Review Article:
“Human Papilloma Virus Vaccination for cervical cancer prevention. Is it safe and effective?”

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Abstract
Human papillomavirus (HPV) causes cervical cancer, which is the fourth most common cancer in women. Most of the cervical cancers are linked to genital infection with HPV and it is the most common viral infection of the reproductive tract. At present, there are three types of HPV vaccines available. Even though HPV vaccination is a primary prevention tool, that does not eliminate the need for routine cervical screening, since the vaccines do not protect against all high-risk HPV types. Ninety percent of HPV infections have no clinical consequences at all whether they are high-risk or low-risk subtypes of HPV. All three types of HPV vaccines have very high vaccine efficacy for prevention of HPV infection among females aged 14 to 26 years. Proper assessment of the safety of HPV vaccine is a problem even after proper systematic review since the most of the clinical trials on the safety of the vaccines were used Hepatitis A vaccine or high immunogenicity enhancing aluminium adjuvant as their placebo. HPV vaccination would be very cost effective for the countries when there is no cervical screening program or if the programme coverage is very poor.

Introduction
Cervical cancer is the fourth most common cancer in women. ‘Human Papilloma Virus’ (HPV) is the most common cause behind cervical cancer. There is an estimated 266,000 deaths and 528,000 new cases in 2012. Around 85% of the global burden cervical cancer occurs in the less developed regions, where it accounts for almost 12% of all female cancers. HPV infections are transmitted through sexual contacts1. Well organised screening programmes have been responsible for reducing the cervical cancer burden in the developed countries during last few decades. High disease prevalence in, the developing world is mainly due to the fact that women in these regions may not undergo even a single screening in their lifetime. Further, even though HPV vaccination is a primary prevention tool, that does not eliminate the need for routine cervical screening2. This review provides an overview of key information, on the use of HPV vaccination as a preventive strategy of cervical cancers, for policy makers.

Literature search and review
The literature was reviewed by performing a google and google scholar database search, using the keywords; “Human papilloma virus”, “Cervical cancer”, “HPV infection”, “HPV vaccination”, “Cost-effectiveness” and “Safety”, individually and in combination as appropriate. Search was restricted to publication dates between January 2012 to August 2017. References cited in retrieved articles were also evaluated and included if appropriate.

HPV infection and cervical cancer
According to World Health Organization (WHO), allmost all cervical cancer cases (99%) are linked to genital infection with HPV1. Genital HPV infection is one of the most common sexually transmitted infection worldwide. It has been estimated that around 10% of women worldwide with normal cytological findings carry a detectable HPV infection, regional variances are documented ranging from 6.1% to 35.5%3. There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma. Squamous cell

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carcinomas account for 80 to 90 percent of cervical cancers and Adenocarcinomas makeup 10 to 20 percent of cervical cancers. Ninety percent of HPV infections have no clinical consequences at all whether they are high-risk or low-risk subtypes of HPV. Persistent infection with oncogenic HPV subtype is necessary for the development of cervical cancer. Approximately 15 oncogenic HPV types out of 100 HPVs have been identified to date. Of which HPV-16 and HPV-18 are the most prevalent in cervical cancer, accounting for approximately 70% of cases.

Jaisamrarn et al. reported that cervical infection with oncogenic HPV types increased the risk of CIN 2+ and CIN 3+. Further, out of the different oncogenic HPV types, HPV-16 and HPV-31 infections were least likely to clear. The study also indicates that higher risk of development of CIN 2+ with HPV 16, HPV 33, HPV 31, HPV 45 and HPV 18 infections. In a study done by using paraffin-embedded samples of histologically confirmed cases of invasive cervical cancer, were collected from 38 countries showed that 87 % of samples of squamous cell carcinoma were HPV positive, whereas only 62% of adenocarcinoma samples were HPV positive. As argued by Wilyman, even though HPV infection is a necessary precursor to most cervical cancers, most high-risk HPV infections do not progress to cervical cancer. Therefore, HPV infection with any strain cannot be considered as a sufficient cause on its own to cause cervical cancer. There may be few other cofactors which are necessary to induce cervical cancer along with the HPV infection.

**Human Papillomavirus (HPV) Vaccines**

At present, there are three types of HPV vaccines available. Cervarix is manufactured by Glaxo Smith Kline. Gardasil and Gardasil-9 are manufactured by Merck & Co. All these vaccines help to prevent infection by HPV 16 and HPV 18. These types are responsible for 70% of all cervical cancers and precancers. Gardasil also prevents infection by HPV 6 and HPV 11 that cause most genital warts. Gardasil-9 prevents infection with the same 4 types of Gardasil plus 5 other high-risk types 31,33,45,52 & 58. This combination of HPV subtypes is associated with 90% of cervical cancer.

