Role of HPV Vaccination in Fighting Cervical Cancer

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ABSTRACT

Type 16 and Type 18 Human Papilloma Virus are highly associated with cervical cancer. Vaccination against these two types has been proved to be the most successful method to control this sexually transmitted disease. The vaccines have also been proved to be safe, but unfortunately, the incidence is still rising. In this review, we consider the accumulated evidence that HPV vaccines are already reducing burned in cervical cancer and preventing HPV infection, summarize the efficacy from different angles from scientific, social and economy while discussing the new generation nine-valent HPV vaccines.

Keywords: Cervical cancer, Human papilloma virus, Vaccines, Nine-valent

1. INTRODUCTION

Cervical cancer is the fourth most common cancer among women and the most common cancer in gynecology. In 2012 it was estimated that there are 528,000 new cases and 266,000 deaths each year worldwide(1). It is now known that certain types of Human Papilloma Virus (HPV) are highly associated with cervical cancer. Among the 18 known high-risk HPVs, the most carcinogenic types are found to be type 16 and 18 which responsible for around 50% and 20% of cervical cancer respectively. As the known etiology is found, vaccination is the most successful method to control this infectious disease. Currently, the quadrivalent (HPV 16,18,6 and 11) and bivalent (HPV 16 and 18) HPV vaccines(2) are being used, and studies have demonstrated that the vaccines are safe. Since the discovery of the vaccines, the burden of cervical cancer has significantly reduced. However, the incidence is still rising.

The problem of rising incidence of cervical cancer can be tackled through several issues, from the availability of vaccine programs to acceptability for HPV vaccines to young girls. For instance, In June of 2013, the Japanese Ministry of Health partially suspended its HPV vaccination program(3), which demonstrates that immunization programs can be seriously compromised by safety and possibly political concerns. Acceptability is also a problem in which many Asian countries are still more conservative and is lower as compared with many western countries. Hong Kong as one of the most modern countries in Asia had only 7~9%(4) teenage girls that received vaccines by 2012. Whereas many western countries had as high as 17% to 81%(2). Both of the quadrivalent and bivalent vaccines require three doses of intramuscular injection at intervals of 0, 2 and 6 months. Delayed doses or incomplete vaccination may also be one factor that affects the efficacy of the vaccines although little is known(5). Most trials use CIN2/3 disease and not cervical cancer as their end point, the presumptive assumption of HPV and cervical cancer is questionable.
In this review, we consider the accumulated evidence that HPV vaccines are already reducing burden in cervical cancer and preventing HPV infection, summarize the efficacy from different angles from scientific, social and economy while discussing the new generation nine-valent HPV vaccines.

2. SCIENTIFIC FACTOR

A study done in 2012 by Lehtinen et al.\(^{(6)}\) shows that the efficacy against CIN3+ associated with HPV 16/18 was 100%. While the efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) was 93.2%. The result shows that HPV vaccines are excellent vaccine efficacy against CIN3+. However several other medical factors are taken into consideration in tackling the effectiveness of HPV Vaccines.

**Age of Vaccination**

The overall efficacy shows that HPV vaccines are highly effective irrespective of association with HPV. However, the effectiveness of HPV Vaccines should be seen from many aspects. One of the aspects is the age in which young girl received the vaccination. Vaccination is advised before exposure to HPV and hence sexual debut, which occurs during adolescence for most people\(^{(7)}\). PATRICA study from Apter et al.\(^{(8)}\) examined the efficacy of HPV 16 and 18 adjuvanted vaccines against cervical infection in young women. The result shows that HPV-16 and HPV-18 antibody titers post-vaccination tended to be higher among 15- to 17-year-olds than among 18- to 25-year-olds. The study concluded that vaccinating adolescents before sexual debut has a substantial impact on the overall incidence of high-grade cervical abnormalities, and catch-up vaccination up to 18 years of age is most likely effective. The vaccine has been recommended to be initiated at the early age of 9 years. Yet in reality, only 67% primary care physicians were reported to be likely to prescribe HPV vaccine to 11- and 12-year-old patients\(^{(9)}\), a number that is expected to be higher.

