

## CURRENT ISSUES FACING THE INTRODUCTION OF HUMAN PAPILLOMAVIRUS VACCINE IN MALAYSIA

LP Wong,<sup>1</sup> IC Sam<sup>2</sup>

<sup>1</sup>Wong Li Ping, *MSc, PhD*, Lecturer, Health Research Development Unit (HeRDU), Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. Tel: 603-79675738, Fax: 603-79675769, Email: [wonglp@ummc.edu.my](mailto:wonglp@ummc.edu.my) (corresponding author)

<sup>2</sup>I-Ching Sam, *MRCP, MRCPATH*, Associate Professor, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

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### ABSTRACT

Certain human papillomavirus (HPV) types are strongly associated with cervical cancer. Recently-described effective vaccines against these HPV types represent a great medical breakthrough in preventing cervical cancer. In Malaysia, the vaccine has just received regulatory approval. We are likely to face similar barriers to implementing HPV vaccination as reported by countries where vaccination has been introduced. Most women have poor understanding of HPV and its link to cervical cancer. Physicians who will be recommending HPV vaccines may not have extensive knowledge or experience with HPV-related disease. Furthermore, a vaccine against a sexually-transmitted infection may elicit negative reactions from potential recipients or their carers, particularly in a conservative society. Given the high cost of the vaccine, reaching the most vulnerable women is a concern. To foster broad acceptance of HPV vaccine, education must be provided to health care providers, parents and young women about the risks of HPV infection and the benefits of vaccination.

**Keywords:** Cervical cancer, human papillomavirus, vaccination

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### INTRODUCTION

In most developing countries, cervical cancer is one of the leading causes of cancer-related deaths among women.<sup>1</sup> In Malaysia, cervical cancer is the second most common female cancer, constituting 12.9% of all female cancers.<sup>2</sup> The Malaysian National Cancer Registry reported an average of 2,000-3,000 hospital admissions of cervical cancer per year in Malaysia, with the majority presenting at late stages of the disease.<sup>2</sup>

Cytology-based screening using the Papanicolaou (Pap) smear is the main screening method used for the secondary prevention of cervical cancer. However, only about 5% of women in developing countries are screened, compared with 40-50% in developed countries.<sup>3</sup> In many high-resource countries, the implementation of a wide-coverage Pap smear screening programme has reduced cervical cancer incidence and mortality. In developing countries, the lack of screening due to the lack of resources, infrastructure, and technological expertise has contributed to the continued increase in the incidence of cervical cancer.<sup>4</sup> In addition, due to the low sensitivity of the Pap test, 50% of adenocarcinomas and 25% of squamous cell carcinomas occur in adequately screened women.<sup>5</sup> In Malaysia, cervical cancer screening coverage is poor, at <2% in 1992, 3.5% in 1995 and 6.2% in 1996.<sup>6</sup>

Possible reasons for this include uneven distribution of medical facilities throughout the country,<sup>7</sup> lack of knowledge about the availability of screening,<sup>8</sup> and reluctance to undergo Pap smears for cultural reasons.<sup>8</sup> A further problem is poor sampling technique leading to inadequate smears.<sup>9</sup>

### HUMAN PAPILLOMAVIRUS (HPV)

HPV is a non-enveloped, double-stranded DNA virus. There are over 100 HPV types, of which 40 typically affect the anal and genital areas (Figure 1). Thirty types are associated with cervical cancer, with the high-risk types 16 and 18 accounting for over 70% of all cases worldwide,<sup>10</sup> including in Malaysia.<sup>11</sup> Other less prevalent oncogenic types include types 31, 33, 45, 52, 58, and 59.<sup>10</sup> More than 99.7% of cervical tumour specimens contain detectable HPV DNA,<sup>12</sup> making the association between HPV infection and cervical cancer one of the strongest in cancer epidemiology. HPV types 6 and 11 are common low-risk oncogenic types, which are associated with >90% cases of genital warts.<sup>12</sup> Transmission of HPV infection usually occurs from penetrating intercourse and genital skin-to-skin contact. Most infections are asymptomatic, transient, and have no adverse effects. Thus, transmission may occur unknowingly and infected persons are often unaware that

