Epidemiology Unit
Ministry of Health

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My No EPID/391/2007/II
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Dear all,

Expert group meeting to review and recommend on Human Papilloma Virus (HPV) vaccine introduction in Sri Lanka.

Expert group meetings to explore the requirement of HPV vaccine introduction to the country has held on following days.

- 1 st meeting-12.02.2015
- 2 nd meeting-13.03.2015
- 3 rd meeting-10.04.2015

Members who participated in each meeting were as follows.

No	1 st meeting (12/02/2015)	2 nd meeting(13/03/2015)	3 rd meeting(10/04/2015)
01.	Prof. Krishantha Weerasuriya (Chairperson)	Prof. Krishantha Weerasuriya (Chairperson)	Prof. Krishantha Weerasuriya (Chairperson)
02.	Dr.Paba Palihawadana	Dr.Paba Palihawadana	Dr.Paba Palihawadana
03.	Dr.Ananda Amarasinghe	Dr.Ananda Amarasinghe	Dr.Ananda Amarasinghe
04.	Dr.Deepa Gamage	Dr.Deepa Gamage	Dr.Deepa Gamage
05.	Dr.Samitha Ginige	Dr.N.Mapithigama	Dr.N.Mapithigama
06.	Prof. Lalitha Mendis	Prof. Athula Kaluarachchi	Prof. Athula Kaluarachchi
07	Dr.N.Mapithigama	Dr.Kanishka Karunarathne	Dr.Ishani Fernando
08.	Prof. Athula Kaluarachchi	Dr.Geethani Galagoda	Dr.Kanishka Karunarathne
09.	Dr.Ishani Fernando	Dr.Rajiva de Silva	Dr.Geethani Galagoda
10.	Dr.Kanishka Karunarathne	Prof.Sujeewa Amarasena	Dr.Rajiva de Silva
11.	Dr.Aindra Balasuriya	Dr.Samanthi Premarathna	Prof.Sujeewa Amarasena
12.	Dr.Geethani Galagoda	Dr.Manjula Danansuriya	Dr.Kanthi Nanayakkara
13.	Dr.Rajiva de Silva	Dr.A.A.H.Priyani	Dr.Samanthi Premarathna
14.	Prof.Sujeewa Amarasena	Mrs.Kumudini Hettiarachchi	Dr.Chiranthika Vithana
15.	Dr.Kanthi Nanayakkara		Dr.Sisira Liyananage
16.	Dr.Samanthi Premarathna		Dr.Ayesha Lokubalasuriya
17.	Dr.Chinthana Hapuarachchi		Mrs.Kumudini Hettiarachchi
18.	Mrs.Kumudini Hettiarachchi		

Committee reviewed all relevant information and decided that strengthening of cervical cancer screening is a high priority and on a long term public health interventions on HPV vaccine introduction should be considered.

The committee developed and discussed the attached concept paper on HPV vaccine introduction to be submitted to the Advisory Committee on Communicable Diseases (ACCD) and it considered as minutes of all meetings.

Thank you.

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Dr.Paba Palihawadana,
Chief Epidemiologist.
Secretary/Expert group meeting on HPV
Vaccine introduction.

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Introduction of Human Papilloma Virus (HPV) Vaccine into the National Immunization Programme (NIP), Sri Lanka

This concept paper is developed by the Expert group on review and recommend HPV vaccine introduction in Sri Lanka

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Human Papilloma Virus (HPV) related cancer is a concern of both clinicians and public health stakeholders in Sri Lanka, as the reported incidence is gradually increasing. Introduction of HPV vaccine into the national Immunization Programme (NIP) is debated at many technical forums and this was discussed at the National Immunization summit held in January 2015. At this summit, Director General of Health Services (DGHS) has directed the related authorities to review and recommend on prevention and control strategies against HPV related cancer in Sri Lanka. The Expert group formed by the DGHS has reviewed the available information and developed this concept paper with two priority strategies in prevention and control of HPV related cancer: screening and vaccination.

Global burden of HPV related cancer

Cervical cancer is caused by the HPV. More than 100 HPV types have been identified, about 40 of which can infect the genital area. Two high-risk geno types of HPV virus, types 16 and 18, account for about 70% of all cervical cancer cases. HPV can also cause other types of anogenital cancer (vagina, vulva, anus, penis), head and neck cancers, and genital warts in both men and women.

