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- Extending Quadrivalent Human Papilloma Virus (HPV) Vaccination To Males — What Is The Current Evidence?

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Dr Vincent Chan Hian Hui

ABSTRACT

Introduction: Human papilloma virus (HPV)-related genital warts and cancers can lead to significant morbidity. The ACIP 2011 from the United States recommends routine quadrivalent HPV vaccination for both males and females for primary prevention.[1] This study reviews current evidence on vaccinating males routinely, and determines if it can be applied to Singapore.

Methods: Relevant articles from PubMed were obtained by searches using the search words "quadrivalent HPV vaccination", "males", "cancer" and "prevention". Three retrieved articles are included in this review and 3 additional articles are included from the references of the selected articles.

Results: Quadrivalent HPV vaccination is effective in the primary prevention of HPV-related genital warts and cancers in both genders. Effectiveness in the secondary prevention of HPV-related recurrent high-grade intra-epithelial neoplasia (HGAIN) was suggested in a cohort study among men. The vaccine is safe with minor side effects of localised injection site pain.

Conclusion: Given the efficacy and safety of quadrivalent HPV vaccination in both males and females, local studies should be done to confirm the benefits of routine vaccination.

Keywords:

Quadrivalent HPV Vaccination, Cancer, Males, Prevention, Genital Warts, Human Papilloma Virus

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INTRODUCTION

The human papilloma virus (HPV) belongs to a group of small DNA viruses, and there are more than 100 types of the virus. Of these, more than 40 mucosal types are commonly found on the genitals and are transmitted by sexual contact. HPV infection is specific to humans [2] and can be subdivided into oncogenic and non-oncogenic types. Non-oncogenic types include HPV 6 and 11, which cause more than 90 percent of genital warts and most cases of recurrent respiratory papillomatosis. Key oncogenic types are HPV 16 and 18 which cause 70 to 76 percent of cervical cancers and 63 to 95 percent of non-cervical cancers, including vulvar, vaginal, penile, anal, oropharyngeal and other oral cavity carcinomas.[3,4] Presently, quadrivalent HPV vaccination is already in use for the prevention of HPV-related infection, cancer and genital warts in female patients.

Singapore also experiences these problems and, between 1993 and 1997, there were 4353 male patients with anogenital and oropharyngeal cancers compared with 3331 female patients. With regards to genital warts, the incidence in 2010 was 33.9 per 100,000 population for men and 8.1 per 100,000 population for women, and a total of 21.5 per 100,000 population. Locally, both bivalent and quadrivalent HPV vaccinations are available for the prevention of these conditions, though only bivalent vaccination for girls aged 9 to 27 years old is claimable under the national compulsory healthcare savings plan known as Medisave.

In December 2011, the Advisory Committee for Immunisation Practices (ACIP) recommended extending routine quadrivalent HPV vaccination to boys in addition to girls aged 11 to 12 years.[1] They also advised vaccinating male patients aged 13 to 21 years old, especially if they had never been vaccinated or had failed to complete their 3-course HPV vaccination injections. For males aged 22 to 26 years of age, the quadrivalent HPV vaccination is optional. The objective of this narrative topic review is therefore to review existing studies to assess ACIP's recommendation and whether it can be applied to the local context.

