CERVICAL CANCER VACCINE: GARDASIL® AND CERVARIX®

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EXECUTIVE SUMMARY

Introduction

Cervical cancer is one of the deadly cancers among woman all over the world. Most of the causes are linked to genital infection with human papillomavirus (HPVs). An HPV infection is a common, omnipresent sexually transmitted infection. There are more than 130 subtypes of HPV and about 70 subtypes infect human. Out of these, about 40 different genotypes of HPV can infect the ano-genital area in men and women. These have been classified into high-risk and low-risk genotypes indicating their level of association with cervical cancer.

In cervical cancer, conventional Papanicolaou smear (Pap smear) is remain the main screening form, as it has been proven to reduce the incidence by 43%. However, the sensitivity of Pap smear is varies from 30-87%. Instead of using the screening programme, vaccination is another alternative to prevent the disease, since this virus is the root cause of cervical cancer. Vaccination is more relevant in developing countries as comprehensive screening programme are not feasible due to limited resources.

This technology review was requested by Deputy Director, Health Technology Assessment Section, Ministry of Health following the issue raised by Senior Manager of National Consumer Complaints Centre on Gardasil®.

Objective/Aim

The objective of this technology review was to assess the safety, and efficacy of quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) and bivalent HPV-16/18 vaccine (Cervarix®) as Cervical Cancer Vaccine in teenage girls.

Results and conclusions

Efficacy/Effectiveness

There was good level of evidence to show that both Gardasil® (quadrivalent) and Cervarix® (bivalent) were efficacious to prevent cervical cancer in young women.

Safety

There was fair level of evidence to show that quadrivalent HPV vaccine (Gardasil®) and bivalent vaccine (Cervarix®) were safe, although deaths were reported but direct temporal relationship with the use of Gardasil® cannot be determined. Adverse events such as headache, fatigue, fever and joint pains were reported in the clinical trials in those who received these vaccines.

Cost-Effectiveness

There was good level of evidence to show that vaccination program using Gardasil® and Cervarix® for prevention of cervical cancer was cost-effective compared to screening

program alone. However, the quadrivalent vaccine (Gardasil®) was more cost-effective compared to bivalent vaccine (Cervarix®) due to its additional benefit in reducing genital warts.

Methods

Electronic databases were searched, included PubMed, Ovid Medline (R) from 1990-2006 (EBM Reviews – Cochcrane Databases of Systematic Reviews), Ovid Medline (R) from 1990-2006 (EBM Reviews – Cochcrane Databases of Controlled Trial), National Horizon Scanning, INAHTA and FDA website, for published reports. There was no limit in the search. Additional articles were identified from reviewing the bibliographies of retrieved articles.

CERVICAL CANCER VACCINE: GARDASIL® AND CERVARIX®

1. INTRODUCTION

Cervical cancer is one of deadly cancer among woman all over the world. Most of the causes are linked to genital infection with human papillomavirus (HPVs).[1] HPV infections is a common, omnipresent sexually transmitted infection.[2] There are more than 130 subtypes of HPV and about 70 subtypes infect human.[3] Out of these, about 40 different genotypes of HPV can infect the ano-genital area in men and women. These have been classified into high-risk and low-risk genotypes indicating their level of association with cervical cancer.[2,3]

Based on molecular biological and epidemiological studies, the genital HPV types are classified as follows:[3]

i)	High Risk	:	HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
ii)	Probable High Risk	:	HPV types 26, 53, 66, 68, 73, 82
iii)	Low Risk	:	HPV types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

High-risk HPV types are detectable in virtually all cases of cervical cancer. Apart from HPV infection, other risk factors are of significance to cervical cancer, including smoking and other life-style factors.[3]

Most of the HPV infections resolve spontaneously. However, only persistent infections will lead to precancerous lesions which can evolve into invasive cervical cancer.[1,2] The younger the age of the woman involves in sexual activity the higher is her risk to get HPV infection. The same goes if she has multiple sex partners or the male partners have multiple sex partners. The risk is higher if the male partners have wives or spouses or have had sexual relations with women who died of cervical cancer. Infection by HPV is very common however, not every woman who gets the virus develops dysplasia or invasive cancer, indicating that most of the infection is cleared spontaneously. Certain women progress to cancer because of the presence of co-factors or co-carcinogens which can act as precursor to transform infected cells to neoplastic form.[4]

Therefore, conventional Papanicolaou smear (Pap smear) remains the main screening form for this cancer as it has been proven to reduce the incidence by 43%. However, the sensitivity of Pap smear is variable from 30-87%. However, in countries limited by financial resources, it is not cost effective to screen for HPV in women younger than 30 years old.[4]

Nowadays, vaccination is become as one of alternative to prevent the disease. Vaccination is more relevant in developing countries as comprehensive screening programme is not feasible due to limited resources. However, development of the vaccine has been slowed by a number of problems related to the biology of HPV. HPV is difficult to be cultured in vitro. There is no ready source of live virus available for attenuated live vaccine like the polio vaccine. HPV infection has a very minimum blood phase; therefore, natural antibody against it does not develop. HPV infection remains in the epithelium, thus antibodies must traverse the basement membrane to reach the layers of the skin or mucosa to be effective in preventing infection. The infected patients do not produce significant immunoglobulin A (IgA) mucosal antibody. The immunity against this virus is through cellular immune response mainly by CD8, and CD4 cytotoxic T cells.[4]

This technology review was requested by Deputy Director, Health Technology Assessment Section, Ministry of Health following the issue raised by a Senior Manager of National Consumer Complaints Centre on Gardasil®.

