Introduction

Oral human papillomavirus (HPV) is a sexually transmitted infection affecting 0.9-7.5% of American adults. Genital HPV prevalence is estimated to be 27-43% in American females aged 14-59 years. HPV is causally linked to multiple cancers, including cervical and oropharyngeal cancers (OPCs). The Centers for Disease Control and Prevention (CDC) reports that ~ 26,000 Americans are affected by HPV-related cancers annually. A few specific types (strains) of HPV are present in >70% of OPCs. HPV vaccination programs have demonstrated improvement in cervical cancer rate; this improvement suggests that HPV vaccination programs may be an effective prevention strategy to decrease morbidity and mortality of HPV-related OPCs. This policy brief will outline the potential cost-benefit relation of HPV immunization for the prevention of OPC in the United States (US).

In the US, 23 states and the District of Columbia (DC) already have introduced legislation to mandate the HPV vaccine as a requisite for middle school entry. Of the 42 states that have adopted a HPV vaccine policy since 2006, only Virginia and D.C. have mandated vaccination for sixth grade females. As of September 2013, there had been more than 111 million vaccine doses distributed in the US, however it is unknown how many doses have actually been administered.

The rising costs of health care pose a formidable challenge for policymakers. Health care in the US already accounts for 16% ($ 2.54 trillion) of the Gross Domestic Product (GDP, ~$ 15.9 trillion in 2014) and the cost of healthcare is projected to increase to 25% by 2025. Spending on health care is likely to accelerate due to a number of factors, including an aging population, a rising burden of chronic diseases, and higher costs for pharmaceuticals and other medical treatments. For many years, policymakers, politicians, and professionals, have advanced the economic argument that prevention saves money. One study in 2008 reported that non-cervical HPV related diseases may cost America between $ 160 million and $ 1.6 billion. Another study indicated that costs associated with HPV infections run into $ 5 billion yearly, excluding associated psychosocial costs and quality of life related issues. By year 2020, HPV-related OPC will have a higher incidence than cervical cancers.
Vaccines are highly effective when the prevention strategy is adopted through a massive, free and mandatory national vaccination program covering all the country; in this instance, a program would be designed for a specific target population. Our recommended/selected focus group is for children of both sexes between the ages of 10 and 14; this age bracket was chosen because studies have demonstrated that the vaccine is most effective before the commencement of sexual activity, and because the vaccine does not help clear an infection acquired prior to vaccination.

**Oral HPV Infection**

HPV is a DNA virus, and skin-to-skin sexual contact is the mode of transmission. Performing oral sex on the genitals and/or anus of an infected person is the usual route for spreading HPV into the oral cavity. Transmission from mother to newborn during delivery is also thought to be possible, while other risk factors for oral HPV include male gender and tobacco exposure. In otherwise healthy patients, it is anticipated that the body can clear itself of oral HPV infection within 12-24 months.

HPV oral lesions have a “wart-like” appearance. A solitary oral wart is most often associated with a benign strain of HPV. When multiple oral warts are seen, a more infectious and potentially higher-risk type of HPV infection is suspected. Oral biopsy is the gold standard to establish the final diagnosis and to rule out pre-cancer/cancer. The most common oral cancer (> 90 %) is squamous cell carcinoma. Once an oral cancer has been diagnosed, a more detailed medical work-up is performed, and this is when the cancer can be checked for the presence or absence of HPV. There has been a significant increase in HPV-positive OPC, as reported in a US cancer registry study that found a 225% increase in HPV-positive head and neck squamous cell carcinoma from 1988-2004. Chaturvedi AK et al. report a 16.3 % HPV prevalence in OPC tumors in the 1980s and 72.7% during the 2000s.

**HPV Vaccination**

Vaccination against HPV strains 16 and 18 are currently available: Cervarix® (GlaxoSmithKline Inc.) and Gardasil® (Merck Sharp & Dohme Corp.). These vaccines protect against the development of cervical cancer. The vaccine is administered in a series of 3 doses over 6 months; because of the dosing schedule, finalizing the full vaccination course can be challenging to complete.

