parent you educated your daughter to seek Pap screening at the appropriate age (21 years) for her entire life, then she would have been very unlikely to be at risk for being "one" and would not be "one less." She would not have been "one" to begin with!

Yes, the marketing campaign was designed to incite the greatest fear possible in parents, so that there would be uptake of the vaccine. If parents and girls were told the benefits and harms of Pap screening and HPV vaccines as described above, an informed and valued decision would have been able to be made. Many may have chosen to continue with a lifetime of Pap screening and forgo the vaccines, with the unknowns of duration of efficacy and safety unable to be answered for many more years."

Are the protocols of the CDC and VAERS (Vaccine Adverse Event Reporting System) properly processing reports of adverse reactions and deaths due to the vaccine? What do you see as the weak link in the VAERS system of collecting data?

"VAERS is biased in both directions, not allowing any veritable conclusions to be drawn about vaccine safety. If an association with an adverse event is detected statistically, there is not enough information collected in VAERS to determine causation, which is a multi-step process. Likewise, if no association with an adverse event is detected statistically, there is not enough information to reassure the public that no serious adverse events occur. With our new health care reform, we need to budget money to collect true registries of vaccinated individuals and what happens to them after vaccination so that appropriate conclusions can be drawn."

Could you clarify the content and context of the statements that you made at the 4th International Public Conference on Vaccination in October 2009, which have been so widely read and misquoted? Specifically the reported quote, "The rate of serious adverse effects is greater than the incidence rate of cervical cancer."

"The rate of serious adverse events reported is 3.4/100,000 *doses distributed*. The current incidence rate of cervical cancer in the United States is 7/100,000 women. This is what I said."

Should there be an informed consent/full disclosure statement that doctors are compelled to deliver to parents before advising them about giving the injection to their daughters, stating that there are small but real risks of death surrounding the administration of Gardasil?

"The informed consent/full disclosure as I described initially must be disclosed to parents and young women. The questions should be raised, 'How do you want to prevent cervical cancer? Pap screening? Vaccination? Both?"

Do you think that those who have received the HPV vaccine will become lax with getting their Pap smears, ultimately leading to a greater rate of cervical cancer within the United States population?

"No one wants the incidence of cervical cancer to increase. *But*, there is a problem with women's' understanding of what Gardasil offered them. Many vaccinated women have returned to me in clinic with more abnormal Pap tests and more HPV disease. They are tremendously disappointed when told that Gardasil does not protect against all types of HPV, and that they are still at risk for cervical cancer.

In answer to your question, *Yes*. Finland has shown us that even a lack of screening for five years, resulting in less than 70% of the population being screened, is enough to increase the population incidence rate of cervical cancer. Yes, there is a real risk that

cervical cancer will increase in the U.S. if those women getting Gardasil do not realize that:

- Gardasil will not protect them for life
- They can get other HPV infections that lead to cancer that are not covered by Gardasil
- They need to continue to have Pap tests throughout their lifetime"

Recent reports state that Gardasil may have triggered MS (Multiple Sclerosis) in some girls receiving the vaccine. What are your thoughts on this?

"Neurologists at the American Neurological Association have indeed concluded that Gardasil is temporally associated with autoimmune attacks on the neurologic system. The range of neurologic disorders is unknown."

Can you point out specific "misstatements" that Merck has promulgated about the Gardasil vaccine?

"Less misstatements, than incomplete statements. For instance, the cumulative incidence of HPV infections for women in the U.S. through the age of 50 years old is 80%. That statement is true. That statement infers that nearly every one is infected with HPV at least one point in their life.

What is left out is that 95% of all HPV infections are cleared spontaneously by the body's immune system. The remaining 5% progress to cancer precursors. Cancer precursors, specifically CIN 3, progresses to invasive cancer in the following proportions: 20% of women with CIN 3 progress to invasive cervical cancer in five years; 40% progress to cervical cancer in thirty years. There is ample time to detect and treat the early precancers and early stage cancers for 100% cure.

Other examples include inferences that Gardasil will last a lifetime, with no mention of boosters or limited protection possible. Regarding wart protection promotion, there is no mention that the data showed protection against genital warts in men for only a 2.4-year period of time.

Gardasil is not really a cervical cancer vaccine. The vaccine prevents HPV infection. not the development of cervical cancer."

Are there any final comments that you would like to make about the Gardasil vaccine?

"Until Merck funds a multi-ethnic efficacy study lasting at least fifteen years, the vaccine should be used primarily by women within the first *six* years of their onset of sexual activity, to gain the most protection possible...*if* they choose to be vaccinated. The women can also choose to continue Pap screening for their lifetime.

Within the "first *six* years" comes from the National Cancer Institute data compiled from the Guanacaste study (Rodriguez - first author) that shows that the prevention rate is 32/1000 women, still much higher than the 17/1000 rate when vaccinating virgins who go on to become sexually active, but less than the 57/1000 women if vaccinated within the first year of sexual activity.

Cervarix is the superior cervical cancer vaccine, in that it prevents five types of cancer causing HPV infections. Gardasil is the superior vaccine in preventing HPV types causing genital warts."

In the next installment, mothers speak out.

"Photo courtesy of the UMKC School of Medicine."

This article originally appeared on Empowher.

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