

HPV VACCINE: PANACEA OR PANDORA'S BOX? THE COSTS AND DECEPTIVENESS OF THE NEW TECHNOLOGY

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Introduction:

The United States has the most affluent and technologically advanced healthcare system in the developed world, offering increased life-expectancy and quality of life to many. Yet it is also the most inequitable system in the developed world, with many of its own residents lacking access to this system of care—a fact which weighs heavily on our national conscience. Consequently, healthcare reform is again an urgent political issue, with the most recent reform package estimated to cost over \$3 trillion to institute.

It is in this context that one of the newer technological advances, HPV (human papilloma virus) vaccination, must be evaluated. The first quadrivalent vaccine was licensed for use in 2006 but not widely utilized until the completion of phase three trials in 2007.¹ Even though the clinically relevant endpoint of this trial was the prevention of CIN (cervical intraepithelial neoplasia) II and III,² it was quickly marketed as the first cancer vaccine: if administered to preadolescent girls, before the onset of sexual activity, it would prevent the later development of cervical cancer. This was rapidly followed by an egregiously premature move to make vaccination against HPV a mandatory requirement through the school system, a move which lacked the empirical foundation necessary to withstand critical opposition, except in the state of Texas.³

What is HPV?

Human papilloma virus is a DNA virus that is transmitted by skin-to-skin contact, and is similar to papilloma viruses that cause “warts” on other areas of the body. There are approximately 40 species that specifically infect the genital tract, causing genital warts and—in the presence of other co-factors, such as smoking or immune deficiency—cancers of the cervix, vagina, and vulva.⁴ While the virus is more prevalent in men, they rarely develop significant consequences of infection. The virus has been isolated on sperm,⁵ but skin-to-skin contact is the primary means of transmission with scrotal skin serving as a passive reservoir for male-female transmission.⁶ It is the incorporation of viral DNA into the genome of the infected cell that produces cellular changes leading to clinical “disease.”

Historical Perspective

Our understanding of the mechanism of infection with HPV has changed significantly over the past 30 years, from permanence

to transience; from general to specific; and from progression to regression. Originally, infection was felt to be a permanent condition, much like that seen with herpes viruses. Conversely, in recent years we have come to understand that infections with HPV are most often transient, with the median duration of infection ranging from 4.8 months for low risk viruses to 8.1 months for high risk viruses, and with clearance rates as high as 92% in 2-5 years.⁷ Moreover, the infection is most transient in young girls, with women over 30 less able and less likely to clear the virus.⁸ Secondly, whereas all species of HPV were originally thought to carry a risk of cervical cancer, we now know that these genital viruses have differing oncogenic potential; they are therefore categorized as either “low risk” or “high risk” based on the potential to initiate malignant and premalignant changes in the cervical epithelium. It is the oncogenic (“high risk”) viruses that raise serious medical concern. The third significant change in our understanding is that just as the infection is not permanent, neither is the disease necessarily progressive: mild precancerous changes do not necessarily and inexorably lead to cancer, as we once believed. Most often the changes are regressive: with clearance of the virus, the virally-induced cellular changes also regress. Therefore, attempting to eradicate all virally-induced changes is no longer believed to be necessary nor is it recommended.⁹

The Burden of HPV

The prevalence of HPV has increased exponentially in recent years concurrent with the exponential increase in promiscuous sexual activity in our culture. There are currently 24 million people in the U.S. infected with the virus, including 26-35% of sexually active couples. Moreover, there is an 80% chance of acquiring the virus by age 50.¹⁰ Generally speaking, subclinical infection, in which virus is present but virally-induced cellular changes are absent, is 10-30 times more common than clinical infection, but often clears spontaneously. Clinical infections include genital warts (~1% of the population), laryngeal papillomatosis, cervical dysplasia, and cervical, vulvar, and vaginal cancers. Cervical cancer is diagnosed in 11,000 women each year with 3500 women dying yearly from the disease. The average age at diagnosis is 45.

The monetary burden of this virus is not insignificant. The cost of screening, testing, and treating HPV in the year 2000 was \$3 billion (\$3.4 billion if costs of treating cancer were included). In that same year, \$167 million was spent to treat genital warts.