METHODOLOGY

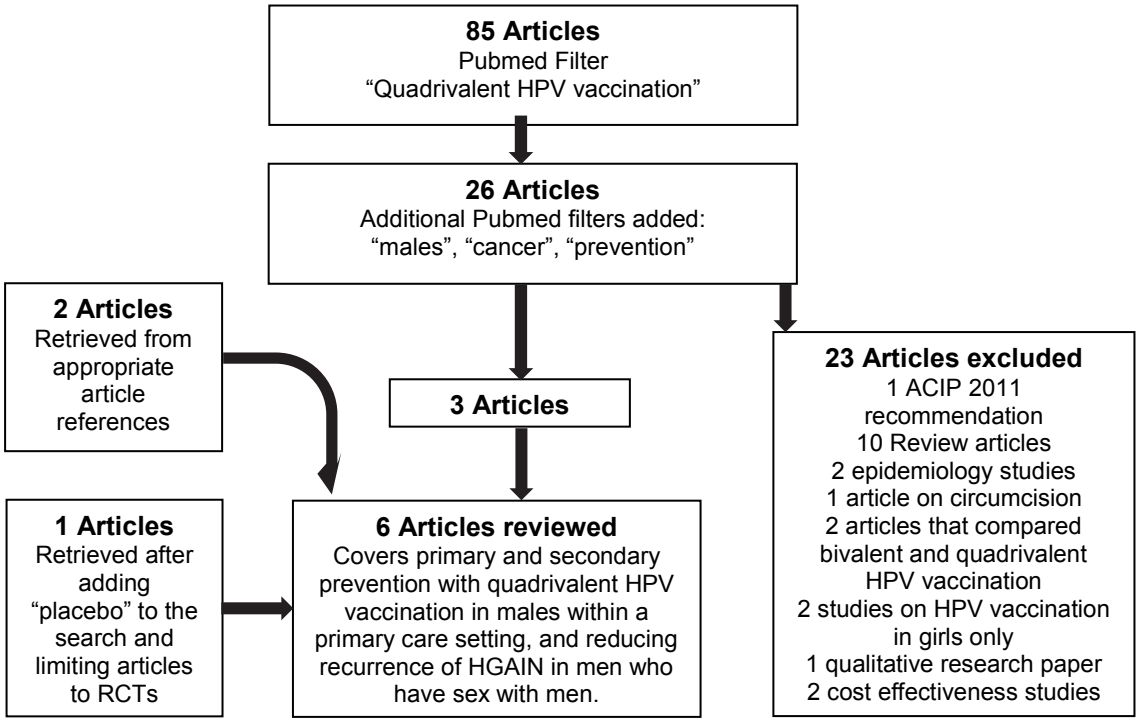
Articles for the review were obtained through a PubMed search. Filters were set to include only human studies written in English, and published within the last 10 years. Using the search term "quadrivalent HPV vaccination", a total of 85 articles were retrieved. After adding the following search terms of "males", "cancer" and "prevention", the search narrowed to 26 articles.

Of these, 3 articles were included in this topic review, as they addressed study objectives about whether quadrivalent HPV vaccination was safe and effective in male subjects as compared to females, and whether implementing it at a national scale would bring benefit. Two additional articles found within the article references were also added, as they were relevant in this regard. One additional randomised control study on the topic was also retrieved by hand search and included in this review. The inclusion criteria included studies that assessed the efficacy and safety of quadrivalent HPV vaccination in males with regards to the prevention of HPV infection and the development of HPV-related external genital lesions. Figure 1 shows the selection process of the retrieved papers.

There is presently a paucity of local data on the use of quadrivalent HPV vaccination in males, this review thus had to reply on studies done overseas.

VINCENT CHAN HIAN HUI
MBBS, MMED(FM), FCFP(S), FAMS
Drs Lim & Chan Clinic

Figure 1: Search methodology with PubMed



RESULTS

1. Good immunogenicity to HPV vaccination is seen in both males and females across a broad range of patient characteristics

In a randomised control trial done by Giuliano et al (2007), it was found that the immunogenicity of quadrivalent HPV vaccination was similar across patients of differing characteristics, and was 95 to 100 percent effective in preventing genital and cervical diseases caused by HPV virus types 6, 11, 16 and 18. The authors thus felt that the data supported a broad-based vaccination programme.[5]

In that study, they assessed 3 groups of patients, namely virginal males and females aged 9 to 15 years of age and a third group of mostly sexually active young women aged 16 to 26 years old. A total of 12,343 subjects were recruited cutting across different ethnicities and socio-economic groups. The investigators found that the age of vaccination was inversely proportional to the anti-HPV immune response induced by the vaccine. The immune response caused by the quadrivalent HPV vaccination was also stronger than that caused by HPV virus infection. On smoking, they noted that this reduced the ability of the body to eradicate the HPV infection leading to heightened risks of HPV persistence and subsequent higher risk of cervical cancer.

This study was complemented by Hilllman et al,[6] in that they studied the immunogenicity of quadrivalent HPV vaccination in young men aged 16 to 26 years, a group missing in the earlier Giuliano study. Altogether 3463 heterosexual men and 602 men who had sex with men (MSM) were recruited into the double-blind randomised control study between 3 September 2004 and 29 August 2008. The investigators found quadrivalent HPV vaccination to be highly immunogenic with seroconversion rates of more than 97.4 percent of patients for HPV 6, 11, 16 and 18 at 7 months. This immunogenicity fell slightly however, and by 36 months, 88.9 percent, 94.0 percent, 97.9 percent, and 57.0 percent of patients remained seropositive for HPV 6, 11, 16, and 18 respectively.