In 2005 February Merck and GSK both got the patent for Virus Like Particle (VLP) technology to manufacture HPV vaccine, after entering cross-license agreement between two companies. Despite the fact, there is no scientific evidence that HPV alone cause cervical cancer, FDA granted approval for Gardasil as a cervical cancer preventive vaccine in the US in June 2006. Interestingly no safety concerns were raised about this vaccine, begin the first vaccine to use genetically engineered virus-like particles. Cervarix got their 1st approval in May 2007 in Australia.

All three types of HPV vaccines have very high vaccine efficacy (> 96%) for prevention of HPV infection among females aged 14 to 26 years. In 2009 GSK funded trial compared the immunogenicity and safety of Cervarix and Gardasil. According to the study findings, Cervarix generated higher antibody levels than Gardasil, indicating higher efficacy.

The American College of Obstetricians and Gynecologists (ACOG) recommends Bivalent, Quadrivalent and nine-valent vaccines for females aged 9 to 26 years and Quadrivalent and nine-valent vaccines for males aged 9 to 26 years. All three vaccines are given in a three-dose series with a schedule of 0,1 and 6 months. Recently, an alternative HPV vaccination schedule was proposed by the WHO. In that, two doses are recommended at 0 and 6 months for females those aged < 15 years and three-dose schedule is recommended (0, 1-2, and 6 months) for females >15 years at the time of first dose.

According to the Committee on adolescent health care and Immunisation expert work group of ACOG, the HPV vaccination can significantly reduce the incidence of anogenital cancer, genital warts and oropharyngeal cancer. But they were unable to give any scientific evidence to prove the fact the HPV vaccination prevents cervical cancer.

Within 6 years of HPV vaccine introduction in the US, the prevalence of HPV subtypes (HPV 6,11,16,18) covered by quadrivalent HPV vaccine decreased by 64% among females aged 14 to 19 years and by 34% among those aged 20 to 24 years. Further within the vaccine era among sexually active females aged between 14 to 24 years, the combined prevalence of above subtypes was lower in vaccinated (≥ 1 dose)compared with unvaccinated females 2.1% vs 16.9%.

The most prevalent subtypes of HPV infection was different from geographical region to region. Further, there are various studies even from the same geographical area reported the different distribution of HPV subtypes from time to time. These findings have obvious implications on the decision of implementing HPV vaccination as a preventive approach.
strategy for cervical cancer and also to pick the appropriate vaccine for the programme. As predicted by Brisson et al.\textsuperscript{20} elimination of HPV 16,18,6 and 11 is possible if 80% coverage of HPV vaccination in girls and boys is reached and if high vaccine efficacy is maintained over time.

**Safety of Human Papilloma Virus vaccine**

Review of available data on Adverse Effects Following Immunization (AEFI) associated with HPV vaccination done by Still et al.\textsuperscript{21}, concludes that the both bivalent and quadrivalent vaccines are generally safe and well tolerated. Further, they have reported that occurrence of serious adverse events was similar in both vaccines.

On the other hand, Tomljenovic and Shaw\textsuperscript{22} highlighted the fact that the total number of AEFIs reported for Cervarix appears to be 24 to 104 times higher than that reported for any of the other vaccines in the UK immunisation schedule. This clearly showed that this HPV vaccine has a higher risk of AEFI compared to other vaccines. As reported by Tomljenovic and Shaw\textsuperscript{22} most of the trial done on HPV vaccine safety were funded by the HPV vaccine manufacturers. Therefore, it is hard to find independent evidence on the safety of the HPV vaccines.

When consider the AEFI data base\textsuperscript{22} in Australia, just after the introduction of HPV vaccine in 2007 AEFI rates were doubled. For the year 2007 and 2008, the number of HPV-related AEFI became the top, even after considering all the vaccines used in Australia. More than 90% of the time HPV vaccine was the only suspected vaccine given to those cases. Further, very recently the number of HPV-related AEFI become the 1\textsuperscript{st} in 2013 and 2\textsuperscript{nd} in 2014 after considering all the vaccine types given in Australia. More interestingly, when considering the AEFI reported annually from the vaccinations done for age group 7 to 17 years, the number of HPV vaccine related AEFI became the highest in every year, since its introduction in 2007 in Australia.