2. OBEJCTIVE/AIM

The objective of this technology review was mainly to assess the safety, and efficacy of quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) and bivalent HPV-16/18 vaccine (Cervarix®) as Cervical Cancer Vaccine in teenage girls.

3. TECHNICAL FEATURES

Ministry of Health (MOH) of Malaysia has started the HPV vaccination programme since 2010. The only vaccine proposed by the ministry to be used in hospitals and clinics of MOH is bivalent type (Cervarix®) from GlaxoSmithKline (GSK) Biological manufacturer (was chosen based on a tender system) to prevent a cervical cancer caused by HPV type 16 and type 18. The other HPV cervical cancer vaccine is Gardasil®, the tetravalent or quadrivalent type which is also available in Malaysia especially in private practices (General Practitioners). Here are some technical features of both vaccines.

3.1 Gardasil: A Quadrivalent Cervical Cancer Vaccine

Gardasil® is a quadrivalent vaccine against certain types of human papillomavirus (HPV) developed by Merk.[2,3] It is a suspension for injections that contains purified protein or antigen for two types of high risk genotypes human papillomavirus (types 16 and 18) and two types of low risk genotypes (types 6 and 11). Instead of protecting against 70% of cervical cancer and some other HPV-related cancer forms in genital organ and anus, large proportion of venereal warts also will be prevented with this vaccine. Actually, venereal warts are very common but they are benign. This problem are caused by HPV type 6 and 8.[3]

The vaccine consisted of a mixture of four recombinant HPV type-specific viral like particles (VLPs) composed of the major capsid proteins (L1) of HPV types 6, 11, 16 and 18 produced in *Saccharomyces cerevisiae* (Figure 1). *Saccharomyces cerevisiae* is a species of budding yeast use in baking and brewing. This species is used to produce certain capsid protein including the HPV capsid proteins.[5] Each 0.5 ml dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. Each 0.5 ml dose of the vaccine also contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein per dose, and water for injection. The product does not contain a preservative or antibiotics.[3,6,7]

The Gardasil® is available in vials or prefilled syringes (Figure 2 and Figure 3). The vaccine is administered by intramuscular and most likely functions by stimulating the immune response more efficiently than a natural infection located superficially in the mucous membrane of the cervix uteri.[3]

Figure 1: ***Saccharomyces cerevisiae***

Figure 2: Gardasil® in Vials and Prefilled Syringes By Merk

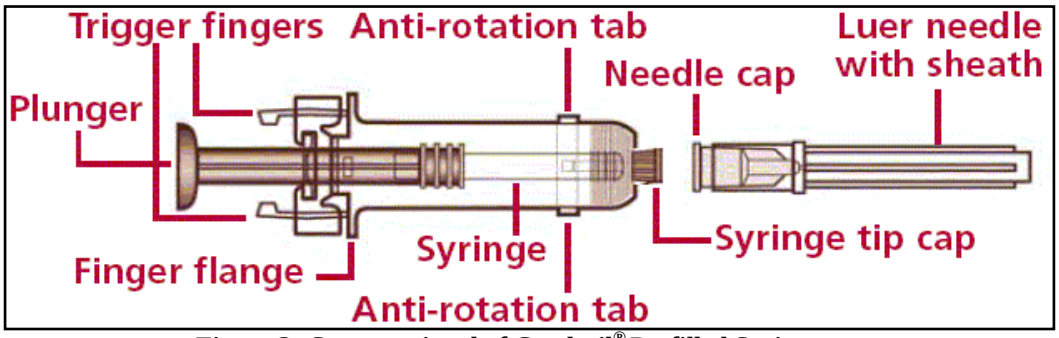

Figure 3: Cross sectional of Gardasil® Prefilled Syringes

3.2 Cervarix®: A Bivalent Cervical Cancer Vaccine

Cervarix® is a prophylactic human papillomavirus (HPV) type 16 and 18 vaccine which is developed specifically to prevent cervical cancer caused by HPV type 16 and 18. The vaccine antigens are HPV-16 and HPV-18 L1 virus-like particles (VLPs) made from baculovirus expression vector system (BEVS).[8] The BEVS is one of the most powerful and versatile eukaryotic expression systems available. The BEVS is a helper-independent viral system which has been used to express heterologous genes from many different sources, including fungi, plants, bacteria and viruses, in insect cells. The Baculovirus strains (figure 4) are highly species-specific. Its genome is replicated and transcribed in the nuclei of host cell and is packaged into rod-shaped nucleocapsids. Since the size of these nucleocapsids is flexible, recombinant Baculovirus particles can accommodate large amounts of foreign DNA including antigens of HPV-16 and HPV -18.[9]