**Dosing Schedule and Completion**

A normal full dose of HPV vaccines is to be injected for three doses at intervals of 1, 60 and 180 days. A study done in India found that a two-dose HPV vaccine is non-inferior to the three-dose group\(^{(10)}\). The study was done in a prospective cohort study dividing girls into four cohorts, namely one-dose, two-dose 1 and 180, two-dose 1 and 60 and three-dose cohort. The three-dose cohort was given vaccines on 1, 60 and 180 days or later, two doses cohort were divided by 1 and 180 days, 1 and 60 days and the one dose cohort. The immune response was recorded by means of fluorescence intensity. This study supports the guideline from WHO in which two-dose HPV schedules with a 6-month interval in young adolescents is enough\(^{(11)}\). As compared to the three dose vaccines, two-dose vaccines can remarkably reduce the cost of vaccines. In which in many countries can be a great benefit when cost is actually a big deal. The efficacy of the one-dose vaccine is currently being reviewed\(^{(12)}\). Although the two-dose vaccine immunogenicity is found to be non-inferior as compared to three-dose, it is found that for the quadrivalent vaccine, T and B-cell memory responses were lower in two-dose vaccines\(^{(13)}\). The significant of the findings are still not known. Knowing that at least two doses are needed for vaccines to be effective, the completion of the regime is important. Unfortunately, many patients still do not complete their regime. A study in the USA found that Caucasian girls are more likely to complete their program as compared to African American, and the number gets even lower in Hispanic with 61.2% do not complete the program\(^{(2)}\). Other factors like age and healthcare coverage\(^{(2)}\) also affect the completion of the regime.

**Vaccines against other HPV types**

The most widely prescribed vaccines available are currently the bivalent and quadrivalent. The bivalent works against HPV 16 and 18 while the quadrivalent works against HPV 16, 18, 6 and 11. Although HPV 16 and 18 are found to be the most carcinogenic accounts 50 and 20% respectively, there are actually a total number of 40 types out of 170 that are identified as purely mucosal subtypes. From these 40 types, 15 are considered high-risk oncogenic type\(^{(14)}\)(Table 1). The bivalent and quadrivalent vaccines are also known to have cross-reactivity against some types. HPV 16 is phylogenetically related to HPV strains 31, 33,52 and 58 and HPV 18 is related to HPV strains 45\(^{(15,16)}\), so these vaccines do actually give some protection against these strains. However, being protected against 6, 11, 16, 18, 31, 33, 45, 52 and 58 are still not even half of the 40 known types or even 20 of the low-risk and high-risk types. As a result even after the vaccination, the tendency for patients to be infected with other strains still exists. Hence, both bivalent and quadrivalent do not cover 20-30% of HPV-associated cancers\(^{(17)}\).
Table 1. Pathogenic HPV viruses

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Low Risk</th>
<th>Non-Classified</th>
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<tbody>
<tr>
<td>16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 66, 68</td>
<td>6, 11, 42, 44, 45</td>
<td>2a, 3, 7, 13, 26, 27, 28, 29, 30, 34, 40, 52, 54, 57, 61, 70, 72, 73, 74, 81, 82, 83, 84, 87, 89, 90, 91</td>
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Safety
Safety is a big issue when it comes to patients. As in June of 2013, the Japanese Ministry of Health partially suspended its HPV vaccination program(3) due to an adverse reaction from the vaccines. A study done by Japan reported that there were reactions from mild symptoms such as pain, redness and swelling at the injection site to serious adverse events such as brain contusion, skull fracture and appendicitis(18). The study also reported one spontaneous abortion possibly related to vaccination which occurred 2 weeks after the vaccination. However, a more multinational study found that the number of adverse events in vaccine group was similar to their placebo control, including pregnancy outcomes(19). Another study done by Korea comparing the safety of HPV vaccines and visually indistinguishable aluminium-containing placebo shows that even three-dose vaccines are well tolerated with only serious adverse events that include rhinitis, vertigo and tension headache(20).

3. SOCIAL AND ECONOMIC FACTORS

Social and economic factors are unavoidable vital factors when it comes to preventing cervical cancer. Factors such as race, religion, education level and economic factor are shown to be varying in acceptance of HPV vaccines. In a relatively more conservative culture like Asian countries(21) as compared to Western Countries(22), there is lesser acceptance among Asian women.

