

## Human Papilloma Virus Vaccination: Should it be Mandatory?

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### ABSTRACT

Cervical cancer is the second most common malignancy and a leading killer among women worldwide. Seventy percent of these cervical cancers are known to be caused by Human Papilloma Virus, which is transmitted primarily by sexual contact. The use of Human Papilloma Virus prophylactic vaccine among young adolescents, who have not been previously exposed to the infection, as primary prevention holds most promise for the prevention of this cervical cancer. Each year 80% of the 274,000 deaths caused by cervical cancer occur in developing nations like Nepal. Largest promise of this vaccine is in such countries where screening program is difficult to implement and maintain. However this also raises concerns and debates about the enduring effectiveness and the long term side effects of the vaccine, which are yet unknown. Garnering public trust and public acceptance is key to the success of any public health intervention. More research on the long term safety and efficacy on Human Papilloma Virus vaccine and dissemination of these findings is recommended to increase the acceptance of the program before making it a state mandate.

**Key words:** *developing nations, human papilloma virus, vaccine*

### INTRODUCTION

Cervical cancer is the second most common cancer among women world wide. It affects women relatively early in their midlives. The morbidity and mortality of women during the most productive years of their lives has a devastating effect on the well being of the family.

World Health Organization (WHO) and United Nations Population Funds (UNFPA) report states that 500,000 cases of cervical cancer are estimated to occur each year and 270,000 of them die due to the disease and

Over 80% of these occur in the developing countries where neither screening nor optimal treatment is available.<sup>1</sup> It has been estimated and reported that every two minutes a women dies of cervical cancer somewhere around the world.<sup>2</sup>

In United States of America cervical cancer afflicts more than 10,000 women in a year. The American cancer society has estimated that about 11,150 new cases of invasive cervical cancer will be diagnosed by the end of 2007 and about 3,670 women will die from cervical cancer.<sup>3</sup> Cervical cancer rates have markedly plummeted globally since the introduction of the

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Papanicolou test a screening program. But the disease is still second most common malignancy and a leading killer of women world wide.<sup>4</sup>

Human Papilloma Virus (HPV) has now been established as the major cause of cervical cancer. Almost 70 of the cervical cancers are caused by HPV genotype 16 and 18.<sup>5</sup>

World health organization (WHO) report on worldwide prevalence of HPV is 440 million.<sup>6</sup>

A study conducted by Dunne et al for the National Health Nutrition Examination Survey (NHANES) 2003-2004 to determine the prevalence of HPV infection among women in United States of America have concluded that the prevalence of both high risk and low risk Human Papilloma Virus type is 26.8%.<sup>7</sup> Food and Drug Administration (FDA) too has reported that Human Papilloma Virus is the most common type of sexually transmitted disease and has now become ubiquitous in United States.<sup>8</sup>

A vast majority of the Human Papilloma Virus infections are eliminated by the body's own self defence mechanism. However the genotypes 16 and 18 can persist and cause cytological changes in the cervix leading to carcinoma cervix.

#### HPV Vaccination

Advisory Committee on Immunization Practices (ACIP) began reviewing the data related to Gardasil vaccine in February of 2004. After several rounds of discussions, presentations, recommendations and modifications in June of 2006, HPV vaccine that demonstrated significant protection against Human Papilloma Virus 6, 11, 16 and 18 was approved by FDA for marketing in the United States and was recommended by Center for Disease Control and Prevention (CDC) for routine vaccination. A second vaccine that protects specifically against 16 and 18 is likely to be licensed soon. Both these vaccines are prophylactic, they are not therapeutic.

The efficacy of Gardasil was assessed in four multicentric, double blind, placebo controlled phase II and Phase III clinical trials evaluating 20, 541 women ages between sixteen to twenty six years at enrollment.<sup>9</sup> The results showed that in naïve cases Gardasil was 100% effective in preventing precancerous cervical lesions, precancerous vulval and vaginal lesions genital wart infections with HPV types against which the vaccines was directed. The results demonstrated that the vaccine was shown to be most effective when given prior to infection that is prior to the onset of sexual activity.<sup>10</sup>

CDC recommendations for vaccination of girls 11 to 12 years is based on several considerations:<sup>11,12</sup>

1. Studies suggesting that the quadrivalent vaccine among girls this young is safe 100% effective, no serious adverse event reported so far.
2. Studies confirming high antibody titre achieved after vaccination at age eleven to twelve. The vaccine has demonstrated significant protection for at least five years without waning protection.
3. Epidemiology and age of sexual debut in United States. A girl who has not been infected any of the four types of Human Papilloma Virus will derive the full benefits of the vaccine.
4. High probability of Human Papilloma Virus infection acquisition within a few years of sexual debut.