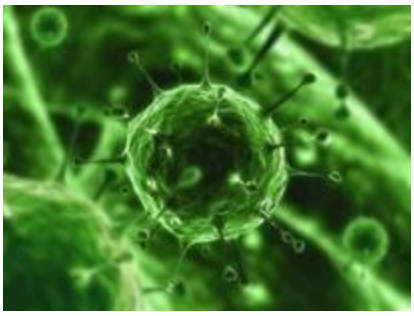

Figure 4: Baculovirus

Figure 5: Cervarix by GlaxoSmithKline (GSK)

Each injection contains: 20µg HPV 16 VLP and 20µg HPV 18 VLP. The adjuvant in the vaccine is 500µg aluminum hydroxide with 50µg monophosphoryl lipid A (ASO4).[3]

4. METHODOLOGY

4.1. Searching

Electronic databases were searched, included PubMed, 1990-2011 EBM Reviews – Cochcrane Databases of Systematic Reviews, EBM Reviews - Health Technology Assessment, and EBM Reviews – Cochcrane Databases of Controlled Trial, National Horizon Scanning, INAHTA, ARSENIP-S, CADTH and FDA website, for published reports. There was no limit in the search. Additional articles were identified from reviewing the bibliographies of retrieved articles.

The search strategy used the terms which were either used singly or in various combinations; 'vaccine AND cervical cancer', 'Gardasil®', 'Cervarix®','cervical cancer', 'tetravalent AND cervical cancer' and 'bivalent AND cervical cancer'.

4.2. Selection

All published articles (systematic review, controlled trials) within 1990-2011 which were related to the efficacy or effectiveness and safety of Cervical Cancer Vaccine: Gardasil® and Cervarix® were included. Only studies on human were included in this review.

5. RESULTS AND DISCUSSION

Two health technology assessments (HTA) in year of 2007 were included in this technology reviews. Those reports were produced by Belgian Health Care Knowledge Centre and National Board of Health, Danish Centre for Health Technology Assessment. Two articles published in 2007 and 2009 were from results of phase III clinical trials on Gardasil® and 3 randomized control trials conducted in 2011 on Cervarix® were included in this review.

5.1 Efficacy/Effectiveness of Cervical Cancer Vaccines

5.1.1 Gardasil®

Health technology assessment (HTA) by Thiry N. *et al*. (2007) reported the efficacy of Gardasil® mainly from four placebo-controlled, double blind, randomized phase II and III trials, so-called protocols 005 (phase II trial), 007 (dose-ranging phase II trial designed to select one of three formulations of Gardasil® for use in phase III studies), 013 (phase III) and 015 (phase III). The studies included 20,541 women in the age group of 16-26 years old covering Europe, United State and Brazil. However, all the trials were industry-funded. The other sources included were technical documents prepared by European Agency for the Evaluation of Medicinal Products (EMEA) and United State Food and Drug Administration (USFDA) for licensing purposes which contain data from some numbers of trials as well as pooled results from several other trials. The systematic review found that, Gardasil® could reduce the rate of HPV 16 or 18 related high grade dysplasia cervical intraepithelial neoplasia (CIN 2+) by 99% (95% CI, 93-100%) and reduce the rate of all high grade dysplasia cervical associated with any type of HPV by 46% (95% CI, 24-62%). Additional to that, the vaccine also reduced the rate of high grade vulval and vaginal dysplasia by 81% (95% CI, 51-94%). On the other hand, in subjects that were infected with HPV-specific vaccine strains, the efficacy of the Gardasil® to prevent CIN 2+ lesions was 18%. The percentage was regardless of HPV types as the subjects enrolled in the Gardasil RCTs were as follows; 27% were positive for at least one of the four HPV vaccine types at baseline and 21% for either HPV 16 and / or 18.[2, Level 1]

Another HTA (2007) by Kristensen F.B also reported about the HPV vaccination. The assessment focused more on the cervical cancer vaccination programme as a whole instead of single vaccine. The main objectives of the HTA were to investigate the consequences of introducing the HPV vaccination in Denmark including the appropriateness of the vaccine, public acceptance especially parents' towards the programme, ethical issues, how to organize the programme as well as the economic evaluation, safety and the efficacy of the vaccines. From the numbers of studies included in this review, the authors stated that, the quadrivalent HPV vaccine type 6, 11, 16 and 18 (Gardasil) had potential to protect against approximately 70% of cervical cancer cases and some other HPV-

related cancer forms in genital organs and anus. They also found that the vaccine was able to prevent venereal warts.[3, Level 1]

Joura E.A *et al*. (2007) analysed data from phase III studies after 36 months of follow up. The aim of the study was to combine analysis of three randomised clinical trials to assess the effect of a prophylactic quadrivalent HPV vaccine on the incidence of cervical cancer. After 36 months of the trials, the vaccine was 100% effective (95% CI, 72-100%) against high-grade vulval intraepithelial neoplasia (VIN2-3) or vaginal intraepithelial neoplasia (VaIN2-3) associated with HPV types 16 or 18 in naive women (naive to HPV 16 or HPV 18). Meanwhile in intention-to-treat population (could have been infected with HPV 16 or HPV 18) the vaccine was 71% effective (95% CI, 37-88%) against VIN2-3 or VaIN2-3 associated with HPV types 16 or 18. Another finding was 49% (95% CI, 18-69%) effective against all VIN2-3 or VaIN2-3 irrespective whether or not HPV DNA was detected in the lesion. The author concluded that prophylactic administration of quadrivalent HPV vaccine was effective in preventing high-grade vulval and vaginal lesions associated with HPV 16 and HPV 18 infection in women who were naive to these types before vaccination.[7]