Vaccination against high-risk strains of HPV during the pre-teen years of life allows the body to develop an effective immune-response and affords protection before the start of sexual activity. Since HPV vaccinations are efficacious in preventing cervical cancer and appear to afford strong protection against high-risk oral HPV strains, it is next reasonable to assess the vaccine effectiveness in preventing HPV-related OPC. An economic perspective and cost/benefit analysis of HPV vaccination for the prevention of OPC in the US to help guide future public health and policy decisions is presented in the following section.

**Economic Costs, Benefits & Analysis**

When is prevention worth its cost? The answer is: when prevention costs less than future costs associated with surgery, medical treatments, medication, hospital stays, and years of lifetime minus life expectancy.

Long-term costs may assume different categories; some can be expressed in monetary terms, but others may not:

1. Hospitalization
2. Prolongation of an existing hospitalization
3. Permanent disability
4. Life threatening illness
5. Death
6. Psychosocial impact in patients and relatives
The CDC recommends that all 11 or 12 year old girls get the 3 doses, and also that females between the ages of 13 through 26 years should get the HPV vaccine if they have not received any or all doses when they were younger. The CDC recommends the HPV vaccine for all boys aged 11 or 12 years, and for males aged 13 through 21 years who did not get any or all of the three recommended doses when they were younger. All men may receive the vaccine up to age 26.

Three potential benefits of OPC prevention in the long-term include:

(i) Family savings in personal medical treatments, when a single OPC is avoided.
(ii) Reduction of mortality indices.
(iii) Reduction in the # of work-day absenteeism.

It is necessary to compare the sum of these three potential benefits with the total cost of the program, in order to determine whether or not the program has a positive economic result.

However, a more simple and practical alternative cost/benefit analysis is the method of estimating the disability-adjusted life year (DALY) - originally developed by Harvard University for the World Bank in 1990. DALY was later adopted by the World Health Organization (WHO) in 1996, and is a measure of overall disease burden expressed as the number of years lost due to ill-health, disability or early death. The DALY "extends the concept of potential years of life lost due to premature death, to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability." Traditionally, health liabilities are expressed using 'Years of Life Lost' (YLL), which does not account for the impact of disability ['Years Lived with Disability' (YLD)].

$$\text{DALY} = \text{YLL} + \text{YLD}$$

One DALY is equal to one year of healthy life lost, and the benefit would be the number of DALYs avoided.

In Health Economics, the DALY method is often used in cost-efficiency analysis to estimate the ratio of cost to DALYs saved, for a particular health care intervention. What is the opportunity cost of a DALY? A reasonable value could be the annual per capita GDP (now ~ $51,500 in the US). Any DALY saved at a cost below $51,500 would indicate that the benefit of the vaccination program is larger than its cost. In other words, a good economic result means that the cost of vaccination per DALY to society as a whole should be less than $51,500.

The Trust for America’s Health reported that prevention programs could save the country more than $16 billion annually within five years, a return of $5.60 per dollar invested. In economic terms, health is a good, and goods—whether they are national security, clean water or a new car—are not purchased to save money. Goods are purchased for the nonmonetary benefits they provide. Again, using economic terms, value is the ratio between the cost of a service and its benefits. A widely used metric in health care is the cost-effectiveness (CE) ratio. It is the cost of an intervention (numerator) divided by some measure of health gain (denominator), such as life years, quality-adjusted life years (DALY), or other health metrics. Published CE ratios can vary based on the intervention(s) and/or health gain(s) selected.

<table>
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<tr>
<th>Table 1. Estimated average annual percentage and number of oropharyngeal cancers (OPCs) attributable to HPV by sex – United States 2004-2008</th>
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<tr>
<td><strong>Percent Attributable to HPV</strong></td>
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<td><strong>Average Annual Number</strong></td>
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The CE model applied here consists of supposing a hypothetical situation in which a national HPV vaccination program would be started in the US in 2014-2015. As a first objective, the program would test the coverage of different alternatives of focus groups or population targets (six alternatives depending on the budget available). From 2015 – 2044 (a period of 30 years), the program would continue vaccinating only the cohort of people aged 10 years old with two options: only girls, and children of both sexes.

For cost of vaccination in our hypothetical model, we presumed that the federal government would buy the vaccine doses from the Pan-American Health Organization (PAHO), who sells them at a very low price in relation to market prices. The PAHO price for Cervarix® is $13.08/dose. The three doses would cost $39.24, plus 3.5% for the PAHO Rotative Fund (PAHO-RF), for a total of $40.61. Gardasil® is $13.79/dose ($41.37 for the three doses) and totals $42.82 with the 3.5% PAHO-RF commission. We should also add extra costs: ~1% (transportation, distribution, insurance, storage), the cost of hand labor (nurse: 2 minutes each shot with an average salary of $36.36/hourxiv), and the cost of millions of syringes/needles.