they are carriers. As many as 75% of adults may acquire HPV infection during their lives, and the highest rates for HPV infection occur in women between 18-28 years.<sup>14</sup> Cervical immaturity, due to factors such as metaplastic changes during puberty, may increase the susceptibility of adolescents to HPV infection.<sup>15</sup>

cervical epithelium via micro-abrasions. Ongoing viral replication is associated with progressively dysplastic histological changes, through cervical intraepithelial neoplasia (CIN) grades 1-3. The integration of HPV into the host DNA leads to up-regulation of the viral oncogenes E6 and E7, which disrupt host p53 and RB control of the cell cycle, and result in invasive cancer.

The pathogenesis of HPV-associated cervical cancer has been reviewed (Figure 2).<sup>16</sup> HPV infects basal cells of the

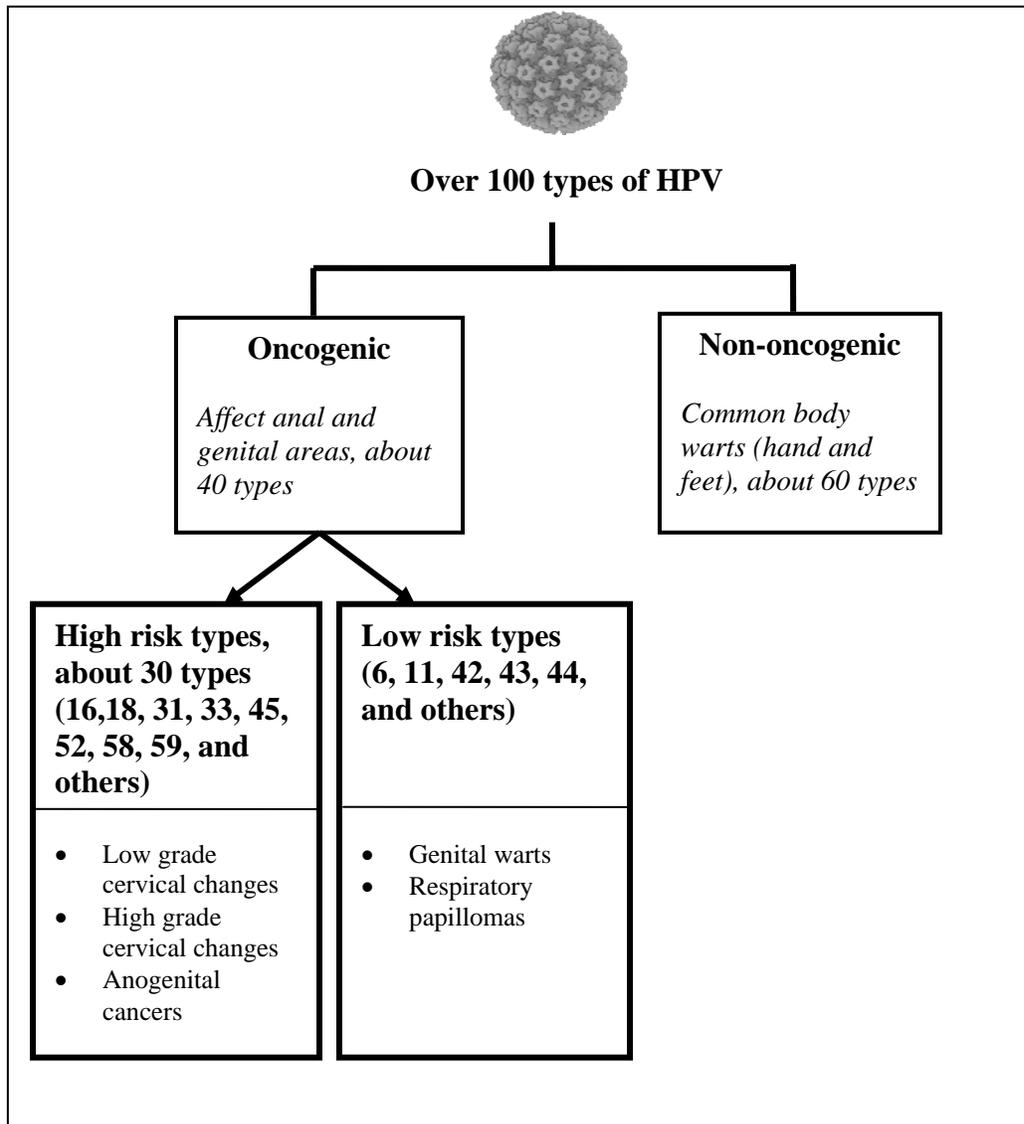


Figure 1. Illustration of oncogenic and non-oncogenic HPV types.

## HPV VACCINES

Vaccines against HPV have been recently introduced in developed countries. The vaccines consist of recombinant HPV major capsid protein L1, which generate virus-like particles (VLP) resembling HPV virions, but which are non-infectious, and immunogenic. The US Food and Drug Administration (FDA) recently approved a quadrivalent vaccine (Gardasil, from Merck) against types 6, 11, 16 and 18. The vaccine is recommended for routine use in girls aged 11 to 12 years, and permissive use for females aged 9-26 years.<sup>17</sup> A bivalent vaccine (Cervarix, from GlaxoSmithKline), which protects against HPV types 16 and 18, should become available soon.

Both vaccines have shown excellent efficacy and safety. The quadrivalent vaccine was 90.7-100% effective in preventing infection of the four HPV types, and associated genital warts, CIN, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia.<sup>17,18</sup> The bivalent vaccine also showed similarly high efficacy in protecting against

persistent HPV infection and CIN.<sup>19</sup> Although antibody levels and clinical efficacy appear to be sustained for at least 4.5 years after vaccination,<sup>19,20</sup> the full duration of protection and the possible need for boosters is unclear. Indeed, the limited follow-up duration of current studies may be insufficient to detect persistent high-grade cervical dysplasia, which may take many years to develop.

It should be emphasised that the vaccines do not protect against less common or unidentified strains of HPV that are associated with cervical cancer. Furthermore, HPV infection alone may not be sufficient to induce cervical cancer. Potentially important co-factors in the development of neoplasia include smoking, multiparity, prolonged oral contraceptive use, herpes simplex virus type 2, and other sexually transmitted infections (STIs).<sup>21,22</sup> There is also the theoretical possibility that other oncogenic types may fill the biological niche left behind if types 16 and 18 are eradicated, leading to a rise in cervical cancers caused by non-16 and 18 types.<sup>23</sup>