Concerns with Vaccination

HPV vaccines have proven to be 100% effective in preventing the neoplastic changes associated with HPV 16 and 18, and 100% effective in preventing genital warts resulting from infection with HPV 6 and 11. Yet in spite of these positive statistics, there are significant concerns. In order to be effective, a vaccine must be administered before the onset of sexual activity and hence before exposure to the viruses. The ideal age of vaccination has therefore been determined to be 11-12. But the virus is highly transient in adolescents in whom cervical cancer has never been diagnosed, and the duration of protection from the vaccination is unknown. It is therefore possible that the protective effects of the vaccination will wane at the time when women are most susceptible to the oncogenic effects of the virus (those over 30), providing protection to those who do not need it (adolescents) and failing to provide protection to those who do (women over 30).

Secondly, the quadrivalent vaccine covers only 4 of the approximately 40 papilloma viruses that infect the genital tract (HPV 6, 11, 16 and 18). The newer bivalent vaccine released this past year covers only HPV 16 and 18. HPV 6 and 11 are low risk viruses that will resolve spontaneously within one year, rendering any vaccine against them a waste of valuable resources and healthcare dollars.¹¹ HPV 16 and 18 have oncogenic potential, but even 80% of these infections will resolve without treatment.

Additionally, the four HPV types covered by the vaccine account for only 3.4% of all HPV infections in the U.S., and HPV 16 and 18 account for only 2.3% of the high risk viral infections in the U.S. (HPV 6: 1.3%; HPV 11: 0.1%; HPV 16: 1.5%; and HPV 18: 0.8%).¹² Moreover, not all of those who acquire these two viruses will develop cervical cancer. Even the American College of Obstetricians and Gynecologists states that “very few individuals with an HPV infection will develop cancer.”¹³ Since the duration of protection is unknown and the average age of diagnosis of cervical cancer is 45, it has not been demonstrated that the vaccination of all 11-12 year olds will prevent cancer at age 45. There is no long term data to support such a program, only speculation based on “knowledge” that is incomplete and ever-evolving.¹⁴

Under naturally occurring circumstances, infection with HPV triggers an immune response that provides a natural source of protection against the virus.¹⁵ Vaccination may inhibit this response, and if the vaccination then fails to provide permanent protection, these once-vaccinated young women will also lack any natural immunity, rendering them more susceptible to infection at a time when they are also more vulnerable to the oncogenic potential of the virus. Additionally, there is some concern that vaccination may generate shifts in oncogenic potential, escalating the risk of other viral strains for which there is no vaccine, a phenomenon recognized with influenza viruses.

HPV vaccines are exorbitantly expensive, exceeding the cost of all other vaccinations combined, and making it unfeasible for use in the general population. At a cost of \$500-900 for the series of 3 injections, vaccination will be inaccessible to many, thereby

diminishing the overall effectiveness through loss of “herd immunity.” And in spite of its price-tag, it does not eliminate costs of screening that are currently utilized: due to the large number of other viruses not covered by the vaccine, current screening methods will still be required.

The cost-effectiveness of vaccination is dependent upon a reduction in the rate of cervical cancer, an effect that has not to date been proven, which will not be realized for 4 or 5 decades, and which is dependent on achieving a high level of protection among a substantial portion of the population. And at a time when cost of medical care is under scrutiny, the crucial question is: who will pay? A recent study determined that if the protection the vaccination offered was permanent, vaccination of 11-12 year olds would cost an additional \$43,600 per QALY,¹⁶ over and above the cost of current screening methods, a level that was felt to fall within the range of cost-effectiveness.¹⁷ However, if a booster is required, the cost-effectiveness of the vaccination will be further

diminished. And logic belies the data: to vaccinate 10 million 11-12 year olds each year will cost approximately \$5 billion/year, a cost which will merely diminish the risk of cervical cancer from HPV 16/18 for approximately 4600 women.¹⁸ And these women will still be at risk for cervical cancer from other or new oncogenic strains of virus, as it is estimated that 50% of vaccinated women will still develop high grade cervical lesions due to the other viruses.¹⁹ The high prevalence of these viruses, the transience

of infection, the low prevalence of the virus in question, and the low incidence of serious disease would argue against cost-effectiveness of the vaccine and suggest that despite the rigorous statistical analysis employed by this study, a methodological error exists.

