



5-1-2009

Modeling Gardasil: Issues and Perspectives

Julia Margulis
University of Pennsylvania

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The successful implementation of a new health care technology depends in large part on accurate and realistic scientific models that can predict what impact that technology will have in a variety of scenarios. These models help determine the new technology's optimal price, target population, and route of administration or access. Such projection involves a variety of assumptions about the new technology's cost, efficacy, safety, ease of access, and practicability. Although a model, by definition, necessitates making such assumptions, these assumptions will never fit the reality of the health care situation exactly. The populations themselves and the ways in which they respond to the implementation of a health care technology are by and large heterogeneous, such that notions of efficacy, ease of access, and other parameters will not apply in the same way to every consumer of the health care technology in question. How does this interaction between projection and reality manifest itself? And where does this interaction play out? Such questions are important not only to refine the aforementioned models but also to gain a greater awareness of how the public health reality can best be addressed in order to successfully traverse the many health care challenges that we face today and will face in the near future.

The recent introduction of Gardasil®, Merck's quadrivalent HPV vaccine, provides a unique opportunity to analyze the scientific models that serve as a basis for arguments for and against mandating the vaccine as a condition for school enrollment. As of February 2008, Merck had distributed 13 million doses of its vaccine in the United States alone. At a cost of \$360 for the three doses required over a six-month period, this amounts to \$4.7 billion already spent on the vaccine, with an annual profit for Merck of \$1.5 billion.¹ As administration of the vaccine expands to younger and younger girls (the current suggested age range for vaccine administration is 11-12 years old) and even boys, tens of millions more doses of the vaccine will be administered in the next few years. Moreover, Gardasil is now compulsory for all immigrants into the United States (an ethical issue all its own), which will only increase the vaccine's predominance. Recent discussions about Gardasil have centered on arguments for or against mandating the vaccine for school entry. Many other common childhood vaccinations, such as diphtheria, tetanus, and acellular pertussis (DTaP), polio, and measles, are required by all states in order for a child to enter kindergarten.² It has now been suggested that Gardasil join them. In fact, Texas governor Rick Perry signed into law in February of 2007 a mandate requiring all 11-12 year old girls to receive the HPV vaccine before entering the sixth grade (which was later blocked by Texas legislators, however).³ Increasing numbers of efficacy and cost effectiveness models have sprung up to deal with the controversy surrounding the vaccine and its widespread administration. In this paper, I will consider the reach and relevance of the HPV vaccine model (particularly its claims of efficacy) and the limitations of this model given the reality of the "public" that will actually become the consumers of this medical technology.

The rationale for the creation of a vaccine for HPV is based on the link between HPV infection and cervical cancer in women. HPV is the most common sexually transmitted infection in the United States today; approximately six million people are newly infected with the virus each year, and some models estimate that up to 80% of sexually active women will have contracted the virus at some point in their lives by the time they reach 50 years of age.⁴ In addition, 500,000 women develop cervical cancer every year. Half of those die as a result.⁵ 99% of cervical cancers are attributable to infection with HPV virus strains. HPV can manifest itself as a variety of high- and low-risk types; low-risk types (including types 6 and 11, both present in Merck's vaccine) are generally associated with genital warts and benign or low-grade cervical cell changes (i.e. those not linked to a transformation into cancerous lesions). High-risk types of the virus can cause both low- and high-grade abnormalities that are precursors to cancer. High-risk

types 16 and 18, which are detected in 70% of cervical cancers worldwide, are also included in Merck's vaccine. Gardasil was approved by the FDA in June 2006 for use in females 9-26 years of age for prevention of cervical cancer and its precursors as well as prevention of anogenital warts. However, this vaccine does not include all HPV types that cause cervical cancer; thus, it does not eliminate the need for cervical cancer screening. Current recommendations state that Gardasil should be routinely administered in 11-12 year old girls in three separate doses; the series can be started in girls as young as 9 years old. Catch-up vaccination of 13-26 year old girls is recommended as well.⁶

Gardasil was proven to be nearly 100% effective in preventing precancerous lesions in women without prior HPV infection based on the results of four randomized, double blind, placebo-controlled studies in 21,000 women ages 16 to 26.⁷ The duration of antibody protection was not studied past five years post-administration; it is unclear at this time whether or not booster shots will be necessary every five or more years. There is no current evidence that the vaccine's immunogenicity declines significantly over time. The most common adverse event due to vaccine administration was pain at the injection site. Serious adverse events occurred in <0.1% of study participants.⁸ Although the vaccine seems to be relatively safe given the available data, study participants were only followed for five years after vaccine administration so any long-term side effects would not be noted. In addition, current adverse event reporting systems, such as the Vaccine Adverse Event Reporting System (VAERS), are voluntary and present a necessarily incomplete picture of vaccine safety. The vaccine is currently priced at \$120 per shot, or \$360 for the entire three-shot series. This cost is covered by most, but not all, insurance companies. Most universities, such as the University of Pennsylvania, do not yet cover the cost of the vaccine.