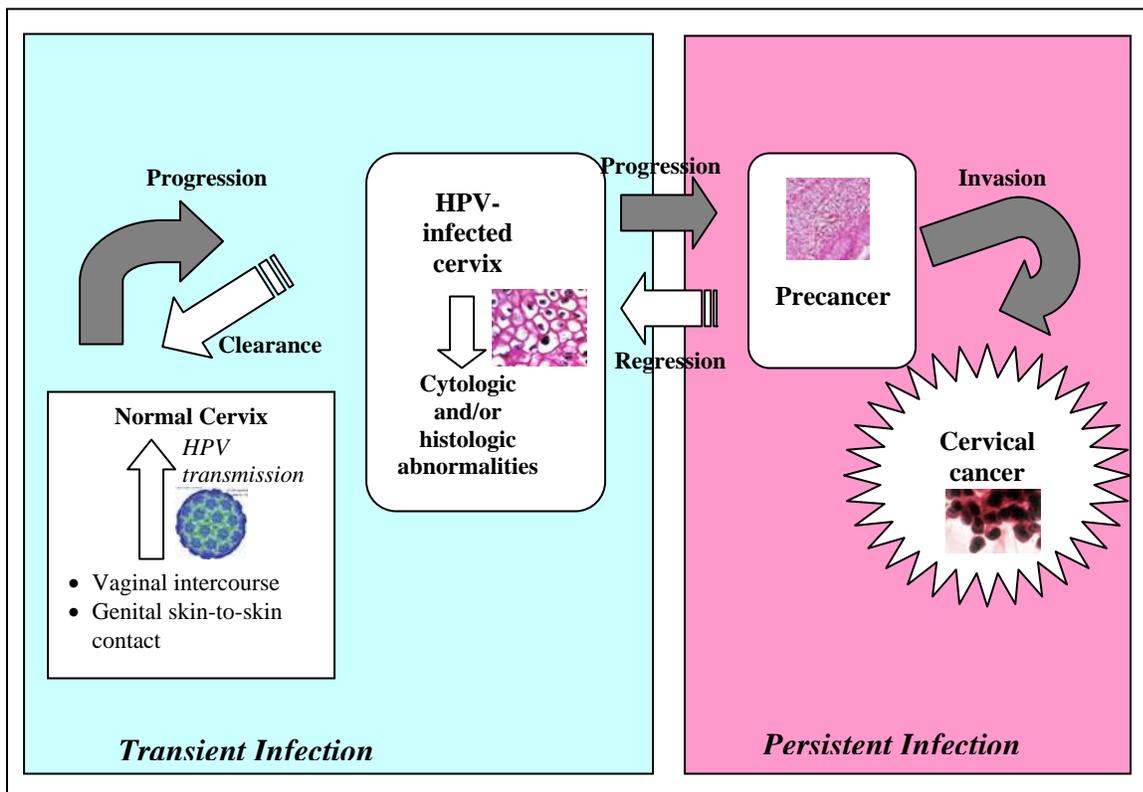


Figure 2. Schematic representation of HPV infection

### Benefits of HPV vaccination

Due to the length of time required for malignant transformation, it is likely to be decades before the full impact of HPV vaccination on the incidence of cervical cancer can be determined. A study predicted that the vaccines would reduce the number of cervical cancer cases associated with HPV 16 and HPV 18 by as much as 95%.<sup>24</sup> Vaccination could also allow less frequent screening and a later age of screening initiation,<sup>24</sup> and reduce other HPV-related diseases, such as genital warts, along with their associated psychosocial and economic burden.

### Immunisation of boys and men

Currently the vaccines are only approved for use in females. However, HPV infection is equally common in men and women of all ages. Most HPV vaccine studies have been conducted in women, who are at greater risk of cervical cancer than men are of acquiring anogenital cancers. The HPV types that cause cervical cancer have also been linked with both anal and penile cancers in men, although these are rare.<sup>25</sup> Thus the vaccines should protect men from genital warts and anogenital cancers.

The vaccine appears to be highly immunogenic and safe for men as well as women.<sup>26</sup> Herd immunity effects of vaccination can protect unvaccinated individuals, thus it has been suggested that both boys and girls should be vaccinated.<sup>27</sup> As men may be carriers of oncogenic HPV types,<sup>28</sup> vaccinating men could reduce HPV transmission, and potentially lower cervical cancer rates among women. However, some researchers have used mathematical modelling to suggest that vaccination of males in addition to females offers little additive benefit in preventing cervical cancer.<sup>24</sup> Efficacy trials in young men are ongoing, and the results should contribute to the debate.

## POTENTIAL CHALLENGES TO VACCINATION ACCEPTANCE IN MALAYSIA

In Malaysia, the vaccine received regulatory approval in November 2006. However, there is no data available on the Malaysian public's knowledge on HPV or attitudes to HPV vaccine. Comprehensive surveys need to be carried out to address this, if the vaccine is to be considered for widespread use. The general lack of knowledge about HPV is a major factor that might adversely affect HPV vaccine acceptability. Generally, studies from other countries show poor knowledge among women of HPV and associated diseases. A British survey revealed that <1% could name HPV as a cause of cervical cancer,<sup>29</sup> while just 13% of high-school adolescents in Canada had heard of HPV.<sup>30</sup>