Olsson S *et al*. (2009) reporting the phase III trials after 40 months average of follow up. The trials had demonstrated that a prophylactic quadrivalent (HPV types 6, 11, 16, 18) HPV L1 virus like-particle (VLP) vaccine (Gardasil®) was highly effective in preventing HPV 6, 11, 16, or 18 related cervical, vaginal and vulvar neoplasias and persistent infection in women. At the end of follow up periods, seven subjects in the placebo group developed cervical disease and eight subjects developed external genital disease related to a vaccine HPV type they had previously infected. No vaccinated subjects developed cervical disease due to an HPV type with which they had previously been infected. Vaccine efficacy against HPV 6/11/16/18-related cervical intraepithelial neoplasia (CIN 1+) or worse in subjects seropositive and DNA negative to the relevant HPV type at baseline was 100% (95% CI: 28.7, 100). Efficacy against the incidence of HPV 6, 11, 16 and 18-related external genital lesions in subjects seropositive and DNA negative to the relevant HPV type at baseline was also 100% (95% CI: 39.5, 100).[10, Level II-1]

5.1.2 Cervarix®

Thiry N. *et al*. (2007) stated that, publicly available data on efficacy and safety of Cervarix were still insufficient to draw definitive conclusions, as only either phase II or interim analyses of a phase III RCT were published, and since data submitted to the regulatory authorities were not entirely available to the authors. Preliminary data show a vaccine efficacy on CIN 2+ lesions related to vaccine strains that was similar to Gardasil. There were no data on genital condilomas since the HPV strains 6 and 11 were not included in this vaccine. However, follow-up was short and the authors could not find any data of vaccine efficacy in reducing overall CIN 2+ regardless of HPV strain involved (apart from phase II trial data).[2, Level 1]

However, Zhu FC *et al*. (2011) conducted an open-labelled trial (phase-1) sponsored by GlaxoSmithKline (GSK) Biologicals in a single centre in Jiangsu Province, China to assess the safety, tolerability and immunogenicity of HPV-16/18 AS04-adjuvanated vaccine Cervarix® among Chinese. Thirty healthy females aged 15 to 45 years (Chinese origin and reside in China) were enrolled into the study in December 2007. Those subjects were given 3 doses of Cervarix® in Months 0, 1 and 6 with four visits were planned per subject, scheduled in Months 0, 1, 6 and 7. The primary endpoints of the study were safety and reactogenicity. Out of the 29 subjects who completed the study, 24 participants were negative for both anti-HPV-16 and HPV-18 antibodies at baseline, 4 were negative for anti HPV-16 but positive for anti HPV-18, and 1 was positive for anti HPV-16 and negative for anti HPV-18. Pre-vaccination geometric mean titers (GMT) were 4.1 ELISA units per millilitre (EU/mL) (95% CI, 3.9 to 4.4 EU/mL) for anti HPV-16 and 4.4 EU/mL (95% CI, 3.4 to 4.5 EU/mL) for anti HPV-18. In Month 7, 100% seroconversion and seropositivity were observed for both anti HPV-16 and HPV-18. GMT for initially seronegative subjects was 6230.5 EU/mL (95% CI, 4755.1 to 8163.7 EU/mL) for anti HPV-16 and 2411.1 EU/mL (95% CI, 1734.0 to 3352.7 EU/mL) for anti HPV-18. The authors concluded that the HPV-16/18 AS04-adjuvanated vaccine (Cervarix®) was well tolerated and immunogenic in Chinese females age 15 to 45 years. [11, Level II-1]

Schwarz TF. *et al*. (2011) conducted an extension study conducted in Germany and Poland from July 2008 to February 2009 as an open-label, age-stratified, multicentre, follow-up study design to evaluate the safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to Month 48 in women vaccinated at age of 15-55 years. The study was funded by GSK Biologicals. The study involved 667 women enrolled in the primary vaccination study (from October 2004 to July 2005 in 6 centres in Germany and Poland). Each participant should receive 3 doses of HPV-16/18 vaccination at 0, 1 and 6 months. The HPV-16 and HPV-18 antibody titers were measure by ELISA using type-specific viral-like particles (VLPs) as coating antigens. Seropositivity was defined as an antibody titer greater than or equal to 8 EL.U/mL for HPV-16 and 7 EL.U/mL for HPV-18. After the study period, all subjects have seroconverted for anti HPV-16 and anti HPV-18 antibodies at Month 7. At Month 48, all subjects were still seropositive for anti HPV-16 antibodies and all but one subject in the 46-55 years age group (99.4%) remained seropositive for anti HPV-18 antibodies. Geometric mean titers (GMTs) of anti HPV-16/18 antibodies peaked at Month 7, then gradually declines in all age groups. However, between Months 36 and 48 the antibody level was decrease and from the antibody response curves it shows that the graph was started to plateau over the time period. At Month 48, GMTs for anti HPV-16 antibodies in initially seronegative subjects were 1382.7 ELISA units (EL.U)/ml in the 15–25 years age group, 524.2 EL.U/ml in the 26–45 years age group, and 324.0 EL.U/ml in the 46–55 years age group. GMTs for anti-HPV-18 antibodies at Month 48 were 475.5 El.U/ml in 15-25 years age group, 189.0 El.U/ml in 26-45 years age group and 122.9 EL.U/ml 46-55 years age group.[12, Level II-1]