Although it has been recommended for that age girls/ women aged 13 to 26 years will also benefit from the vaccine although as mentioned above full benefits will be derived by only those that have not already acquired the disease.<sup>11</sup>

#### Impact of the vaccine on the disease outcome:

The lifetime risk of acquiring cancer due to HPV is 80% and studies have indisputably linked cervical cancer to persistent infection of oncogenic high risk.<sup>13,14</sup>

Goldie et al in their research developed a comprehensive model of Human Papilloma Virus infection and cervical cancer to estimate the clinical impact of a prophylactic Human Papilloma Virus sixteen, eighteen vaccine. They successfully demonstrated that the prophylactic vaccine preventing HPV 16 and 18 infections can be expected to effectively reduce associated high grade squamous cell lesion and cervical cancer.<sup>15</sup>

These reports serve to justify that there is no down side on vaccinating a girl/women with a vaccine that has shown 100% efficacy in decreasing the deadly consequences of the HPV affliction.

CDC has recommended three dose schedules for the vaccination, the second and the third doses to be administered two months and six months after the first dose.<sup>11</sup> CDC has however reiterated that vaccine will not replace the routine Papanicolou (PAP) screening. The routine ongoing Papanicolou based screening program, a very sensitive screening test that detects early cytological changes which has been very successful at reducing the global cervical cancer incidence and mortality associated with it.<sup>14</sup>

#### Cost effectiveness of the vaccination program

Cost effectiveness is a tool that helps to identify the most effective use of resources by comparing the

net cost of the vaccine with the potential benefits expressed as the year's quality adjusted years of life saved (QALY).

Exploring the cost effectiveness, the costs and benefits of HPV vaccination program involves numerous considerations like

1. Age specific incidence of Human Papilloma Virus
2. Natural history of the carcinogenesis
3. Acceptability of the vaccine
4. Availability of the screening programs
5. Vaccine efficacy and
6. Coverage

Each dose in United States costs \$120 US dollar, therefore three doses will cost \$360. Goldie and co authors applied a computer based model to assess the costs of and clinical benefits associated with a variety of hypothetical cervical cancer control policies consisting of primary cancer prevention component, that is vaccination and a secondary cancer prevention component that is cervical cytological screening.

They have concluded that a combined program of vaccination and screening that allows a later age of screening initiation with a less frequent follow ups than the present recommended protocol will likely be cost effective in limiting the health care resources.<sup>16</sup>

In another exploratory analytic study Shalini and Evan, utilized a Markov model of analysis to identify potential cost effective method for adding vaccination to an already existing organized screening program. The study showed that vaccination with annual screening beginning at age eighteen had a large overall reduction in cancer incidence and morbidity at a cost of \$ 23, 6250 per life year gained compared with vaccination annual screening beginning at twenty two years. They found that the cost effectiveness of the vaccination plus the delayed screening was highly sensitive to age of vaccination, duration of vaccination, the efficacy and cost of vaccination. They have thus recommended more studies to identify optimal age for vaccination.<sup>17</sup>

CDC reports yet another study on Markov model conducted to examine the cost effectiveness of vaccinating females aged twelve years. Assuming 100% vaccination rates, the authors have concluded that 58% reduction was achieved in the life time risk of cervical cancer for the vaccinated cohort at a cost of \$ 24,300 per QALY compared with no vaccination.<sup>11</sup>

Goldie et al state that about \$ six billion is spent each year in United States on the evaluation and management of the low grade cervical lesion.<sup>16</sup>

The cost effectiveness studies of HPV vaccination have suggested that the cost per quality- adjusted life year (QALY) saved by HPV vaccination would be in the range of \$ 15,00 - \$ 25,000 range per QALY.<sup>16</sup>

Whereas other childhood vaccines are federally funded and free, the cost for HPV vaccine is high. Three dose schedule costs \$ 360. Though many major health plans have implemented coverage for the vaccine, there are still many health insurances that do not cover the vaccine because of its high price and thus the vaccine is inaccessible to many who desire to be vaccinated in USA.

So far Merck has sold out more than five million doses of HPV vaccine, but the high price has made it inaccessible to many in USA. As the volume of demand for the vaccine increases more suppliers will enter the market and the price of the vaccine may fall and become stable in the future. Till then policy makers need to come up with a policy to reduce the price or an alternative policy or coverage system to make it more accessible to all desiring to be vaccinated.

Gardasil took more than twenty years to be developed and must be constantly refrigerated. Jennifer Allen, the spokesperson for Merck stated that the price for the vaccine has been based on all these costs plus the value that it brings to the individuals and the society.<sup>18</sup>

Given these circumstances and data to substantiate, with an organized vaccine program in place less frequent screenings could be recommended in future.