Globally 1.4 million suffer from cervical cancer and nearly 528,000 new cases with 266,000 deaths (GLOBOCAN data 2012) occur annually. Cervical cancer is the second common cause of cancer deaths causing nearly 80% of deaths in developing countries. It has been globally estimated that almost 12% of all female cancers are cervical cancers. In the South East Asian Region, this accounts for 175,000 new cases and 94,000 deaths (2012) annually.

HPV is sexually transmitted and most people become infected sometime during their lifetime, with the majority soon after becoming sexually active. Most infections are asymptomatic and usually clear up accounting for 90% within two years. Only 10% of persistent HPV infections with certain geno types of HPV can persist and progress to cervical dysplasia. If infection from cancer-causing HPV types persists over 10-15 years, women can go on to develop precancerous lesions that, if left untreated, develop into cervical cancer. This process takes on average 20-30 years from infection to development of cervical cancer.

Burden of HPV related cancer in Sri Lanka

In Sri Lanka, it is estimated that 7.52 million are at risk of developing cervical cancer, 1395 cases with 11.8 age specific standardized rates and 814 deaths (International Agency for Research on Cancer). According to the National Cervical Cancer Control Programme data, a total of 850 cases of cervical cancer have been identified in 2008 with an incidence rate of 7.3 / 100,000 women with 7.4 age standardized rates (2007). Cervical cancer is the 2nd most common female cancers and accounts for 10% of all female cancers in Sri Lanka.

Research evidence in Sri Lanka has shown the community prevalence rate of HPV infection among normal women as 3.3% with a prevalence rate of HPV genotype 16 and 18 as 1.2%. Prevalence of genotype 16 and 18 among cervical cancers accounts for 80%. The population risk attribution in developing cervical cancer by genotype 16 and 18 has accounted for 69% which is closely compatible with the global figure of 70%.

It is also estimated that a minimum of 1739 women need to be screened to detect one cervical cancer patient and a minimum of 2521 women are needed to be protected from infection with HPV genotypes 16 and 18 to prevent one case of cervical cancer caused by these geno types. Therefore, one case of cervical cancer originated from geno types 16 and 18 can be prevented by vaccinating 2521 adolescents if the current similar risk behaviour pattern exists.

A research study has further estimated the minimum unit cost incurred by the government for management of cervical cancer stages 1a, 1b, and 11a which was the Radical hysterectomy [Werthime's hysterectomy] was 13,670 SLR and minimum unit cost of management of cervical cancer stages 11 b, 111 a, 111 b IV a, IV b, which were Chemo-radiation was 23,340 SLR during 2009. (Gamage et al 2012). Considering the annual increasing treatment costs and the changes of treatment modalities, additional costs would be expected to the government every year.

In addition un-estimated psycho-social and family burden caused by premature death of the woman in the family, needs to be accounted significant from this preventable cancer since highest cervical cancer incidence is in the active phase of the woman's life (40-49 years). Family, social and psychosocial agony due to cervical cancer, complications of treatment, recurrences and secondary cancers are to be considered very important.

Vaccines available against HPV

Currently licensed HPV vaccines prevent cervical cancer by preventing infection from HPV types 16 and 18. The vaccines are most effective when administered prior to exposure to HPV infection. HPV vaccines are not therapeutic and cannot be used for treatment of cervical cancer or HPV infection.

There are two HPV vaccines currently pre-qualified by WHO and available for use.

1. A bivalent vaccine– protects against two HPV types 16 and 18 that cause the majority of cervical cancers; and

2. A quadrivalent vaccine– protects against HPV types 16 and 18, as well as HPV 6 and 11 that are responsible for anogenital warts.

Bivalent HPV vaccine contains the adjuvant ASO4. ASO4 is a combination of aluminum hydroxide and monophosphoryl lipid A (MPL) and this adjuvant has the advantage of enhancing the immune response of the vaccinated individuals.

Quadrevalent vaccine has the advantage of providing protection to 2 additional HPV genotypes of 6 and 11, which we responsible for causing benign anogenital warts and subsequent reduction of such genotype circulation in the community.