Kreimer AR. *et al* (2011) evaluated the vaccine efficacy of fewer than three doses of the HPV 16/18 vaccine Cervarix® in Vaccine Trial conducted in Costa Rica. The trial involved 7466 women who were enrolled in June 2004 and December 2005. Those were healthy 18-25 years women who resided in the regions of Guanacaste and Puntarenas Costa Rica. The participants were randomly assigned in a double-blinded to receive either Cervarix® or a control (hepatitis A vaccine) and were administered at 0, 1 and 6 months. At the 6 Month of vaccination visit, sexually experienced women self-collected a cervicovaginal exfoliated cell specimen for HPV DNA testing. Vaccine efficacy was evaluated in each dosage groups by determination via the HPV DNA testing of the number of newly detected HPV 16 or HPV 18 infections that persisted at least 1 year. No differences in serologic status at enrolment can be observed among women who received 3 doses of Cervarix®. Meanwhile, women in control group was more likely to have been HPV 16 and/or HPV 18 DNA positive at enrolment than vaccinated women (8.9% versus 7.5%, P = 0.05). In the control group, the attack rated of incident HPV 16 and HPV 18 infections that persisted for 1 year were similar among control women in 3 doses group (4.4%), 2 doses group (4.5%) and 1 dose group (5.3%) which was indicated that they were similar risk for acquiring HPV infections regardless of the number of doses received. For 3 dose against newly detected HPV 16 or HPV 18 that persisted at least 1 year was 80.9% (95% CI = 71.7% to 87.7%); 25 events in HPV groups and 133 events in control group. Then, for 2 doses against newly detected HPV 16 or HPV 18 that persisted at least 1 year was 84.1% (95% CI = 50.2% to 96.3%); 3 events in HPV group and 17 events in control group. One dose against newly detected HPV 16 or HPV 18 that persisted at least 1 year was 100% (95% CI = 66.5% to 100%); 0 event in HPV group and 10 events in control group. From the findings, it was showed that there was no statistically significant trend for increasing vaccine efficacy (VE) with fewer doses was observed (P trend = 0.21) and the VE results were similar for 6 month persistent HPV 16 and/or HPV 18 infection endpoint.[13, Level 1]

5.2 Safety Of Cervical Cancer Vaccines

5.2.1 Gardasil®

Gardasil® is a quadrivalent Human papillomavirus (HPV) vaccine produced by Merck. This vaccine did receive approval by United States Food and Drug Administration (USFDA) for sale and marketing to girls and women ages 9 to 26 years old on 8th July 2006. Later the Centre for Disease Control (CDC) Advisory Committe on Immunizations Practice (ACIP) recommended routine vaccination of females aged 11 to 26 years with 3 doses of Gardasil® on a schedule of 0, 2 and 6 months.[2,14]

Vaccine and Related Biological Products Advisory Committee of United States Food and Drug Administration (VRBPAC) (2006) reported that, serious adverse events (SAEs) or deaths between Gardasil® groups and placebo groups in the clinical trials were similar in frequencies. Eleven deaths in the subjects who

received Gardasil® were due to different problems such as traumatic injuries, drug overdose, pancreatic cancer, deep vein thrombosis, pneumonia and sepsis. Meanwhile, seven deaths reported in the placebo groups were due to traumatic injuries, suicide, complications of labour or pulmonary embolism. Most of the deaths occurred in the months or years after the third vaccination. Thus, the VRBPAC summarized that those adverse events and the deaths were not having temporal association with the administration of the vaccine (Gardasil®) under study.[15]

According to the Health Technology Assessment 2007 by Kristensen F.B, during the placebo-controlled, double blind, randomized phase II and III trials, a few numbers of adverse events regarding the vaccine were reported. During phase II study, 83% of the Gardasil®-vaccinated subjects complained of having pain, swelling and irritation at site of injection while 73% occurred in the placebo-injected subjects. Both groups also reported several numbers of systemic adverse reactions; the reactions included light fever, headache and nausea. However, high grade fever (above 38.9ºC) was also reported in both groups (1.5% of the subjects in the vaccine group and 1.1% in the placebo group). Four cases of bronchospasms, gastroenteritis, hypertension and joint pain also occurred in the vaccine group. Two serious adverse events were also found in the placebo group; which were hypersensitivity and chills with fever and headache.[3, Level 1]