For subjects who were sero-positive prior to vaccination, Hillman et al noted the presence of an anamnestic antibody response. They also concluded that the quadrivalent HPV vaccine was highly immunogenic in males aged 16 to 23 years, and patient responses to the vaccine were comparable to those seen in female subjects. Furthermore, the immune responses to the vaccine were consistently effective in the prevention of incident and persistent HPV infection, anogenital warts and anal intra-epithelial neoplasia.

In another double-blind randomised control trial by Reisinger (2007),[7] 1781 virginal children from both genders aged 9 to 15 years old were recruited and assigned to the quadrivalent vaccination and placebo groups. Three injections were organised at day 1 and months 2 and 6. The authors found that seroconversion rates at month 7 were more than 99.5 percent for all vaccine HPV types, and these rates remained high at more

than 91.5 percent at 18 months, regardless of gender. Quadrivalent HPV vaccination had a persistent anti-HPV serological response in the majority of patients for at least 1 year, following the completion of the 3-injection schedule. The authors felt that this supported a universal quadrivalent HPV vaccination programme for all adolescents.

This view was supported by Block et al, who studied the immunogenic responses to all 4 HPV viruses, including types 6, 11, 16 and 18, among 3 patient populations, namely young women aged 16 to 23 years of age, girls and boys aged 10 to 15 years old.[8] In that study, they recruited 506 girls, 510 boys and 513 young women. These participants were vaccinated at day 1, month 2 and month 6. Serology tests were then conducted at day 1, month 3 and month 7. They found that by month 7, anti-HPV titres were on average 1.7 to 2.7 times higher than that recorded for young women. They thus concluded that since immunogenic responses in boys and girls were "non-inferior" to that seen in young women, a "gender neutral" HPV vaccination programme should be supported.

2. HPV vaccination is safe with only minor side effects reported

Reported adverse effects from the quadrivalent HPV vaccination were minor, as reported by Giuliano et al (2011). Most of these adverse reactions were related to the injection, with injection site pain significantly more in HPV-vaccinated patients as compared to those in the placebo population (57% vs. 51%, P<0.001), with a relative risk of 1.1. Of these patients, only 1.3 percent of vaccinated patients and 1.0 percent in the placebo group reported the injection-site pain to be "severe", with a relative risk of 1.3.

Reisinger concluded likewise and also found the vaccine to be safe, with 75.3 percent of vaccine recipients reporting mild injection site local effects as compared to 50.0 percent in the placebo group. They did not report any serious vaccine-related adverse effects.

No other adverse effects were of statistical significance, as noted by Giuliano et al (2011). This included fever, as defined as an increase in orally taken temperature to 37.8°C or higher between day 1 and day 5 post vaccination. Here, fever was reported in 6.0 percent of vaccinated patients as compared to 5.8 percent who received the placebo (p=0.82).

The SL Block study (2006) also explored the issue of side effects of quadrivalent HPV vaccination, and they divided their study population into 3 groups, namely 10- to 15-year-old boys, 10- to 15-year-old girls, and 16- to 23-year-old young women. In that study, they found that a statistically significant percentage of young women developed injection site erythema or pain compared to boys and girls aged 10 to 15 years old (86.3%, 71.4 and 79.4% respectively, p<0.001). On the other hand, more boys and girls aged 10 to 15 years old developed fever of more than 37.8°C than young women (12.8%, 13.8%, and 7.3% respectively). Fortunately, 96.4 percent of reported vaccine-related fevers were of temperatures less than 39°C.

3. Quadrivalent HPV vaccination is effective against HPV infection and the development of external genital lesions

Giuliano et all (2011) had conducted a separate study on the same study population as in Hillman, consisting of 4065 male patients. The authors had found quadrivalent HPV vaccination to be effective against HPV infection and the development of external genital lesions.[9] In the intention-to-treat population, the observed efficacy against the development of external genital lesions related to HPV viruses was 60.2 percent (95% confidence interval of 40.8 to 73.8) in the vaccinated population. The calculated ARR was 1.2 per 100 person-year at risk, and the numbers needed to treat (NTT) was 83. (Refer to the data in Table 1 of Giuliano et all [2011].)

This observed vaccine efficacy against HPV types 6, 11, 16 and 18 related external genital lesions increased to 90.4 percent (confidence interval of 69.2 to 98.1) in the per-protocol HPV-vaccinated patient population. Per-protocol population refers to the patients who successfully completed the full 3-course injections of quadrivalent HPV vaccine within a year. Here, the calculated ARR was 0.99 per 100 person-year at risk, and the numbers needed to treat (NTT) was 101. (Refer to data in Table 2 of Giuliano et all [2011].)

