Awareness of Human Papilloma Virus and Acceptability of Its Vaccination amongst Female Medical Students

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ABSTRACT

Background: Human Papilloma Virus (HPV) is a known causative organism for most female genital cancers.

Objectives: (1) To study the level of awareness about HPV and the acceptability of HPV vaccine amongst female medical students.(2) To document any adverse effects of the vaccine in this population.

Methods: This was a questionnaire survey participated by female medical students who chose to have the vaccination, after voluntarily purchasing the vaccine. The questionnaire mainly focused on the students’ awareness of HPV vaccine, her sources of information, acceptability and of adverse effects after taking the HPV vaccine. The participants were asked to recall any occurrence of side effects following any of the three doses administered. The adverse effects reported were tabulated and compared with the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) by Chi square using SPSS Version 16.0.0.

Results: The awareness of HPV amongst the medical students was 98% however the acceptability was 29%.This was mainly due to financial reasons and apprehensions about vaccine efficacy and safety. The adverse effects reported were namely redness and swelling at injection site, myalgia, headache, fever and they corroborated with VAERS data except pain at injection site which was lower {59% vs 92% (p<0.01)} and pruritus which was higher {19% vs 1% (p<0.001)}. No other serious adverse effects were notified.

Conclusion: There was a mismatch between awareness and acceptability. To bridge this gap and improve acceptability, more health education awareness should be given to both the parents and females who are eligible with the help of social media (television, radio, and internet) and also make provisions for subsidization of the cost of the vaccines. HPV vaccine is a safe and well tolerated amongst the many other study groups including our cohort.

Keywords: acceptability, side effects, bivalent, HPV, cancers, vaccine

INTRODUCTION

Human Papilloma virus (HPV) is an oncogenic virus which causes 5.2% of all the cancers in the world with a prevalence of 40% in genital tract malignancies of women. ¹ Apart from cervical cancer, HPV also
played a causative role in 60-65% of vaginal [2] and 20-50% of vulvar cancers. [3] The search for vaccine against HPV was initiated in the mid-80s and the first HPV vaccine was approved by FDA in 2006 which also became the first anti-cancer vaccine to be approved. [4] This vaccine was a quadrivalent vaccine and it prevented the effects of HPV types 16, 18, 6 and 11. The second HPV vaccine to get FDA approval in 2009 was a bivalent vaccine [5] which rendered protection against HPV types 16 and 18. A review of these vaccines from various studies showed that they were highly immunogenic, efficacious and devoid of adverse effects and its development in the field of immunotherapeutic science might prove to be pertinent method to combat cancer in future. [6] However the result on awareness of this vaccine in this study was disappointing. Jared Rosenberg in his studies over four countries (India, Uganda, Peru and Vietnam) showed that the awareness was also very poor in these countries. [7] In addition, the apprehension for these new vaccines was palpable as the clinical trials on long term side effects following its use over a larger population are still ongoing. To keep a track of the adverse effects, post market surveillance was done and the findings were noted in U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). [8]

In this study, the objectives were to assess the level of awareness of HPV and acceptability of this vaccine amongst female medical students to look for any adverse effects of the vaccine on these students who took the bivalent HPV vaccination. The occurrence of adverse effects in our study was then compared with the reporting in VAERS to analyze for significant variation.

**MATERIALS AND METHODS**

**Study design:** Cross Sectional.
management of survey questionnaire administration were assessed. An item analysis along with test-retest validity and intra-observer reliability (Cronbach’s alpha) of the survey questionnaire were also assessed during this pilot study. The survey questionnaire was further refined with the help of two content experts and an English language professional. The overall intra-observer reliability from Cronbach’s Alpha was found to be 0.822. The intra-observer reliability ranged between 0.734 and 0.806 for item deletion in Cronbach’s Alpha analysis. Since, none of the Cronbach’s Alpha values exceeded 0.822 in item deletion; all the items of survey questionnaire were included in the final analysis.

**Ethical Considerations:** Approval for the present study was obtained from the research and ethical committee of the Melaka-Manipal Medical College in Malaysia. The information obtained during the data collection was strictly kept confidential. In order to maintain anonymity, a random code number was issued to each participant of this study while responding to the questionnaire. Informed written consent was obtained from every participant prior to the inception of this study.

**Data Analysis:** The data collected was tabulated and analyzed by using the Statistical Package for Social Sciences (SPSS) version 16.0. The results were expressed in terms of Proportion. Chi-square Test was applied for comparison purpose. In this study, a $p$-value <0.05 was considered as statistically significant.