Proper assessment of the safety of HPV vaccine is a problem even after proper systematic review since the most of the clinical trials on the safety of the vaccines were used Hepatitis A vaccine or high immunogenicity enhancing aluminium adjuvant as their placebo. Further, almost all the safety trials available were funded by the manufacturers\textsuperscript{22}.

As stated by Sankaranarayanan et al.\textsuperscript{24} The International monitoring agencies such as the Global Advisory Committee on Vaccine Safety (GACVS), the WHO and the European Medicines Agency is monitoring the vaccine safety and critically evaluating all the serious adverse events. Based on the recent reports GACVS considers HPV vaccines to be extremely safe and there are no undue safety concerns to withhold or stop the vaccination and the benefits far outweigh the risks\textsuperscript{24,25}. But the controversy in relation to the HPV vaccination is that we have to outweigh the risk against an unproven benefit of vaccine towards the prevention of cervical cancer. The safety conclusion of the above organisations is mainly based on lack of scientific evidence to say that these concerned AEFIs are due to HPV vaccination. But the controversial point is that allmost all the safety trials on HPV vaccine were conducted by using inappropriate control groups\textsuperscript{22}.

**Cost effectiveness of the HPV vaccination**

Even though it is not scientifically proven yet, all the cost-effective evaluations on HPV vaccination were based on the assumption that, the long-term benefit of HPV vaccination to prevent cervical cancer was proven and its protection is lifelong.

In 2013, Mark offered to sell Gardasil to GAVI for US $ 4.50 and according to the Mark, it is only the cost of goods. But very recent cost estimate\textsuperscript{26} of the complex manufacturing process of new generation vaccines Gardasil and Cervarix showed that it is not so. As estimated by Clendenin et al.\textsuperscript{26}, the manufacturing cost of Gardasil-4 for developing countries ranged between $ 0.48 and $ 0.59a dose, a fraction of its alleged cost of $ 4.50. Due to the low market share of Cervarix, its per unit costs are much higher than the Gardasil4, though at comparable volumes its costs would be similar to Gardasil.

This raises the concern about these company’s sympathy towards developing countries and their governments. GAVI contract to provide HPV vaccines to middle and lower income countries is only for 4 to 5 years’ duration. Therefore, countries have to bear the cost of vaccines on their own most probably at a higher rate. The lowest know prices outside GAVI are US $ 12.83 for Gardasil-4 and US $ 12.87 for Cervarix in South Africa per dose.\textsuperscript{22} People for the HPV vaccination programme compare the HPV vaccine with the Hepatitis B vaccination programme since both vaccines are considered to prevent cancers. But the fact to concern is at the beginning of Hepatic B programme, GAVI received Hepatitis B vaccine at a cost around US $ 1\textsuperscript{27}.

Cost effective analysis of HPV vaccination done in Indonesia\textsuperscript{28} found that the implementation of Visual
Inspection with Acetic Acid (VIA) screening alone and in combination with HPV vaccination would reduce the cervical cancer incidence by 7.9% and 58.5% respectively. Further, they also estimated that HPV vaccination combined with VIA screening apparently yield a lower incremental cost-effective ratio at international dollar compared with VIA screening alone. But both strategies found to be very cost-effective interventions based on the threshold suggested by WHO. Among the parameters used for this analysis, they assume vaccine coverage 76.6% and 3 yearly cervical screening coverage as 63.3%, which seems to be too high for most of the developing countries. Model-based economic evaluation done in South Vietnam concluded that vaccination of boys may be cost effective at low vaccine costs, but provides little benefit over vaccinating girls only.

As started by Bailey et al. even though the low and middle-income countries received through the GAVI agreement, HPV vaccinations, to be cost effective those countries per dose cost need to be around US $1 to 2 dollars.

In a Mexican cost effective analysis, the strategy of using only HPV vaccination (45 USD for 3 doses) as a preventive measure of cervical cancer was a very cost effective strategy (USD 68 / LYS). The strategy of vaccination with traditional screening through pap test every 3 years predict higher cost due to the lower performance of cervical cancer cytology in Mexico.

As reported by Čavaljuga et al. despite the heterogeneity, most of the studies generally conclude that HPV vaccination of preadolescent females is cost effective, particularly in settings without organised cervical cancer screening programme. An inclusion of males in the vaccination programme is not cost effective.

Policy implication and controversies over HPV vaccination

As Wilyman concludes in his review, most of the government policy decisions and marketing of HPV vaccines have not been based on the best available scientific evidence. Further, as he stated, this vaccine is an HPV vaccine and not a cervical cancer vaccine. There is inconclusive evidence that it will reduce any cervical cancer and the long-term risk of using this vaccine have not been determined yet. This is detrimental to the health of the population and needs to be addressed in order to maintain trust in the institutions that are supposed to protect public health. Clinical trials for the HPV vaccine did not prove the fact that the vaccine preventing any cervical cancers.