Using this information, cost is calculated supposing six population targets:

**OPTION 1 AND 2:** 10-14 years old (only females, and both sexes, respectively)

**OPTION 3 AND 4:** 10-19 years old (only females, and both sexes, respectively)

**OPTION 5 AND 6:** 10-24 years old (females, and both sexes, respectively)

Vaccine effectiveness in the target population varies from 42% to 59.5%. Our estimations show a minimum of 6 DALYs are reduced (aka, 6 additional years lived) per each OPC hypothetical case, with a vaccine effectiveness of 60%. However, when the vaccine effectiveness is reduced to 40%, only three DALYs are reduced (aka, 3 additional years lived) per each OPC hypothetical case.

Since 2009, approximately 30 countries started universal HPV vaccination programs, most of them only targeting 10 to 12 year-old girls; only a few countries include boys of that age. The less developed countries receive regular donations of doses from laboratories and other international donors. PAHO and the WHO buy millions of doses from the manufacturers at very low prices (<10% of market prices) and sell them to governments.

**Conclusions**

From an economic perspective, it is difficult to arrive at conclusive Cost/Benefit analysis as many variables affect the estimates, including variances in cost of care, age when OPC is diagnosed, survival rate, and many others. There are hundreds of academic papers and researchers from different institutions that use varying measures: sample sizes, geographic coverage and countries, target population groups vaccinated, cohort populations, and methodologies to examine the data related to different periods of time.

Hypothetically, a universal, mandatory nationwide program of HPV vaccination would be the best
solution, but the impact in the national health budget would be costly.

A second best solution would be to focus the program to a priority or targeted group (pre-adolescents and adolescents who have not yet become sexually active): both male and female adolescents aged 10-14 years as a first step, and then, every next year (for at least the next 30 years) only vaccinate to cohort 10 years old boys and girls.

For a national HPV vaccination program (with vaccine effectiveness of 60%), our estimates show that a minimum of six years of additional healthy life would be gained per each OPC hypothetical case. When vaccine effectiveness is reduced to 40%, a maximum of only three years of additional healthy life would be gained.

Regarding the target group suggested, a hypothetical nationwide HPV vaccination program spanning 2015 – 2044 would cost ~ $4.94 – 7.56 billion (figure 1). The long-term (30 years) benefit in reduction of OPC cases would range between 109,473 and 155,088 cases, depending on vaccine effectiveness. Benefits, stated in terms of total DALYs reduced, would range from 328,419 to 656,838 DALYs reduced with the lower vaccine effectiveness percentage, and from 465,264 to 930,528 DALYs reduced with the higher vaccine effectiveness percentage.

Assuming a conservative estimation that only 50% of those DALYs reduced (or avoided) are workable years throughout those OPC patients’ lives, and assigning each workable year an average market monetary value equal to a per capita GDP (valued at $53,143 in 2013)\(^{10}\), the long-term (30 years) economic benefit of the nationwide vaccination program would range from ~ $8.45 – $16.91 billion in the lower vaccine effectiveness percentage and from ~$11.98 – $23.96 billion with the higher vaccine effectiveness rate.

Across all these possible alternative scenarios, the benefits gained would be greater than the higher vaccine cost estimate of $7.56 billion (figure 1), providing a **return of ~ $1.11 to $3.16 per dollar** invested. If we consider that all DALYs are workable, because the average age of people with OPC is between 40 and 59 years of age, then the return per dollar invested ranges approximately between $2.22 to $6.32.

This issue brief provides an economic assessment framework that the authors hope will better inform policymakers and provide public health officials with additional tools to assess the long-term economic and societal gain of improved health outcomes.

Immunization prevents millions of deaths every year. We encourage a new look into how increasing immunity for systemic diseases may also improve oral health outcomes for all Americans. As highlighted in this paper, HPV vaccines may help eradicate HPV-related oropharyngeal cancers in cost-effective manner.
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xiv U.S. Census Bureau (average hour salary statistics, reported 2012).