Numerous studies have evaluated acceptability and attitudes regarding the HPV vaccine, but almost all were carried out in developed nations. The characteristics of the vaccine itself, patients' knowledge and health beliefs, sexual nature of the disease being prevented, and physician recommendations all strongly influence vaccine acceptability.<sup>31</sup>

### Social stigma

Vaccine acceptability undoubtedly will be maximised by effective communication of risks associated with HPV infection and the benefits of vaccination. However, the vaccine may be contentious due to the sexually-transmitted nature of HPV, which carries the stigma of unacceptable sexual behaviour. Receiving a diagnosis of HPV produced emotional distress, anxiety, fear, sexual problems, concerns about transmission, negative self-image and feelings of stigma.<sup>32</sup> Young people may feel that by obtaining HPV immunisation, they would be perceived as being more likely to engage in sexual activity. This social stigma may give rise to uncertainty and hesitation when considering vaccination. In addition, as male involvement in contraception is still unfavourable and unacceptable to some men in our society, it will be a challenge to include men in a vaccination programme that aims to prevent cervical cancer in women.

### Parental attitudes and perceptions

Parental acceptance of HPV vaccination is critical since the vaccines are recommended for children and young adolescents before the onset of sexual activity. Children and adolescents rely on their parents for guidance as well as consent for vaccination. Two important factors associated with increased acceptance of HPV immunisation among parents were knowledge of vaccine benefits and perception that their child is at risk of infection.<sup>10,33</sup> Due to religious or moral values, some may perceive that their children are at low risk for contracting the infection, and thus believe that vaccination is unnecessary. Parents may fear that vaccination of their children might promote sexuality and result in increased unsafe sexual behaviour. It was found that intention to vaccinate was higher when the vaccine was described as preventing cervical cancer, rather than preventing cervical cancer as well as STI.<sup>34</sup> Furthermore, as sexual issues are taboo in many Asian cultures, parents may find it difficult to explain to their children the need for vaccination against a STI. Parents may also be wary of new vaccines with no long-standing track record of safety, and unknown duration of protection. They may prefer to wait until the vaccine has been well established before subjecting their child to it.

### Religious issues

Religion plays an important role in our society. It is not known how our society and local religious conservatives would react to vaccinating youngsters against a sexually transmitted virus. In the US, for instance, religious groups oppose HPV vaccination, preferring instead to advocate abstinence for prevention of STIs.<sup>35</sup>

### STRATEGIES FOR FOSTERING HPV VACCINE ACCEPTANCE

**Increase awareness of HPV and remove social stigma**  
In Malaysia, the level of knowledge on HPV is not known, but is not expected to be any higher than reported elsewhere. Education to raise awareness and de-stigmatise HPV may positively influence uptake of vaccine. Following educational intervention, some initially reluctant parents subsequently became willing to have their children vaccinated.<sup>36</sup>

Secondly, education efforts should target young adults to improve knowledge about HPV and to prevent HPV infection and cervical cancer. Educational programmes should include information on different HPV types, transmission, implications for sexual partners, prevalence, latency and regression of HPV, management options and the risks of anogenital cancers. Such knowledge may provide a stronger motivation to improve safe-sex practices and lead to primary prevention of HPV infection. It has also been shown that informing men about cervical cancer can impact positively on their female partners' willingness to be vaccinated.<sup>36</sup>

A universal recommendation for HPV immunisation for children will help remove the social stigma associated with receiving the vaccine. However, advocating mandatory vaccination, which has been controversially carried out in some US states, may be perceived as infringing on parental rights.<sup>35</sup>

### Improve public's knowledge of HPV and HPV vaccines

It is important that the public should not be coerced or frightened into thinking that HPV vaccine is a "must-have" for themselves or their children without knowing more about the vaccine, what it can and cannot do. On the basis of accurate and appropriate information, a person can then judge whether or not to accept the vaccine. Information for the public should include:

1. HPV is one of the most common sexually transmitted diseases in the world. Some types cause genital warts, while some types are strongly linked to cervical cancer.
2. The new quadrivalent HPV vaccine provides effective protection against four main HPV types that cause genital warts and cervical cancer. However, the

vaccine cannot protect females against diseases caused by other HPV types that are not in the vaccines.