Vaccine mandate discussions invoke the concept of herd immunity, "in which the protective effect of vaccines extends beyond the vaccinated individual to others in the population, [which] is the driving force behind mass immunization programs."⁹ For diseases transmitted by contact with or proximity to an infected person, rates of infection will decrease as more and more people in that population become immune to infection due to vaccination. The more resistant individuals are present in the population, the lower the risk of encountering an infected person that can pass the disease to someone else. The concept of herd immunity has no mathematical basis; there is no percentage of immunized individuals that guarantees herd immunity for the rest of the population. However, as the rate of vaccination increases, protection of others indirectly increases until the infection is essentially eradicated. Such a model for disease transmission and efficacy works best for highly transmissible diseases such as measles; in fact, many modern compulsory vaccination laws were enacted in response to the prevalence of measles in schools in the 1960s and 1970s.¹⁰ The incidence of highly transmissible illnesses such as polio, chicken pox, pneumonia, and meningitis is now extremely manageable due to mandatory vaccination programs.

However, the concept of herd immunity breaks down when it is examined in relation to the HPV vaccine. As per current recommendations regarding vaccine administration, it is only to be administered to (and has only been approved for) girls. Studies of the vaccine in boys are ongoing, but this raises the question of whether or not it is ethical to mandate the vaccine for boys so that fewer girls will be infected with HPV. Boys would derive some benefit from the vaccine as well; HPV in men can cause genital warts as well as certain anal and penile cancers. However, many parents may not be satisfied with these justifications, and pure altruism or chivalry will not do much to convince them to give their sons the vaccine if it does become available for boys.¹¹ Thus, the concept of herd immunity in relation to HPV vaccine administration is inappropriate because of the gender-specific character of cervical cancer. Herd immunity as a model to describe disease transmission is irrelevant in a case where a disease only affects one segment of the population but can be transmitted by everyone. The public cannot be generalized as a "herd"; different groups (in this case males and females) respond differently and are differentially susceptible to disease. Thus, the creators of medical technologies will continue to target various

groups according to their particular health care characteristics. Such targeting began years before Gardasil with BiDil, a heart disease drug intended by its manufacturer for African Americans. Innate group differences negate the concept of a “herd”; although modeling vaccine efficacy in such a way can be effective for certain diseases, it is by no means a universally applicable concept.

Arguments for or against mandating HPV vaccine administration for school enrollment are based on a set of criteria used to evaluate the costs and benefits of vaccine on several levels. The most comprehensive set of these has been set out by the Washington State Board of Health’s Immunization Advisory Committee. The Committee grouped its criteria into three categories: disease burden, vaccine effectiveness, and implementation. Each antigen that makes up the vaccine (four separate antigens, in the case of Gardasil) must be considered separately against these criteria. Criteria on the effectiveness of the vaccine question its efficacy in terms of immunogenicity and disease prevention, cost effectiveness, and safety. The disease burden criteria examine the vaccine’s prevention of diseases with significant morbidity and/or mortality and its reduction of person-to-person transmission. Finally, the implementation criteria question the degree to which the vaccine is trusted by the public, the administrative burdens of its delivery and tracking, and the burden of compliance for the parent or caregiver. In effect, the potential benefits of the vaccine, including its efficacy and reduction of disease burden, are weighed against its risks or costs, including both adverse side effects and economic burden.¹²