**RESULTS**

Total of 250 students took part in the study however after excluding the incomplete questionnaires only 224 were included for analysis. The mean age of the cohort was 23.4 years. The total number who was aware of HPV and its vaccine was 220 (98%). The source of their information about HPV is depicted in Figure 1.

![Figure 1: Source of the Awareness for the Study Group. (n= 220)](attachment:image)

The total number of students who took the vaccination was 64 making the acceptability of vaccine as 29%. All the 64 students took the 3 doses as mentioned in the vaccine regimen and there were no drop outs. The remaining 160 (71%) students who refused the vaccination stated their reasons for not accepting the vaccines which is shown in Figure 2.

![Figure 2: Reasons for not accepting HPV vaccine in the Study Group. (n= 160)](attachment:image)
A total of 192 doses were given to 64 students. Some form of side effects were seen in 44 (69%) students. These side effects are divided into three groups namely common (>10%), moderately common (1-10%) and non-specific in VAERS database. [9] However we have tabulated all the side effects along with VAERS data for the purpose of comparison as shown in Table 1.

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Study group (%)</th>
<th>VAERS Data (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>59</td>
<td>92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td>36</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td>47</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>Myalgia</td>
<td>45</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>Rashes</td>
<td>7</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vaginal infection</td>
<td>8</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>20</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Fever</td>
<td>17</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>NS= not significant</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

DISCUSSION

HPV has been shown to be linked in various genital tract malignancies. With newer diagnostic innovations, this link has been proven beyond doubt. The meta-analysis by Vuyst HD and colleagues showed that HPV was prevalent in all grades of vulvar (40%), vaginal (70%) and anal (80%) intraepithelial neoplasia and there was no variation of this prevalence around the geographical locations. [10] Recent study of HPV in cervical carcinoma by using multiplex real time polymerase chain reaction showed that HPV types 16 and 18 were prevalent in 86% of cases and in the remaining 14%. HPV type 73 was seen more commonly. [11] At present there are two types of HPV vaccines available for commercial use. They are quadrivalent (for HPV serotypes 6, 11, 16 and 18) and bivalent HPV vaccines (for HPV serotypes 16 and 18). These vaccines are recombinant vaccines targeting the E6 and E7 oncoproteins of the virus which were seen in the premalignant lesions caused by HPV. [12] The recombinant L1 capsid protein assembled itself as Virus like Particle (VLP) and initiated immunological reaction and rendered protection against the infection caused by the actual virus. [13] There was no viral DNA in the vaccine hence there was no chance of host acquiring the infection or reversion to HPV infection. However the main drawbacks of recombinant vaccine are the need for adjuvant to launch an immunological reaction and the need for multiple administrations of the vaccine. [14] Bivalent HPV vaccine was used in our study and the main ingredients of the vaccine were HPV type 16 L1 protein (20 micrograms), HPV type 18 L1 protein (20 micrograms) along with ASO4 adjuvants 3-O-desacyl-4'-monophosphoryl lipid A (MPL) (50 micrograms) and adsorbed on aluminium hydroxide, hydrated (Al(OH)3) (0.5 milligrams Al3+ in total). [15]

In our study, the awareness of HPV and its vaccine stood out distinctively when compared with the general population as the chosen cohort was female medical students and a high rate of awareness was expected since they would become doctors and educate the general population in future. The comparison of awareness of our cohort with the various studies (done by questionnaire surveys) all over the world is shown in Table 2.
Our study also showed that 70% of the awareness was attributable to teachers and media/internet. This suggests that it will be more productive to have health education on HPV and its vaccination at the level of school and colleges with regular reminders in the social media like television, radio and internet.

Only being aware of HPV will not reduce the burden of cancer. Accepting the HPV vaccine and taking the prescribed vaccine regimen is of prime importance for prevention of HPV related diseases. The acceptability of the vaccine was low when compared to the awareness of HPV in our study. Financial reason (58%) was cited as the main cause by the students. However one-fifth of the cohort did not accept the vaccine due to their apprehension about its efficacy, lack of information about the vaccine (“still under trial”) and also the possible side effects of the vaccine. Almost identical findings were note in a study done by Fisher and his colleagues in Israel, where it was observed that the awareness of HPV was high but the acceptability was only 10%. [21] The reasons for low acceptability were similar to our study group. The comparison of acceptability of our cohort is with other studies is shown in Table 3.