The authors also found quadrivalent HPV vaccination to be effective against persistent HPV type 6, 11, 16 and 18 infections. Taking samples from the penis, scrotum, and perineal and perianal regions, the efficacy in the intention-to-treat population was 47.8 percent (95% CI, 36.0 to 57.6) in the vaccinated population versus 27.1 percent (95% CI, 16.6 to 36.3) in the placebo group. The absolute risk reduction (ARR) was calculated to be 3.31 per 100 person-year at risk, and the numbers needed to treat (NTT) was 30.2. (Refer to Table 3 of Giuliano et al [2011].)

This effect against persistent HPV infection improved in the per-protocol population, where the efficacy was observed to be 85.6 percent (97.5% CI, 73.4 to 92.9) and 44.7 percent (95% CI, 31.5 to 55.6) respectively in the vaccinated and placebo sub-populations. The study was funded by Merck, manufacturers of the HPV vaccine marketed under the brand Gardasil.

4. Reduced recurrence of high-grade anal intraepithelial neoplasia in men who have sex with men

Quadrivalent HPV vaccination was effective in reducing the recurrence of high-grade anal intraepithelial neoplasia (HGAIN) in men who have sex with men (MSM), as reported by Swedish et al, in their non-concurrent cohort study.[10] The study was conducted in one anorectal surgery clinic and 202 patients with a

history of previously treated HGAIN were recruited. They then conducted off-label HPV vaccination for 88 of these patients at day 1, 2 months and 6 months. The remaining 114 patients remained unvaccinated. At the 340.4 person-years follow up, 12 vaccinated patients (13.6%) and 35 unvaccinated patients (30.7%) developed recurrent HGAIN.

Multivariate hazards ratio (HR) analysis found that patients who tested positive for oncogenic HPV viruses within 8 months prior to entry into the study were at increased risks of HGAIN up to 2 years after study entry (HR 4.06; 95% confidence interval [CI], 1.58–10.40; p=0.004). By contrast, quadrivalent HPV vaccination was associated with reduced risks for recurrent HGAIN at 2 years (HR 0.50; 95% CI 0.26 to 0.98; p=0.04).

For patients infected with oncogenic HPV viruses, the vaccine was associated with a reduced risk of recurrent HGAIN at 2 years post study entry (HR 0.47; 95% CI 0.22 to 1.00; p=0.05). The authors therefore concluded that quadrivalent HPV vaccination significantly reduced the recurrence of HGAIN among men who have sex with men (MSM), and vaccination could be considered as part of routine HGAIN treatment. They recommended that a randomised control trial be done to test these findings.

DISCUSSION

The 6 studies reviewed support the ACIP 2011 recommendation of extending routine quadrivalent HPV vaccination to males as well as females as it has efficacy in protecting against HPV-related cancers and genital warts. While there is more general awareness of the effects of HPV-related cancers, the consequence of genital warts is less well acknowledged, except in the afflicted. For patients with genital warts, the condition carries significant psychological, social and sexual morbidity, made worse by its uncertain time course.[11] The prevention of persistent HPV infection could potentially preserve the quality of life for patients who may otherwise have developed these conditions.

In their randomised control trials, both Giuliano and Hillman studies together demonstrated the effectiveness of the quadrivalent HPV vaccination in both males and females, between the ages of 9 and 26 years of age, with differing characteristics. Hillman et al found the vaccine to be highly immunogenic between the ages of 16 and 23 years of age, though this was data derived from recruited patients aged 16 to 26 years old. On the other hand, Block et al found that immunogenic responses from boys and girls aged 10 to 15 years were higher than that for young women aged 16 to 23 years old.

These findings suggested that it would be best to conduct the vaccination at an earlier age, younger than 15, as the immunogenicity is highest. Reisinger also made the point that quadrivalent HPV vaccination is best given before initiation of sexual activity, hence their decision to conduct their study in patients between 9 and 15 years old. It was noted that the vaccine can still be given to patients aged 16 to 23 as the immunogenicity is still high.

Quadrivalent HPV vaccination is also safe, with minor adverse effects reported. The main side effect was local injection site pain, where although 57 percent of patients in Guiliani et al (2011) reported this, only 1.3 percent of vaccinated patients reported this to be "severe". Fever in that study was not found to be significant, though Block et al found that vaccinated boys and girls between 10 and 15 years of age were more likely to develop fever as compared to young women aged 16 and 23. Fortunately, most fevers were less than 39°C. These are minor side effects and quadrivalent HPV vaccination can be regarded as safe.