However, the IAC itself states that it makes several assumptions upon which the aforementioned criteria are based. These assumptions are that “(1) some kind of process exists for exemption from mandated immunization requirements in cases when vaccination is not appropriate (e.g. medical, religious, or philosophical reasons) and (2) that mandated vaccine(s) with the antigen are accessible to those for whom it is mandated and cost is not a barrier.”¹³ Are these assumptions truly reasonable? Almost every state has some sort of process for requesting exemption from an immunization requirement; therefore, (1) is a reasonable assumption to make given the reality of state immunization laws. However, assuming equal access and ability to shoulder the cost of the HPV vaccine ignores the inherent disparities and inequalities that persist in our health care system. Racial and socioeconomic identifiers still play an important role in the degree to which one can access health care. According to the 2007 National Health Disparities Report, black and Hispanic children aged 19-35 months are still the racial and ethnic groups with the lowest percentages of children who receive all recommended vaccines. Poor and near-poor children are also less likely to have received all of their recommended vaccinations compared to middle- and high-income children. In addition, only vaccination levels in white, non-Hispanic white, middle-income, and high-income children met the standard of 80% of children receiving all recommended vaccines set out in the Health People 2010 objectives.¹⁴ The criteria set out by the IAC ignore instances of structural violence present in today’s health care system; instead, it is assumed that all have equal access to the vaccine in spite of obvious indications to the contrary. The vaccine becomes a sort of “magic bullet” whose medical efficacy is sufficient for it to accomplish its intended goals (in this case, preventing HPV infection and precancerous lesions that could lead to cervical cancer). However, the efficacy of a medical technology is negligible when it is unavailable to the majority of those who would benefit from it. João Biehl’s *Will to Live* illustrates this concept in a global health context, where the availability of antiretrovirals in Brazil did nothing to help destitute AIDS patients who were not formally included in Brazil’s health care infrastructure and thus could not gain access to the drugs on a regular basis in spite of the drugs’ proven efficacy and availability. The population that the IAC criteria assume to exist is homogeneous both ethnically and socioeconomically; every 11-12 year old girl who should get the vaccine is supposedly able to get it. The real “public” cannot be characterized as a uniform entity nor can it be referred to or expected to act in a particular way given the invention of a new technology. Reality is far more complicated; although the IAC criteria are useful for evaluating a vaccine, they are also fundamentally flawed considering the complexity of the recipients of the medical technologies they are meant to evaluate.

Given a set of reasonable, though not necessarily accurate, set of assumptions, models can be extremely effective at predicting both disease transmission rates as well as the efficacy of a new medical technology, such as a vaccine, at slowing or reversing these rates. The results of randomized controlled trials can provide proof of efficacy as well. The HPV vaccine and other comparable medical technologies treat the existing prevalence of a particular disease; however, they do not address the root cause of the disease's prevalence in the first place. It can be argued that herd immunity, a supposed product of widespread vaccine administration, eliminates disease prevalence no matter the source; however, as previously discussed, the concept of herd immunity does not apply to Gardasil because of the gender specificity of the health care problem it aims to address.

Cervical cancer incidence varies greatly by racial/ethnic group in the United States. Black women are 1.5 times more likely than white women to develop cervical cancer; the incidence of cervical cancer in Hispanic women is also higher than in white women. In addition, twice as many black women as white women die from the disease. Pap tests are the most effective way of detecting early cervical changes. Approximately 82% of women in the United States have had a Pap test in the last three years. However, women with less than a high school education, foreign-born women, women without health insurance, and certain racial/ethnic groups such as Hispanics have lower screening rates. Half of the women diagnosed with cervical cancer have not had a Pap test in the three years prior to their diagnosis.¹⁵ Of course, high rates of HPV transmission and the relatively high frequency of the virus in the U.S. population contribute to cervical cancer; this is a scientific fact and cannot be ignored. Nonetheless, much of existing cervical cancer prevalence and mortality could be decreased or even eliminated by ensuring that all women, no matter their race, ethnicity, education level, or socioeconomic status, be given access to routine Pap tests and cervical cancer screening. Scientific models of the efficacy of medical technologies do not consider how health care infrastructure or lack thereof contributes to a health problem. Vaccinating young girls with Gardasil may very well have dramatic effects on the spread of HPV; however, such a strategy does not address the existence of high rates of cervical cancer because of inadequacies in access to screening and prevention. Neither medical technologies nor the models used to predict their efficacy address the underlying structural inequalities that can lead to health problems; instead, they act as surface solutions to issues that run much more deeply in the fabric of society.

This problem of structural violence in health care infrastructure is exacerbated globally, where basic necessities such as food and water, much less access to advanced health care technologies such as Pap tests, are sorely inadequate. Compared to the developed world, only 5% of women have had a Pap test in the last five years. As many as 87.3 women per 100,000 are diagnosed with cervical cancer in sub-Saharan Africa and Central America.¹⁶ Comparatively, in the United States, 7.9 women per 100,000 are diagnosed with cervical cancer.¹⁷ Women in developing countries bear the brunt of this disease, and revolutionary technologies such as the HPV vaccine are still prohibitively expensive for poor governments and the people they serve. It is clear from these statistics that models used to predict Gardasil's cost and efficacy in the United States are not applicable to the starkly different public health situation in developing countries. For example, one model of cost-effectiveness of a potential HPV vaccine assumes that 71% of the adult female population receives twice-yearly Pap testing.¹⁸ This statistic is observably realistic, and even conservative, for the U.S. population; however, it is a completely invalid assumption to make for a developing country. Models of efficacy are in no way objective or universal; they are as subjective as the "public" they attempt to describe. The way in which diseases and other health care problems affect this "public" depends not only on the makeup of this entity and its susceptibility to the disease (both parameters that can be measured to a relatively accurate degree) but also on the societal and geographical context in which this "public" exists. Models of efficacy for medical technologies do not take these parameters into account; thus, such models are inherently limited in their scope and applicability.