One of the cornerstones of modern medical practice is that of informed consent. The risks, benefits, side effects and alternatives of any medical procedure must be discussed with the patient before it is performed. Where a procedure is felt to be “necessary,” however, informed consent is often glossed over, if not ignored. And so it is with this vaccine, especially given the speed with which it received FDA approval. But the vaccination is not without associated risks--risks which potentially exceed the theoretical benefit--and these include paralysis, blood clots, Guillain-Barré syndrome, and death. There have been 43 reports of deaths (26 confirmed, 9 under investigation, and 8 unconfirmed) among young women associated with the vaccine,²⁰ yet death from cervical cancer is unknown in adolescents. At age 11 or 12, informed consent is often given to and by the parent or guardian. Is the adolescent being informed? Is she being educated? While mandates and coercion might be warranted in epidemics where public health and safety is at risk, this is not the case with HPV infection. And what is the ethically appropriate response when disagreement exists between the mother and the daughter with regard to the vaccination or completion of the series? The HPV vaccine has been marketed as a vaccination against cervical cancer, yet there is no data to substantiate that the vaccine prevents cervical cancer or that vaccinating adolescents today will indeed prevent cervical cancer later. Such marketing is deceptive and manipulative. Is this being addressed in our “informed consent”? Furthermore, the marketing techniques deceptively promote a

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false sense of security by placing emphasis on the rare oncogenic consequences of infection rather than on the nature of the virus as an STD. In so doing, it fails to acknowledge that the most cost-effective means of preventing cervical cancer is not a vaccine but cessation of smoking (a known co-factor for cervical cancer) and abstinence until marriage for both males and females. It is unlikely that this is part of the informed consent process even though it is one of the alternatives that comprise informed consent and an educational responsibility of healthcare providers.

The burden of this vaccine as well as the infection falls again to the female population. The vaccine has not been tested on males and perhaps for good economic reason: males serve primarily as vectors for the virus, in most cases suffering no significant short- or long-term consequences from infection. It would be a rare young man—or mother of a young man—who would subject himself to the cost, the pain, and the inconvenience of the vaccine for the sake of women 40 years hence.

From a global perspective, HPV vaccination may indeed be a panacea by providing protection where screening is unavailable. But third world countries do not have the resources from which companies can recover their expenses. Conversely, while we in the U.S. have the fiscal resources, we also have a screening program that has proven to be cost-effective in preventing cervical cancer, if utilized. Pap smear screening is also more cost-effective than vaccination, since it is non-discriminatory with respect to viral types.

Conclusion

There has been a subtle but significant paradigm shift in the orientation of American medicine in recent years from preventing and treating illnesses to alleviating the consequences of life-style choices. That shift is costing us greatly, as our choices are boundless and our perceived need insatiable. The rapid, deceptive, and pervasive promotion of the HPV vaccine is illustrative of this shift and raises more questions than answers. Experience in other areas of medicine (osteoporosis, coronary artery disease) has demonstrated that positive changes in clinical markers do not always correlate with disease prevention. With the rapid evolution in our understanding of HPV, it is imprudent to base disease prevention on clinical information that is incomplete and unproven. Given what we do know, the vaccine makes little sense. Why are we vaccinating young women with an expensive, painful vaccine that has not been proven to prevent what it claims? Why are we advocating that all pre-adolescent young women be vaccinated against an uncommon virus that is known to be largely transient? It calls into question the methodological assumptions underlying the research for the vaccine. The original research was initiated in 1991.²¹ Was this under the earlier assumption that the viral infection was permanent, before the transient nature of the infection was known? Now that the vaccine has been developed, does it have to be marketed in order to recover the expenses of the research and development? Why has it been marketed when the long-term effects on the immune system of young girls and the oncogenic potential of other viruses are unknown? Are we perhaps creating more problems than we are preventing? And finally, is this an effective use of scarce medical resources and dollars? These are questions that should have been answered prior to FDA approval, but will need to be answered in the days ahead if we are to preserve a system of healthcare that is accessible to all of our citizens.