In 2008, the European Medicines Agency (EMEA) responded to the death cases which were believed to be related to Gardasil®. After investigations, the agency found that the actual cause of death could not be ascertained. Thus, no causal relationship had been established between the deaths of the young women and the administration of Gardasil®. Because of that, on the basis of the currently available evidence at that time, the EMEA's Committee for Medicinal Products for Human Use (CHMP) stated that the benefits of Gardasil® continue to outweigh its risks and no change to the product information was necessary. However, the EMEA will continue to closely monitor the safety of Gardasil® and will take appropriate actions for any incidence for the benefit-risk profile of the vaccine.[5]

Tarsell E. and Garret J. (2010) conducted survey on adverse events following Gardasil® administration in United States. Since June 2006 until December 2008, Vaccine Adverse Event Reporting System (VAERS) received 12,424 reports of AEFIs, including 32 deaths. The survey involved 39 voluntarily respondents (11 to 26 years old) who experienced Adverse Events Following Injections (AEFIs) following Gardasil® injections. Those respondents were self-selected to complete an on-line National Vaccine Information Centre (NVIC) questionnaire. The questionnaires consists of matching lists of 32 symptoms in each of four conditions; *Pre-Injection* (baseline for measuring change), *Injection 1*, *Injection 2*, and *Injection 3*. All respondents were asked to check any symptoms that existed prior to administration of Gardasil® and after the injections. According to the survey, there was two to four fold increases in occurrence, type and severity of

symptoms with additional exposure to the vaccine in all respondents. The adverse events included chronic fatigue and headache or dizziness which was persistent over time. The other concurrent symptoms were 60% to 70% of numbness, muscle pain, nausea and muscle weakness, more than 50% of joint pain, chest pain, skin disorders and concentration problems, 40% menstrual problems, 33% post-vaccine heart disorders and 13% to 20% seizures. The onset of the symptoms was mostly within 30 days after the administration of the vaccine. Six deaths were also reported where the cause of 5 deaths was undetermined and the other one was waiting for the autopsy. Five of the six deaths occurred after the third injection. However, direct relation between Gardasil® and the death incidence was not clear as the study did not focus on confounding factors because some of respondents were on other medications at the time of injections. However, to completely ignore the causal effects between Gardasil® and the death as well as the adverse event was not reasonable. Moreover, the survey was done on a small number of respondents which also reflected the selection bias in those who only experienced serious adverse events responded.[14, Level III]

5.2.2 Cervarix®

Kristensen F.B *et al*. (2007) stated in their Health Technology Assessment report, local adverse reactions at the injection site (redness, swelling and pain) were reported in 94% who received the Cervarix vaccine and in 88% who received placebo. Systemic adverse reactions, including headache, gastrointestinal symptoms and fatigue, were reported comparably for the vaccine and the placebo groups (86%). Most adverse reactions were reported as being of mild or moderate intensity. 16.6% of the recipients of vaccine and 13.6% of the recipients of placebo developed a temperature above 37.5ºC. There were no vaccine or procedure related to death.[3]

In the open-labelled trial (phase-1) conducted by Zhu FC *et al*. (2011), they also looked at the safety of Cervarix® immunization. For that, each 30 participants involved were provided with diary cards to record any occurrence of solicited local and systemic symptoms within 7 days and unsolicited events within 30 days following each vaccination. Immunogenicity against HPV 16 and HPV 18 was analyzed on the according-to-protocol cohort. Descriptive statistics were applied to analyze safety, reactogenicity and immunogenicity data with 95% CI estimated when appropriate. At the end of the study, 26 participants (86.7%) reported solicited local symptoms [pain at injection site, redness and welling] and 13 participants (43.3%) reported solicited systemic symptoms [fatigue, headache and myalgia] within 7 days after vaccination. All the solicited local symptoms were considered as causally related to vaccination while the incidences of vaccine-related solicited general symptoms were low. Then, within 30 days after vaccination, 4 unsolicited adverse events (aphthous stomatitis, chest discomfort, injection site hematoma, and upper respiratory infection) were reported by 4 subjects. The injection site hematoma was assessed as causally related to the vaccination. Two medically significant adverse events including one serious adverse event were reported during the entire study period; chest discomfort in

one subject (required a physician visit); left breast cancer in another subject who required hospitalization and was withdrew from the study. However, both were assessed as unrelated to the vaccination.[11]

In the extension study conducted by Schwarz TF *et al* (2011) in Germany and Poland from July 2008 to February 2009 also evaluated the safety of HPV-16/18 AS04-adjuvanted vaccine. According to the authors, the vaccine had a clinically acceptable safety profile in all age groups through 48 months after administration of the first vaccine dose. A total of 139 medically significant adverse events (AEs) were reported by 96 subjects. The percentage of subjects reporting medically significant AEs was similar in all age groups. The most frequently reported medically significant AEs were bronchitis which was reported by 9 subjects (3 in each age group), hypertension which was reported by 8 subjects (3 in the 26–45 years age group and 5 in the 46–55 years age group), and depression which was reported by 6 subjects (1 in the 15–25 years age group, 2 in the 26–45 years age group and 3 in the 46–55 years age group). A total of 29 serious adverse events (SAEs) were reported by 25 subjects. Only 1 SAE was considered by the investigator as possibly related to the vaccination: optic neuritis in 1 subject in the 26-45 years age group, which developed in left eye 9 days after vaccine dose.[12]