To improve the acceptability of HPV vaccines, financial issues needs to be addressed and general population should be made aware of the researches done towards efficacy and safety profile of these vaccines. I-Ching S and coworkers suggested from their study that the acceptability can reach 97.8%, if the vaccine was made free of cost. [22] The vaccine taken by our coorthas been studied by many researchers for its efficacy and awareness of these researches will help to alleviate the fears about the vaccines. Follow up studies has been done to prove its efficacy from time to time. Four years back, Romanowski and his group showed sustained immunogenicity and efficacy of this vaccine for 6.4 years [23] followed by Carvalho and his group supporting the sustained efficacy till 7.3 years. [24] Most recently the efficacy was still maintained after 8.4 years of follow up. [25] Apart from the protection of the serotypes 16 and 18, researchers have demonstrated cross protection of the vaccine against other HPV serotypes. Wheeler and colleagues at the 4-year-end analysis of PATRICIA trial

| TABLE 2. Comparison of awareness of HPV between our cohort and the general population |
|---------------------------------------|-----------------|-----------------|----------------|
| **RESEARCHERS**                       | **COUNTRY**     | **SAMPLE SIZE (n)** | **AWARENESS (%)** |
| Feng S et al 2011 [16]                | China           | 1432             | 19              |
| Pitts M et al 2009 [17]               | Singapore       | 2145             | 20              |
| Ilter E et al 2010 [18]               | Turkey          | 525              | 44              |
| Marlow L et al 2009                   | UK (Asian-Africans) | 750          | 18              |
| STUDY GROUP (medical students)        | Malaysia        | 224              | 98              |

| TABLE 3. Comparison of acceptability of HPV vaccine between our cohort and general population |
|---------------------------------------|-----------------|-----------------|----------------|
| **RESEARCHERS**                       | **COUNTRY**     | **SAMPLE SIZE (n)** | **ACCEPTABILITY (%)** |
| Marlow L et al 2009                   | UK (Asian-Africans) | 750         | 20              |
| STUDY GROUP (medical students)        | Malaysia        | 224              | 29              |
showed that the bivalent vaccine (HPV 16 & 18) was also efficacious against HPV 33, 31, 45 and 51. [26] Szarewski and his group added three more serotypes in the list of cross protection namely HPV 6, 11 and 74 for the same bivalent vaccine. [27] Studies also suggested that this bivalent vaccine was effective in women who had CIN3+ and adenocarcinoma in situ (AIS) irrespective of HPV DNA. [28]

HPV vaccines have been deemed safe and well tolerated and more than 100 million doses have been administered worldwide without any serious adverse effect. [29] A detailed post licensure monitoring for side effects was done in the US by VAERS from 2006 till 2013 and it was found that out of 57 million doses given there were reports of 22,000 adverse reactions. Around 92% of these reactions were limited to local reaction like pain, swelling and redness at the injection site and remaining 8% constituted headache, nausea, fatigue, syncope and generalized weakness. [30] There were no reports of disability, severe morbidity or mortality following vaccination. There have been concerns of Guillain Barre Syndrome following HPV vaccination but studies have actually shown there is no association HPV vaccination with this syndrome, [31] and also there were no association with autoimmune disease, neurological disorders and venous thromboembolism. [32,33] There was a case report of premature ovarian failure (POF) following HPV vaccination in a teenager [34] however cause-effect relationship was not established but an elimination of various etiologies of POF was undertaken and the vaccination was merely presumed to be the cause. These anecdotal reports make a long lasting impression in people’s decision making, thereby affecting the acceptability of a vaccination program.

The side effects in our cohort were comparable to the VAERS data except for pain at the injection site which was significantly lower and pruritus which was significantly higher. Lower incidence of pain at injection site could be attributed to higher pain threshold of the medical students. Stress causes lowering of testosterone and thereby lowering of pain threshold [35] and medical students are usually exposed to stress early in their academic career and by the time they come to clinical years there is adjustment with the stress of the medical profession and therefore ‘pain coping’ is better leading to higher pain threshold. [36] This could be a plausible explanation for the significant difference of incidence of pain at injection site. The increase incidence of pruritus is difficult to explain without the blood investigations to show allergenic reactions. However it is an established fact that aluminium based adjuvants can cause local hypersensitivity reaction in varying severity [37] hence we can only presume it to be an exaggerated hypersensitivity reaction.

**CONCLUSION**

In conclusion, the awareness of HPV and its related disease are well known amongst medical students. Despite having a high awareness, the acceptability is low due to financial reasons and apprehension about the efficacy and side effects of the relatively new vaccine. In our study, the sample size of vaccinated subjects was small hence robustic conclusions about side effects cannot be made. However we can conclude HPV vaccination did not cause any serious or disabling side effect in the vaccinated individuals and thereby is safe and tolerated well. This vaccine is still in its infancy and more studies, preferably with a bigger sample size, in different geographical locations and different cohorts will definitely enhance its propagation in future. Health education to parents by social media and subsidization of the vaccine cost would
go a long way in improving the acceptability for vaccination and reducing the cancer load for future generation.

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