- 1 Charlotte J. Haug, "Human Papillomavirus Vaccination—Reason for Caution," *New England Journal of Medicine* 359, no. 8 (August 21, 2008): 861-862.
- 2 Ibid.
- 3 See National Conference of State Legislatures data at www.ncsl.org/IssuesResearch/HPV/Vaccine/StateLegislation/tabid/14381/default.aspx. The State of Texas originally passed legislation by executive order that mandated HPV vaccination for school enrollment, but it was overridden by legislators. As of May 2009, there has been legislation to require, fund, or educate the public regarding HPV vaccine introduced by 41 state legislatures, but only 19 have enacted such legislation, and the District of Columbia is the only other district to mandate vaccination.
- 4 "Human Papilloma Virus Infection," Centers for Disease Control and Prevention, 2009; available at www.cdc.gov/std/hpv/default.htm.
- 5 Olufemi Olatunbosun, Harry Deneerm, and Roger Peirson, "Human Papillomavirus DNA Detection in Sperm Using Polymerase Chain Reaction," *Obstetrics & Gynecology* 97, no. 3 (March 2001): 357-360.
- 6 Rachel L. Winer, et al., "Genital Human Papilloma Virus Infection: Incidence, and Risk Factors in a Cohort of Female University Students," *American Journal of Epidemiology* 157 (2003): 218-226. Hands have also been strongly implicated in transmission, with virus cultured from nail beds.
- 7 ACOG Practice Bulletin no. 61, "Human Papilloma Virus," *Obstetrics & Gynecology* 105, no. 4 (April 2005): 907.
- 8 Ibid. This is also consistent with the fact that the average age of diagnosis of cervical cancer is 45.
- 9 Diane Solomon, et al., "The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology," *JAMA* 287 (2002): 2114-2117. See also ASCCP practice recommendations available at www.asccp.org/edu/practice.shtml.
- 10 "Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *Morbidity and Mortality Weekly, Early Release* 56 (March 12, 2007): 4.
- 11 This remains a significant question for the developers of the vaccine: why did they determine that a vaccination was needed for viruses that would resolve spontaneously, the costs of which would be passed onto the patient in the form of increased cost of the vaccine?
- 12 "Quadrivalent Human Papilloma Virus Vaccine: MMWR, 4.
- 13 ACOG Practice Bulletin no. 61, "Human Papilloma Virus," (2005): 907.
- 14 The speed with which the FDA approved the vaccine raises concerns as well in light of inadequate data regarding its duration, safety, and long-term effectiveness.
- 15 Deane Medved Harper, "The HPV Vaccine Debate: Public Policy vs. Personal Choice," *Devos Medical Ethics Colloquy* (March 24, 2008): 30. See also *MMWR* 56 (March 2007): 3.
- 16 QALY stands for Quality-Adjusted Life Year's measurement and is a method that compares different drugs by measuring their clinical effectiveness.
- 17 Jane J. Kim and Sue J. Goldie; "Health and Economic Implications of HPV Vaccination in the United States," *New England Journal of Medicine* 359, no. 8 (2008): 821-832. Vaccination of women in other age groups, while believed to be necessary, was not shown to be cost-effective.
- 18 10,000,000 @ \$500/vaccination; 2.3% will contract HPV 16/18, but 80% will resolve spontaneously, leaving 20% of the 2.3% of the 10,000,000 at risk.
- 19 Harper, "The HPV Vaccine Debate," 26.
- 20 "Reports of Health Concerns Following HPV Vaccination," Centers for Disease Control VAERS data 2009; available online at www.cdc.gov/vaccinesafety/vaers/gardasil.htm. It must be noted that these risks are associated with the vaccine but the relationship has not been proven to be causal. The concern remains.
- 21 Christopher P. Crum, "The Beginning of the End of Cervical Cancer?" *New England Journal of Medicine* 347, no. 21 (Nov 21, 2002): 1704-5.