In settings where both HPV vaccines are marketed, the choice between the two should be based on the assessment of a number of factors, including the scale of the prevailing HPV problem (cervical cancer, other anogenital cancers, or anogenital warts); the population for whom the vaccine has been approved (girls aged 9 or 10 years through to 13 years, or older females, women, and/or males); delivery strategies; and data on vaccine efficacy against HPV-related diseases.The data available to decision-makers differ by the vaccine. Decision-makers should also consider unique product characteristics, such as price, supply and cold-chain requirements.

The reported safety and efficacy profiles of both vaccines are high. Except the reported cases of pain related adverse reactions among vaccinated groups, there are no serious adverse reactions reported in post licensure surveillance.

Factors to be considered in vaccine introduction

[1] What are the alternative options available?

There are two main public health interventions to prevent the HPV cervical cancer; screening and vaccination.

[a] Cervical cancer Screening:

HPV-induced changes in the cervical epithelium can be detected by cytology using a microscopic examination of exfoliated cells, which is also known as a Papanicolaou (Pap) test. Persistent HPV infection can be diagnosed by repeated tests for HPV DNA. Cytology or testing for HPV DNA, or both, are used for cervical cancer screening and diagnostic follow-up in many countries. In low-

resource settings that lack advanced health facilities, visual inspection of the cervix with acetic acid or Lugol's iodine is used to identify cervical lesions.

Pap smear screening programme is focused on early detection of cases and timely treatment. It is highly an effective intervention and many countries have implemented it as a part of routine cancer prevention strategy. It is recommended for female in age 21 - 65 groups and screening to be performed in every 3-5 year period.

Pap smear screening programme in Sri lanka is in place for the last two decades and all women at the age of 35 years (or above) are offered one time screening at the well women clinics conducted by Medical Officers of Health. This cohort is 1% of the country population and the programme has set a target of 80% coverage among this cohort. However, at present, only around 30% of target population is covered by the programme.

It is estimated by the national cancer control programme, around 1500 new cases of cervical cancer are in the country with 800 deaths. To prevent these deaths, it is estimated that one million women need to be screened annually, which is unrealistic with the present facilities/capacity available for national cervical cancer screening programme in the country. Therefore, the committee has strongly endorsed that the MoH needs to take all possible efforts to improve the capacity of the screening progamme, to make it more efficient in preventing cervical cancers in the country.

[b] Vaccination

The population impact of HPV vaccination programmes in preventing cervical cancer has been estimated for both vaccines using mathematical models that consider a prototype vaccine with VLPs of HPV-16 and HPV-18. Models predict that vaccination programmes for young adolescent females (defined as being roughly within the range of 10–13 years) will substantially reduce the incidence of cervical cancers associated with vaccine-related HPV types if coverage is high (>70%) and vaccine induced protection lasts for ≥10 years. Considerable reductions in incidence may also be expected for the less frequent cancers of the vagina, vulva, anus, and head and neck associated with HPV-16 and HPV-18. Depending on assumptions related to vaccination and screening programmes, vaccination could reduce the lifetime risk of cervical cancer by 35–80%.

Models estimate that the reduction in the incidence of cervical cancer and mortality will be greatest in low income and middle-income countries where there is no screening or only limited screening for cervical cancer. If vaccine uptake is highest in populations who are most likely to be screened later in life, reductions in cervical cancer attributed to vaccination may be less than expected because the diseases prevented by vaccination would otherwise have been detected and treated.

Since HPV vaccines are prophylactic, the largest impact of vaccination is expected to result from high coverage of young adolescent girls before first sexual exposure rather than from vaccinating

older females, because a smaller proportion of older females would be naive to vaccine related types before vaccination. Most models' predictions suggest that with either vaccine, male HPV vaccination will have a limited impact on the incidence of cervical cancer.

[2] What are the possible vaccine introduction strategies?

HPV vaccines are most efficacious in females who are naive to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The primary target population is likely to be girls within the age range of 10 to 13 years.