These studies can possibly be extrapolated to multiethnic and multi-cultural Singapore as both studies, Giuliano (2007) and Hillman, included study subjects from different ethnicities and cultures. The sample sizes in these 2 studies were also sizeable, with 12,343 and 4065 study subjects respectively.

LIMITATIONS OF THE STUDY

There were limitations in this study, in that only PubMed was searched and only articles in English were reviewed. At present, no randomised control trials on quadrivalent HPV vaccination in Singapore are available for this review. This would have provided clearer data on the safety and efficacy of the vaccine among males in Singapore.

CONCLUSION

The studies reviewed show that quadrivalent HPV vaccination is both effective in protecting against HPV-related cancers and genital warts. The various authors also concluded that it is safe in both male and female patients, with immunogenicity comparable in patients between 9 to 26 years of age. Numbers needed to treat with quadrivalent HPV vaccination was 83 in the intention-to-treat group, while the absolute risk reduction (ARR) was 1.2 per 100 person-year at risk. The vaccine was also found to reduce the recurrence of HGAIN in MSM. Given the efficacy and safety of quadrivalent HPV vaccination in both males and females, local studies should be done to assess the benefits of routine vaccination in Singapore.

Table 1. Summaries of cases reviewed

Authors of Cases reviewed	Type of Study	Population	Intervention	Control	Outcome
Giuliano et al (2007)[5]	Randomised control trial. Placebo controlled, double blind study.	12,343 subjects aged 9 to 26 years, including male and female subjects.	Intramuscular deltoid injection of qHPV vaccine.	Intramuscular deltoid injection of placebo.	The immunogenicity of quadrivalent HPV vaccination was similar among patients with different characteristics.
Hillman[6]	Randomised control trial. Placebo controlled, double blind study.	4065 males aged 16 to 26 years old. 3463 were heterosexual men, and 602 were men who have sex with men.	Intramuscular deltoid injection of qHPV vaccine. 3 injections given at day 1, month 2 and month month 6.	Intramuscular deltoid injection of placebo. 3 injections given at day 1, month 2 and month month 6.	Quadrivalent HPV vaccine was highly immunogenic in males aged 16 to 23 years. Responses were similar to that seen in women. The vaccine was effective in preventing incident and persistent HPV infection, anogenital warts and anal intraepithelial neoplasia.
Giuliano et al (2011)[9]	Randomised control trial. Placebo controlled, double blind study.	4065 males aged 16 to 26 years old. 3463 were heterosexual men, and 602 were men who have sex with men. (Note, same study population as in Hillman.)	Intramuscular deltoid injection of qHPV vaccine. 3 injections given at day 1, month 2 and month month 6.	Intramuscular deltoid injection of placebo. 3 injections given at day 1, month 2 and month month 6.	For the study population, quadrivalent HPV vaccination prevents infection with HPV types 6, 11,16 and 18. It also prevents the development of HPV related external genital lesions.
Reisinger et al[7]	Randomised control trial. Placebo controlled, double blind study.	1781 sexually naive children, aged 9 to 15 years.	Intramuscular deltoid injection of qHPV vaccine. 3 injections given at day 1, month 2 and month month 6.	Intramuscular deltoid injection of placebo. 3 injections given at day 1, month 2 and month month 6.	In subjects aged 9 to 15 years old, the quadrivalent HPV vaccine was well tolerated and induced a persistent anti-HPV serologic response in the majority of subjects for at least 12 months.
Block et all[8]	Cohort study	506 girls and 510 boys, aged 10 to 15 years. 513 females aged 16 to 23 years.	Intramuscular injection of qHPV vaccine. 3 injections given at day 1, month 2 and month month 6.	None	Non-inferior immunogenic responses to all HPV types (6,11,16 and 18) were observed in boys and girls, when compared to women. The vaccine was well tolerated.

Swedish et all[10]	Cohort study.	202 patients with a history of previously treated High-Grade Anal intraepithelial Neoplasia (HGAIN)	84 patients were vaccinated with intramuscular quadrivalent HPV vaccination, at month 0, month 2 and month 6.	114 patients were not vaccinated.	Among men-who-have-sex-with-men quadrivalent HPV vaccine reduces the recurrence of HGAIN significantly. The vaccine may be effective in the secondary prevention of HGAIN.

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