5.2.3 Safety Data from National Centre of Adverse Drug Reaction Monitoring, National Pharmaceutical Control Bureau (NPCB)

National Pharmaceutical Control Bureau (NPCB) of Ministry of Health (MOH), Malaysia has collecting adverse effects of HPV vaccine through MADRAC reporting system. The bureau stated that both vaccines demonstrated a favourable safety profile. Majority of the reactions observed in clinical trials and post-marketing reports were generally of mild to moderate severity and not long lasting. The common adverse events observed after administration of vaccine as documented in both product package inserts are:[16]

a) Application site disorders : Injection site pain, injection site redness (erythema), and injection site swelling
b) General disorders : Fever (pyrexia)
c) Nervous system disorders : Headache, Dizziness
d) Gastrointestinal disorders : Nausea, Vomiting
e) Musculoskeletal disorders : Myalgia
f) Skin disorders : Itching, Rash

The following data are information provided by NPCB based on the reports received on HPV vaccines (Gardasil® and Cervarix®) all over Malaysia. The data was divided either adverse effects of Gardasil® or Cervarix®.

A total of 849 cases and 1,758 Adverse Effects Following Immunisation (AEFIs) regarding HPV vaccines had been received by the MADRAC till date (March 2011. Out of the 849 cases, 796 reports were on Cervarix® and 53 reports on Gardasil®.

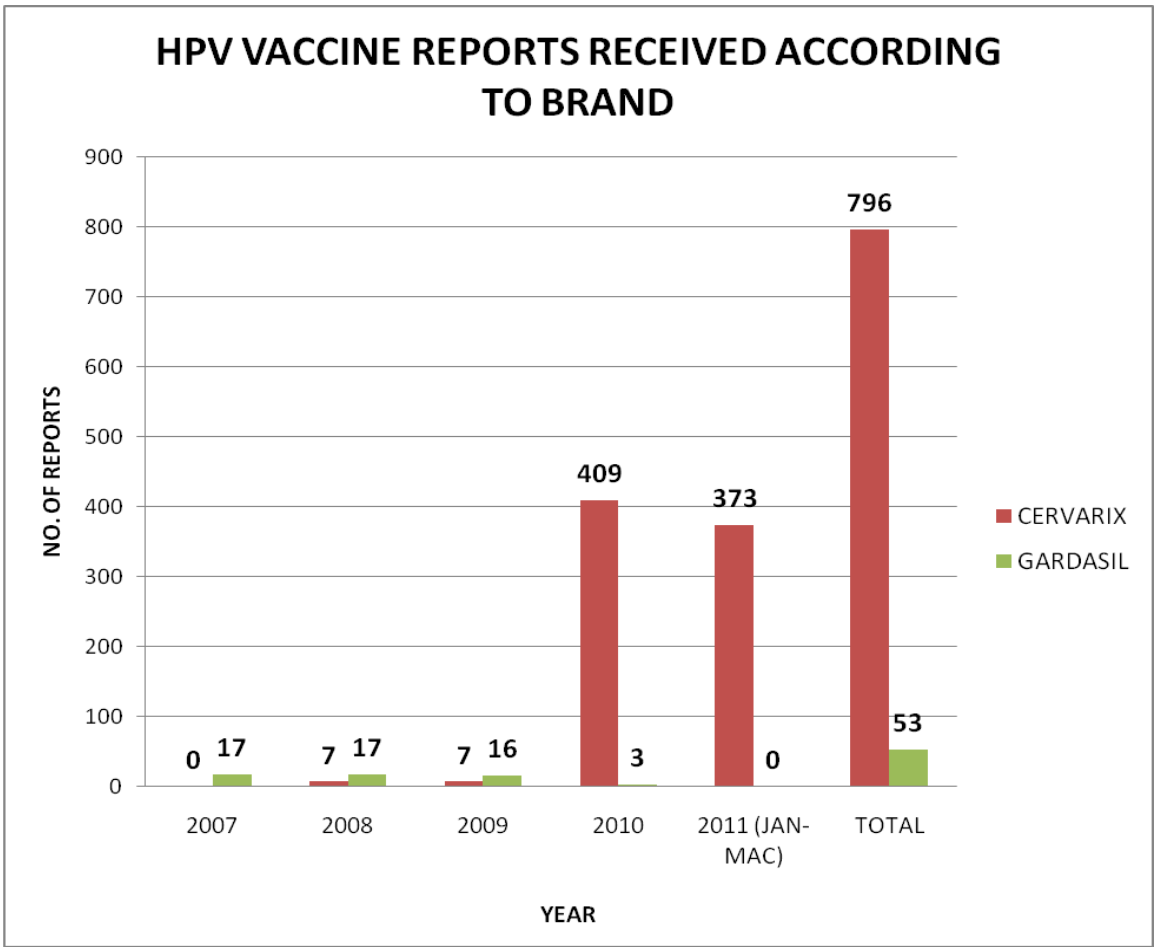

Figure 6: Number of ADRs Reports of HPV Vaccine Since 2007 to 2011

From the above result, Cervarix® received the highest AEFIs compared to the Gardasil®. The committee stated that the apparent difference was due to several reasons. The reasons were the use of a simplified form to ease reporting of AEFI including mild adverse event and the low number of reports from general practitioners in the private sector especially for Gardasil®.