Programmes introduced to prevent cervical cancer should initially prioritize high coverage in the primary target population of young adolescent girls. Vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, and does not divert resources from vaccinating the primary target population or effective cervical cancer screening programmes, and if a significant proportion of the secondary target population is likely to be naive to vaccine-related HPV types.

HPV vaccination of males is not recommended because vaccination strategies that achieve high coverage (>70%) in the primary target population of young adolescent girls are expected to be more cost effective in reducing cervical cancer than including the vaccination of males.

The committee considered two vaccine introduction options in Sri Lanka; nationwide and phase-based. After careful review of past experiences with new vaccine introduction, it is recognized that nationwide introduction is more appropriate than phase-based to the country for following reasons; (i) phase based introduction is used, when there are programme implementation issues recognized, such as vaccine logistic issues, human resource issues, etc. However, with a strong NIP, such challenges in Sri Lanka are minimal and less (ii) Phase based introduction is also recommended when some technical aspects, such as schedule, coverage and, feasibility of target population are uncertain. For HPV vaccine introduction, these aspects are well clear with experiences of other countries and therefore, having demonstration /pilot projects to study such uncertainties are marginally useful than the nation wide introduction of HPV vaccine into the NIP (iii) Phase-based introduction will create communication issues, requiring justification for why only a selected group is being vaccinated, if vaccine is so important to prevent the disease. It may also mislead the public, those only areas where the vaccination is being introduced the target population is at higher risk of exposure than other areas in the country, which is a socially sensitive topic.

WHO recommends a two-dose schedule, if the vaccination started before the age of 14 years. Therefore, the committee identified that the girls in grade 7-8 in school would be the more appropriate target population for HPV vaccine introduction in Sri Lanka. To reach high coverage, it is necessary to combine HPV vaccination into the school medical inspection (SMI) programme. At present, all children in grade 7 are covered by SMI (with adult tetanus –diphtheria -aTd vaccination). Therefore, a strategy to link with grade 7 SMI is necessary and feasible in the country. Technically, both aTd and HPV (first dose) can be given simultaneously, but considering the acceptance and limiting HPV vaccination only for girls, HPV vaccination is recommended to be started after the SMI and aTd vaccination. It is necessary to start the first dose of HPV vaccination for all girls, when they are in Grade 7. The second dose could be given after 6 months from the first dose, while the girl is in grade 7 or 8 in the school. This strategy ensures that all girls will receive two doses of HPV vaccines before they complete the age of 14 years.

However, considering the limited global evidence of long term protectivity, and maintenance of protective antibody levels with the two dose schedule, the committee recommends to follow up with testing antibody levels 2-3 years after vaccination, and identified the possibility of changes in the decided schedule.

At present school health programme is mainly handled by the Medical Officers of Health (MOOH) and Public Health Inspectors (PHII). There are growing work loads among the MOH staff, due to many other priority health issues and therefore introduction of any additional public health intervention into the school health programme, needs to consider the fact of how to accommodate any additional intervention. The committee is of the opinion, that the Ministry of Health needs to strengthen the capacity of MOH staff, particularly the PHI cardres to support school health programme in the country.

[3] Sustainability

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination should be included in the national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitute a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

Based on the WHO guideline that compares incremental cost-effectiveness ratios with per capita gross domestic product (GDP), it was concluded that nationwide administration of HPV vaccine would be cost effective only in countries where GDP is high. Several models indicate that HPV vaccination in low-income and middle-income countries where quality screening is not widespread

may be cost effective if the cost per vaccinated girl (including 3 doses of vaccine and programmatic costs) is <US$ 10–25 – that is, substantially lower than current costs in high-income countries.

Cervical cancer is the second most frequent cancer among Sri Lankan women. There is well documented evidence to suggest that cervical cancer is aetiologically linked to Human Papilloma Virus (HPV) infection. The prevalence of vaccine preventable HPV in Sri Lanka is about 1.2%. While it is argued that the introduction of HPV vaccine to Sri Lanka would result in saving a significant amount of Disability Adjusted Life Years (DALY), a flipside argument exists that it may not be as cost effective as the current cervical cancer screening programme in Sri Lanka. However, to make the screening programme effective to reduce the burden (i.e. to avoid 900 cases/year), it requires around 300 million SLR (This estimate derived from published data, which indicates the minimum screening cost is around 310 SLR/person and therefore to be efficient, the programme requires 1 million women to screen per year). It is important to compare the total cost for each intervention, in terms of sustainability. The cost estimated for introduction of HPV vaccine into the NIP is around 130-150 million SLR annually.(The cost in the first year will be around 225 million SLR, as introduction of any new vaccine requires 6 months buffer stock in the first year). This cost will be applied only if UNICEF procurement channel is used and direct procurement may increase the cost in 2 to 3 folds.