Thus even a partial vaccination program (recommended but not mandatory) will be efficacious and cost effective.<sup>19</sup>

### Ethical issues

The four ethical principles Beneficence, Non maleficence, Autonomy and Justice provide a framework for the ethical application to moral problems in community health.<sup>20</sup> Launching an immunization program has always stirred a storm of controversies. Even though most immunizations satisfy beneficence, nonmaleficence and justice there is always some infringement of autonomy. Specially for any vaccination involving minors who cannot consent for themselves then the decision making falls on the shoulders of the guardians who have a duty to protect them. Thus the issue of compulsory vaccination will raise questions regarding the rationality of the policy and will often clash with the decisions of the parents, who feel that it is an infringement on their parental rights. For this reason almost forty eight states in USA allow exceptions from vaccination on religious and other philosophical grounds. Despite these controversies immunization today has reached all time

high not only in USA, but also in many countries around the globe successfully eradicating some diseases while gaining a good control over others.

This experience makes it worth thinking about ethical justifications for recommendation of mandatory HPV vaccination.

#### Key challenges and Issues in Nepal:

The lack of adequate health infrastructure and poor local health care system that do not support routine Papinocolou (PAP) screening coupled with socio cultural situation preventing women from seeking health care has lead to a high mortality rate due to cervical cancer in Nepal. The official statistics may not show the true burden and geographical distribution of the disease. In developing nations like Nepal the life time risk of cervical cancer for poor women with high fertility exceeds ten percent.<sup>21</sup> Women in Nepal have a more urgent need for primary prevention of cervical cancer as compared to industrialized nations where cervical cancer rates have plummeted due to organized and established screening programmes. Very recently Australian cancer foundation donated cervical cancer vaccine to Nepal. Four teen age girls were vaccinated at a very reduced cost, four percent of the total international cost. The objective of Australian cancer foundation is to provide ten thousand full administration rounds of cervical cancer vaccine per year in Nepal.<sup>22</sup> Similarly Bill and Melinda Gates Foundation, PATH (a global health organization) Global Alliance for Vaccine and Immunization are working together with Local governments of India, Peru, Uganda and Vietnam and have introduced a pilot project to vaccinate young girls in these nations. Historically people in the developing nations would have to wait decades for the new vaccine to be available. With every five year delay in bringing the vaccine to these nations about one point five to two million more women will die of cervical cancer. Cervical cancer is tragically property of a women but preventing cervical cancer is a reproductive health issue which belongs to everyone. With good public health information, education, and a broad based support from international organizations, women of impoverished nations like Nepal will not have to die of a preventive disease simply because of where they live.

#### Should vaccination be mandatory?

Various surveys have been done by many researchers to assess parental attitudes towards HPV vaccination.<sup>23-25</sup>

Some views favoring mandatory vaccinations in those studies are:

1. 100% efficacy, demonstrating maximum beneficence.

2. No harmful or serious adverse event reported so far.

3. Prefer mandatory vaccination to prevent daughter for getting cervical cancer wish a good healthy life for their daughter.<sup>23-25</sup>

#### Views of the critiques of the mandatory vaccination:

1. Feel that this type of initiative will promote promiscuity among teenagers.
2. Infringement of parental autonomy.
3. Health concerns about the long term effects of the vaccine which has not been seen yet.
4. Skepticism that the drug companies are touting the vaccine for their own profits rather than for the public interest.<sup>23-25</sup>

Factors to be considered by policy makers and public health professionals for successful maintainance and outcome of the vaccination initiative are:

1. Effectiveness of the vaccine.
2. Country's disease burden (benefit versus burden of the initiative).
3. The health care infrastructure and its capacity for sustaining the program.
4. Affordability and cost effectiveness.
5. Cultural acceptability and Public support.
6. Infringement on autonomy and human rights and fairness.
7. Political will.

#### CONCLUSION

The HPV vaccination has already been introduced and implemented in many industrialized nations like USA and research has statistically demonstrated the effectiveness of HPV vaccine in reaching the primary end point. However, it is not yet supported by long term safety and efficacy data. If the vaccines were to be made mandatory now, it would be administered to some two million girls between 11-12 years age with some as young as nine years. This has heightened parental concern and public apprehension and the rush to make the vaccine mandatory is likely to raise many financial and ethical concerns that might become counterproductive at this point.<sup>26 - 27</sup>

In developing nations the challenges of successfully launching and implementing the initiative involve the affordability, delivery of the vaccine nationwide and most importantly lack of public awareness regarding the epidemiology of the disease.

This message that HPV has a causative role in the formation of precancerous lesions and subsequently invasive cancer needs to be disseminated widely among school and university students, general public and health professionals everywhere.

In Nepal with resource poor health settings and limitations in maintaining a nationwide effective cervical cancer screening a successful launching and implementation

of a preventive vaccine demonstrates most promise in reducing the global burden of cervical cancer.

Although vaccine has demonstrated great scope for disease prevention, for now it will be best to adopt voluntary measures by recommending early vaccination in preadolescent and adolescent girls without making it a state compulsion till more research data is available to support mandatory vaccination.

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