The harm principle, a common philosophy used in the study of public health, was first stated by John Stuart Mill in his book *On Liberty*: “The only purpose for which power can rightfully be exercised over any member of a civilized community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant.”¹⁹ Mandatory vaccination programs abide by this principal in that they force vaccinations on individuals that may not necessarily benefit from them on the basis of a greater good bestowed onto the entire community, such as herd immunity. What is this community for which we are supposed to sacrifice our own physical or moral good? It cannot be classified as a “herd” or any other sort of homogeneous or generalizable group. Moreover, the effect of a particular medical technology on an individual depends on who that individual is, particularly his or her socioeconomic and racial/ethnic identifier. Thus, although the harm principle sets out a reasonable tenet on which many public health initiatives can base themselves, the concepts of individuals and communities that the principle invokes are not useful unless they are qualified by a specific context and identity.

Ultimately, a medical technology is meant to alleviate a health care burden without imposing an impossible-to-manage economic one. The optimization of this delicate balance between the ideal application of technology and a feasible cost is represented by the scientific model. However, models inherently ignore the complexities of the manifestation of a health problem within a population; a model must assume a set of parameters that often ignore the specificity of a medical technology to a particular subgroup (such as women or African Americans) and the realities of unequal access to medical technologies that both make it impossible to achieve ideal levels of administration of the medical technology and often cause the disease in question to be prevalent in the first place. This inadequacy of models redefines the way in which we think about efficacy and other parameters of health care technology evaluation. These parameters and their quantification are in no way universal or unbiased. A medical technology affects each individual differently based both on that individual’s innate biology and identity as well as his or her environment and its existing infrastructure. A model is limited in its ability to understand how health care infrastructure and structural violence affect each individual. Thus, the manifestation of the interaction between the model’s projection and reality takes place within the individual and his or her relationship with the medical technology in question. In spite of their obvious weaknesses, models can still be effective tools. Given the right perspective on its limitations, a model is vital to the successful implementation of lifesaving and quality of life-improving health care initiatives. In addition, cognizance of these limitations helps bring greater awareness to existing health care disparities and the ways in which new technologies must be adapted to an increasingly globalized world.

Julia Margulis is a senior in the College majoring in Biology with a concentration in Neuroscience. Julia will be starting her doctoral study in Neuroscience at UCSF this fall.

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² Javitt, Gail, Deena Berkowitz, and Lawrence O. Gostin. “Assessing Mandatory HPV Vaccination: Who Should Call the Shots?” *Journal of Law Medicine, and Ethics* 36 (2008): 389.

³ Blumenthal, Ralph. “Texas is First to Require Cancer Shots for Schoolgirls.” *New York Times* 3 Feb 2007.

⁴ Javitt et al., 385.

⁵ Parry, Jane. “Vaccinating Against Cervical Cancer.” *Bulletin of the World Health Organization* 85. 2 (2007).

⁶ “Quadrivalent Human Papillomavirus: Recommendations of the Advisory Committee on Immunization Practices (ACIP).” *CDC Morbidity and Mortality Weekly Report* 56 (2007).

⁷ Javitt et al., 385.

⁸ “Quadrivalent Human Papillomavirus: Recommendations of the Advisory Committee on Immunization Practices (ACIP).”

⁹ Javitt et al., 388.

¹⁰ Hoffman.

¹¹ Ibid.

¹² Immunization Advisory Committee of Washington State, “Criteria for Mandated Vaccines for Childcare Center and/or School Entry.” 12 April 2006, 3-4.

¹³ Immunization Advisory Committee of Washington State, 2.

¹⁴ Agency for Healthcare Research and Quality. “2007 National Health Care Disparities Report.” Feb 2008, 197-8.

¹⁵ “Quadrivalent Human Papillomavirus: Recommendations of the Advisory Committee on Immunization Practices (ACIP).”

¹⁶ Katz, Ingrid T. and Alexi A. Wright. “Preventing Cervical Cancer in the Developing World.” *New England Journal of Medicine* 354. 11 (2006), 1110.

¹⁷ “United States Cancer Statistics: 2004 U.S. Cancers By Type.” *National Program of Cancer Registries*. Center for Disease Control and Prevention. 8 Dec 2008

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¹⁸ Sanders, Gillian D. and Al V. Taira. “Cost-effectiveness of a potential vaccine for human papillomavirus.” *Emerging Infectious Diseases* 9. 1 (2003), 39.

¹⁹ Mill, John Stuart, *On Liberty* (London: Longmans, Green, and Co., 1921) 6.