Knowledge of HPV Vaccines
The current rising of cervical cancer incidence is also related with the low HPV vaccines uptake. The knowledge and education about HPV are needed to let the public to be aware of the importance of HPV vaccination. Race is one of the factors, for instance, a study on African American girls shows vaccination series initiation and completion were lower than the national average(23). In 2008, survey and campaign were conducted in Fiji(24) showed the participants knowledge about HPV were low prior to the campaign. Where only as low as 10.2% of the participants have heard about HPV vaccines, 21.2% reported having heard of cervical cancer, and the majority of these knew someone who had the disease. This result shows that the knowledge of HPV is somehow still low in many places, as this result is consistent with other low income and middle-income countries(25). Masika et al. reported that in Kenya the insufficient information about HPV vaccines is one of the main barriers to recommending the vaccine(26). In some regions, “community influencers” (e.g., teachers, health workers, and other community members) are necessary for helping to raise awareness of cervical cancer as it is reported to play more important role than information given from health providers.

Although the need of media in promoting the vaccines it is found that media has sometimes given negative perceptions like the adverse reactions(24) that would act as a hinder to willingness. Apparently, media does not influence the willingness to vaccinate. A study done in Spain shows that positive health advice from a health professional can have a positive effect on vaccination(27).

Cost and Affordability
The cost of a dose of HPV vaccines may reach several hundred US dollars. While not all countries currently put HPV vaccines as their national health program. As of December 2015 globally there were an estimated 80 national HPV vaccination programs and 37 pilot programs, mostly from developed countries(28,29). Even in a high-income country like Hong Kong(China), the high price of HPV vaccines is still a major barrier(4). With the help of the World Health Organizations and The Global Alliance for Vaccines and Immunization (GAVI), a new hope has been given to provide a more affordable and equal distribution of HPV vaccines, especially in low and middle-income countries(30). One strategy to reduce cost as discussed before is by reducing the dose from three-dose to two-dose, with no change in immunogenicity(10). As the two-dose strategy is said to be critically important to save resources on any extra dose administrated for lower and middle-income countries(25). The support of government funding to make HPV vaccines as national health program is crucial, although, in reality, it is a difficult decision(31). Cost is one of the major barriers in reducing cervical cancer, in the USA a survey was done in 2008 found that only 12% among female adolescents aged 11-17.
who had no health insurance received HPV vaccination\(^{(32)}\). This shows that public is not willing to pay to get vaccinated.

4. NEW HOPE, NINE-VALENT VACCINES

The current bivalent and quadrivalent have been proved to have strong efficacy in protecting two primary oncogenic HPV types 16 and 18 which are responsible for about 70% of cervical cancer. As discussed above there are 40 known HPV types that are related to cervical cancer and even quadrivalent vaccines do not protect 100% against cervical cancer. So to maximize the protection, a nine-valent HPV vaccine has been developed although not used widely. The nine-valent has protection against an additional five oncogenic type namely 31, 33, 45, 52 and 58 that offers prevention up to 90%\(^{(5)}\). Joura et al.\(^{(33)}\) did a study participating 14,000 women aged 16-29 years. They were randomized to three-dose of either quadrivalent or nine-valent vaccine at 0, 2 and 6 months. The result showed that the immune responses in the nine-valent were indeed not inferior compared with the response to the quadrivalent. The overall efficacy for nine-valent was 96.7% [95% confidence interval (CI): 80.9, 99.8] indicates that the nine-valent would offer broader coverage for oncogenic HPV types compared with the quadrivalent vaccine. The study also reported that the nine-valent has higher adverse event although not severe.

The economic cost of nine-valent is reported to be higher than quadrivalent. While the immune response was reported to be equal, the benefits from the nine-valent vaccine are still not yet to be revealed. So the expected hope from the nine-valent vaccine is still a big question mark. Moreover, the nine-valent HPV vaccine still did not prevent infection and disease related to HPV types beyond the nine types covered by the vaccine. The real new hope is for future generations of vaccines that will contain more types, or possess group-specific antigens that have a low adverse effect. Although in the meantime not foreseeable, this new generation might be able to completely eradicate cervical cancer from HPV.

5. CONCLUSION

For the past years, developments and discoveries in the prevention of cervical cancer have been rapid. From the development of new generation vaccines, including vaccines in national vaccines program, lowering doses schedule and cost, educating people about HPV vaccines and new HPV types discovery. The eradication of cervical cancer may already is on the edge of a sword.

REFERENCES