Instead, these trials were focused on pre-cancerous lesions in women 16-26 years of age. This is not scientific since most of these lesions in this age group, clear quickly without requiring any treatment. As argued by Tomljenovic and Shaw, since invasive cancer take up to 20-40 years to develop from the time of acquisition of HPV infection, testing period is too short to evaluate the long-term benefits of HPV vaccination.

From 2010, the government of France refuses to allow HPV vaccines to be marketed as cancer preventive. France become the 1st western government to recognise that HPV vaccines are not cancer preventive based on the current evidence. China had a high rate of cervical cancer in 1985 but this was reduced to a low rate by 2002 even without using a vaccine. Glaxo Smith Kline (GSK) announced on July 18, 2016, they had successfully persuaded the China Food and Drug Administration (CFDA) to license Cervarix as the 1st HPV vaccine to prevent cervical cancer in China. A month later, leading pathologists, Dr Sin Hang Lee sent an open letter to the president and premier of China asking for a delay in the scheduled HPV vaccination of Chinese children and Young women age 9 to 25. In this letter he raises the following serious science-based concerns about proposed HPV vaccine programme; lack of evidence that HPV vaccine prevents cervical cancer, genetic difference of Chinese population and south American population which used to develop the vaccine, availability of long established and low-cost cervical screening to prevent cervical cancer, reported serious adverse reactions, following HPV vaccination and finally use of high immunogenicity enhancing aluminum adjuvant as the placebo in most clinical trials assessed the safety of HPV vaccine. With all these concerns it took another year to incorporate the HPV vaccination in the community health services in China.

India suspended clinical trials of Gardasil and Cervarix after unexplained deaths of four tribal girls following HPV vaccination, under allegations of ethical violations and safety risks in 2010. With that background India was not able to included HPV vaccine in their vaccination programme until today. Controversy, on HPV vaccination in Japan, has led to much confusion among health care professional and parents, as a result vaccine rates have drastically reduced, from around 70% to 1%. In Japan, HPV vaccination was introduced in the NIP in April 2013 and was given for free to girls aged 12 to 16 years.
Japan health authority announced withdrawal of its recommendation for HPV vaccination on 14 June 2013 (After two months of programme) a day after the WHO declared the HPV vaccine to be safe.\(^{35}\)

There is a previous global experience about a cancer preventive vaccine; Hepatitis B. From the introduction of Hepatitis B vaccine in 1982 there was concern about the very high cost of the vaccine. However, with the expired patent and vaccine manufacturing outside the United States reduce the per dose cost from 100 USD to 1 USD within a decade. When the WHO advocate Hepatitis B vaccine to be included in the NIPs the cost of the vaccine was US$ 0.20 per dose. From 2000 to 2011 GAVI-supported the effort of Hepatitis B vaccination and prevented 3.7 million estimated deaths. Due to the low cost of vaccine, it was not become a burden to the countries to maintain their vaccination programme even without the support of GAVI.\(^{27}\)

There are two very clear distinctions between GAVI and WHO effort on Hepatitis B vaccination at that time and HPV vaccination at present. First, is the very high cost of HPV even under the GAVI agreement compared to Hepatitis B. Second, there are only two companies had the patent for HPV vaccine manufacturing process at the movement. At least it will take another 8 years for any other company to come into business after the patent expiration (20 years from 2005).

Usually pharmaceutical companies are applying for the patency for the manufacturing process at a very early stage, even before the initial trials of the vaccine. Therefore, patency period is usually expired within 10 to 12 years’ time following the introduction of the vaccine to the market. That is what happened in relation to the Hepatitis B vaccine. But both Mark and GSK applied for patency at the same time just before they introduce the vaccine to the market. That gives them a chance of utilising the full patency period for their marketing and to maximise the profit.

As a fact, any vaccine which is currently using all over the world can have very rare serious AEFI. Their use is justified based on the benefit of the vaccination. When considering the HPV vaccination justification has been based on an unproven benefit to prevent cervical cancer. More importantly in a background, where safer effective alternatives are available to prevent cervical cancers, such as Pap smear and VIA testing.

As shown by Tomljenovic and Shaw\(^{22}\) that there is a very strong statistically significant correlation between the lack of sufficient pap smear screening coverage and the cervical cancer mortality (p<0.00001). Further, they highlight the fact that the efficiency of regular pap screening procedures in developing countries was evident by 70 % reduction in the incidence of cervical cancer over last five decades.