3. Ideally, the vaccine should be administered before onset of sexual activity. Sexually active women who receive vaccine may still be partially protected if they have not been exposed to all the vaccine HPV types.
4. The vaccination does not substitute for routine cervical cancer screening. Women who receive the vaccines should continue to undergo cervical cancer screening.
5. Vaccinated women should continue with protective sexual practices since the vaccines will not prevent all cases of HPV or other STIs.

### Physician's recommendations

Health care providers' recommendations are important in optimising vaccine delivery. Therefore, it is critical to understand predictors of providers' intentions to recommend immunisation. Patient information should be provided in an individualised fashion to take into account each patient's social background, knowledge, and attitudes. Health care providers may hold personal views and biases which may make them reluctant to discuss sexual issues with patients or parents. Furthermore, they may hesitate to recommend the vaccine in anticipation of negative parental reaction. Educational initiatives targeting all health care providers involved in patient education can positively influence immunisation recommendation patterns and foster vaccine acceptance.<sup>37</sup>

### The need and the means

The recommended three-dose course, costing approximately USD \$360 (RM 1,260), is unaffordable for many patients. Women of lower socioeconomic status have the highest risk of cervical cancer yet often lack access to healthcare services, including screening. These vulnerable women would benefit most, but will be the least likely to receive the vaccine. Therefore, to ensure the widest coverage, the vaccine may need to be subsidised or incorporated into the vaccine programme.

### Cost effectiveness

The cost-effectiveness of HPV vaccines must be considered before widespread implementation. Countries with established cervical cancer screening programmes which introduce routine HPV vaccine still need to continue screening, as there will remain many women who are unvaccinated or already infected with HPV.<sup>24</sup> Thus, in countries which lack screening programmes, HPV vaccination is likely to be the most cost-effective method of reducing cervical cancer. HPV vaccination has been shown to be most cost-effective for girls aged 11-12, prior to onset of sexual activity,<sup>38</sup> but is less economical for catch-up vaccination of older females.<sup>24</sup> Cost-effectiveness was

underestimated in these analyses, which did not include benefits of preventing other HPV-associated diseases. In Malaysia, one of the difficulties in assessing cost-effectiveness for subsequent health planning is the lack of accurate, comprehensive medical documentation.<sup>7</sup> For example, the uneven distribution of diagnostic pathology services may lead to underestimation of the true prevalence of cervical cancer diagnoses and deaths.<sup>7</sup>

## CONCLUSION

Mortality from cervical cancer has undoubtedly been reduced by effective Pap smear screening programmes. Nevertheless, such programmes are costly and difficult to implement in resource-poor settings. The development of highly effective HPV vaccines is thus an important breakthrough as it offers great potential to reduce the incidence of cervical cancer, other HPV-related diseases, and the associated economic and psychological burden.

In order for HPV vaccination to be successfully implemented, social and political issues need to be addressed and agreed upon by stakeholder groups, including physicians, public health officers, parents, adolescents, and community leaders. Limited knowledge about HPV and HPV-associated disease may affect vaccine acceptability. Successful vaccine implementation thus would require educating the general public about HPV, to increase awareness, de-stigmatize HPV infection, and gain acceptance of vaccines.

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### *Male circumcision reduced HIV infection by half in Africa men*

Bailey RC, Moses S, Parker CB, *et al*. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet*. 2007;369(9562):643-56 [[PubMed](#)]

The 2-year HIV incidence was 2.1% in the circumcision group and 4.2% in the control group ( $p=0.0065$ ); the relative risk of HIV infection in circumcised men was 0.47, which corresponds to a reduction in the risk of acquiring an HIV infection of 53%.

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HIV incidence over 24 months was 0.66 cases per 100 person-years in the intervention group and 1.33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%).