The introduction of the HPV vaccine needs to be further supported with strong evidence informing the associated reduction of the burden of disease and a detailed cost effectiveness analysis. Therefore, the committee recommended that economic costing study to generate evidence on cost benefit of HPV vaccination in Sri Lanka is important for future planning and ensuring the vaccine funding.

Introduction of HPV vaccine should not undermine or divert funding from effective screening programmes for cervical cancer. HPV vaccination is a primary prevention tool and does not eliminate the need for screening later in life, since HPV types other than 16 and 18 cause up to 30% of all cases of cervical cancer. Opportunities to link the introduction of HPV vaccine to other programmes targeting young people should be sought (for example, through adolescent health services). However, vaccination should not be deferred in countries because at least 1 of these interventions cannot be implemented at the time when vaccination could be introduced.
Considering the requirement of full implementation of comprehensive cervical cancer prevention and control in the country, the committee identified the possibility of National HPV vaccination programme to be combined with more strengthened cervical cancer screening (Pap/HPV-DNA screening) at least in selected districts, to identify gaps to be improved.

[4] Communication

HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related diseases. This strategy should include education about reducing behaviours that increase the risk of acquiring HPV infection, and information about the diagnosis and treatment of precancerous lesions and cancer.

Educational messages and notification, approval, or consent of patients or parents should be tailored to local cultural contexts and the information needs of various audiences, including those who are targeted for vaccination, their parents or guardians, educators, community leaders and healthcare providers. Messages should emphasize that HPV vaccines do not cure cancer; they prevent some, but not all, HPV-related cancers; they are most effective when given before the onset of sexual activity; they require 2-3 doses; they are not recommended for pregnant females; and they will not prevent HIV infection, other sexually transmitted infections or pregnancy.

The committee endorsed that vaccinees should be advised to seek cervical cancer screening later in life. Because public knowledge about cervical cancer and its association with HPV is limited and therefore awareness about cervical cancer and HPV are recommended as a strategy for increasing vaccine acceptance.
Since, Sri Lanka will target female teenage at 12-13 years for HPV vaccination, it is necessary to have good communication and educational tools to justify why they have been identified for vaccination. Concerns of parents and other social groups over risk exposures of HPV infection need to be addressed scientifically and logically.
Maintaining a high coverage among teenage school based vaccination programme with a 2-dose schedule is a challenging task. This can be further complicated if any serious adverse event (which is extremely rare; HPV vaccine has evidence of a good safety profile) is being reported; even if it is not related to the vaccine or vaccination. Therefore, preparedness of a good risk communication package is necessary.

Recommendations:

1. Cervical screening is the current method to detect cervical cancer. However it is beset with many problems those intrinsic deficiencies as well as implementation problems. In addition with new diagnostic tests that are on the horizon, they could make screening much more acceptable and easier to implement

   Strengthening ongoing cancer screening programme, aiming prevention of HPV cancer is a high priority. It is essential to strengthen its capacity to reach its set target of screening 80% target population, enabling the programme to be cost effective and to save 1000 lives/year.

2. As a long term preventive strategy, introduction of school based, island wide, 2 dose scheduled HPV vaccination is a timely need.

   HPV vaccine appears a good technical fix that will circumvent many of these problems. However while the intrinsic issues in the vaccine exist (will not cover all HPV viruses) they are less than with cervical screening. As for implementation issues, the coverage would be the main problem. The recommendation for the vaccine is based on the current situation but there is potential for a major change to occur due to emerging technologies; this recommendation has to be kept under constant review.
   As the cost of the HPV vaccine is relatively high, if vaccine is being introduced into the NIP, vaccine procurement through the UNICEF channel could be considered as one possible strategy to reduce the cost.

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