Developed countries had the same high rates of cervical cancer in the sixties and seventies as the developing countries today. But they were able to reduce the rates by the introduction of screening\(^5\). Therefore, if we can prevent from getting cervical cancer by 3 years’ pap smear screening, then is it necessary to introduce a vaccine which is not proven to be preventing cervical cancer.

The Very high-cost effectiveness of an intervention does not mean that it is affordable. There may be public health interventions which are very cost-effective. But when a country decides on them, national priority should be given to picking up the most cost-effective option, which comes under their affordability. To determine whether this level of cost-effectiveness is currently economically acceptable or viable for a country, the national per capita gross domestic product (GDP) was used as a criterion for comparison with incremental cost-effectiveness ratio outcomes. This approach was recommended by the Commission on Macroeconomics and Health (CMH) and adopted by the WHO, which considers an intervention “highly cost-effective” when the cost of averting one disability-adjusted life year or DALY is less than the per capita GDP and is not cost-effective if the cost per DALY averted is greater than 3 times the GDP per capita.\(^{16}\) Further, Governments should be careful in taking the decisions on the HPV vaccination. Because, if the government hold or suspend HPV vaccination after including that into the NIP, that will badly affect not only the HPV vaccination but all the other vaccines due to the lose of the public trust.

Most of the high-income countries need very high coverage of HPV vaccination to make it cost effective. As explained by Tomljenovic and Shaw, the reason why high coverage is needed for the vaccine to be cost effective in the developed country setting is the very low incidence of cervical cancer. For example, to prevent a single out of 5.7/100,000 cervical cancer cases in the US, nearly every girl would need to be vaccinated for the HPV vaccine programme to be cost-effective.

HPV vaccination would be very cost effective for
the countries when there is no cervical screening program or if the programme coverage is very poor\textsuperscript{31}. If a country is planning to improve their cervical screening programme up to the level in developed world then, picking up this HPV vaccination strategy needed to be reconsidered.

One limitation highlighted with regard to cervical screening is that, its inability to detect adenocarcinomas of the cervix. Due to two reasons HPV, also can give the protection only to a half of these case. First, one-third of the adenocarcinomas of the cervix is not associated with HPV infection and secondly, Cervarix or Gardasil will only cover 70 to 80\% of oncogenic HPV types. Further as argued by SANEvax\textsuperscript{10}, no one knows whether suppressing HPV 16 and 18 will cause other genotypes to become more virulent and more importantly, no one knows long term impact of genetically engineered virus-like particles on the human body.

Most important aspect any country need to consider is the impact of the inclusion of the HPV vaccine into the NIP on the total NIP cost. As highlighted by Tomljenovic and Shaw to make Gardasil mandatory, the total cost of US vaccination programme need to be doubled. This scenario might be worse with regard to most of the middle and lower income countries. Since their total cost of NIP is far below the US vaccination budget.

Given concerns for autonomy and justice, since not all persons are at risk for HPV, a state mandated HPV vaccination program or school-based HPV vaccine mandates, are not the optimal legislative solution. HPV vaccine has its own characteristics, which makes it significantly different from the other vaccines which have been mandated for children entering school in some countries. HPV does not pose a public health risk as serious as measles or any of the other highly infectious diseases. There is no immediate risk of rapid transmission of HPV in schools, as is the case with measles. HPV is primarily transmitted by sexual contact and lifestyle choices and behavioural decisions are often involved. Therefore the HPV vaccine does not present a risk of harm significant enough to justify overriding parental autonomy and make it mandatory\textsuperscript{37}. Therefore, it would seem much more prudent to keep HPV vaccination as a voluntary option to the public, considering the present-day evidence.

**Summery**

All three types of HPV vaccines have very high vaccine efficacy for prevention of HPV infection. But the proper assessment of the safety of HPV vaccine is a problem since the most of the clinical trials on the safety of the vaccines were used Hepatitis A vaccine or high immunogenicity enhancing aluminium adjuvant as their placebo. Justification of HPV vaccination has been bone based on an unproven benefit to prevent cervical cancer. HPV vaccination would be very cost effective for the countries when there is no cervical screening program or if the programme coverage is very poor. One most important aspect any country need to be considered is the impact of the inclusion of the HPV vaccine into the NIP on the total NIP cost. Given concerns for autonomy and justice, since not all persons are at risk for HPV, a state mandated HPV vaccination program or school-based HPV vaccine mandates are not the optimal legislative solutions.

**Conflict of interest:** None
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