5.3. COST- EFFECTIVENESS

One economic evaluation was reported on quadrivalent vaccine (Gardasil®) in the Health Technology Assessment (HTA) 2007 by Kristensen FB. The analysis based on a dynamic model in which the main result was the introduction of a quadrivalent vaccine HPV vaccine (type 6, 11, 16 and 18) in Denmark. The estimated cost-effect ratio of $4,666 per quality adjusted life year (QALY) when compared with screening alone and when only 12-year old girls were offered vaccination concurrent with catch-up vaccination of 12-24 years old girls. The authors also included economic analysis on annual vaccination programme,

disregarded type of vaccine given. If annual vaccination of 12 year-old girls were introduced with a vaccination cover of 70% without catch-up programme, a cost-effect ratio of approximately DKR85,000 (15,500USD or 11,400Euro) was estimated per gained year of life excluding indirect costs. Catch-up programme meant that when the programme was implemented, a number of age groups above the vaccination age will be offered the vaccine for a given period. Catch-up programme for 13-15 years age group involves relatively large increase in life benefit while the cost-effectiveness ratio will only increase from approximately DKR 85,000 (15,500USD or 11,400Euro) per gained year of life to approximately DKR89,000 (16,200USD or 11,900Euro) per gained year of life [3, Level 1]

Another economic analysis reported in another HTA conducted by Thiry N. *et. al* 2007 were also analyzed the HPV vaccination programme as a whole. The authors stated that HPV vaccination programme of 12 years old girls could be cost-effective compared to current practices (screening and Pap smear). It was based on few analyses from different countries. United States had calculated that incremental cost-effectiveness ratios (ICERs) in dynamic models were lower and range from €2,600 to €14,200 per QALY gained compared to the static models (ICERs range from €22,200 to €23,300 per QALY). Norway stated that the ICER was €39,400 per QALY gained and Danish study only reported on costs per life year gained was €8,700. [2, Level 1]

Lee VJ *et al*. (2011) was conducted cost analysis study on different human papillomavirus vaccine in Singapore. The study was to compare the cost-effectiveness among the 2 vaccines available there; a bivalent vaccine against HPV 16/18 and a quadrivalent vaccine against 6/11/16/18. This study was funded by GlaxoSmithKlien Biologicals. In order to compare between the vaccines, the authors assumed that the bivalent vaccine has higher efficacy against other non-16/18 high risk HPV types compared with the quadrivalent vaccine. For analyses, the authors performed cost-benefit-analysis (CBA) using the cost per life-year saved and cost-effectiveness analyse (CEA) and cost-utility analyse (CUA). The ICER would be acceptable if it is below the per-capita gross domestic product (GDP) for the population. The GDP for Singapore in 2008 was S$53,192. The authors used base-case-results of estimated cases; for bivalent vaccine the range of protection for non-16/18 oncogenic HPC types were between 53.0% and 68.2% and for quadrivalent vaccine the protection for non-16/18 oncogenic HPV types are 32.5% with overall effectiveness 75% and 90% protection against HPV-types that cause genital warts. The authors also assumed that proportion of individuals protected following immunization was 100%, vaccine duration was life-long, effectiveness of both vaccines against HPV types 16/18 were similar at 95%, assumes the prices for both vaccines were equivalent and included all the vaccination costs, assumed that the natural disease history was unaltered and assumes that all girls based on the coverage rate would receive the full vaccine course and be immunized after 1 year. At the end of the analysis, the authors found that bivalent vaccine having advantage of S$1.24million over the quadrivalent vaccine and the incremental saving for bivalent vaccine was S$9.47million compared to S$8.23 million for quadrivalent vaccine. Then, for

cost-per-life year saved by comparing with no vaccine, bivalent vaccine was S$12,827 and quadrivalent vaccine was S$12,866. According to ICER, bivalent vaccine saved more lives for the cost compared to quadrivalent vaccine with S$12,488. Meanwhile, the cost per QALY for the quadrivalent vaccine saved S$9,071 compared to no vaccine, while the costs per QALY for the bivalent vaccine save S$10,932 compared to no vaccine. However, quadrivalent vaccine was better compared to bivalent vaccine due to the effect of reduction in genital warts.[17]

6. CONCLUSION

The above review documented the following:-

Efficacy/Effectiveness

There was good level of evidence to show that both Gardasil® (quadrivalent) and Cervarix® (bivalent) were efficacious to prevent cervical cancer in young women.

Safety

There was fair level of evidence to show that quadrivalent HPV vaccine (Gardasil®) and bivalent vaccine (Cervarix®) were safe, although deaths were reported but direct temporal relationship with the use of Gardasil® cannot be determined. Adverse events such as headache, fatigue, fever, and joint pains were reported in the clinical trials in those who received these vaccines.

Cost-Effectiveness

There was good level of evidence to show that vaccination program using Gardasil® and Cervarix® for prevention of cervical cancer was cost-effective compared to screening program alone. However, the quadrivalent vaccine (Gardasil®) was more cost-effective compared to bivalent vaccine (Cervarix®) due to its additional benefit in reducing genital warts.

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8. APPENDIX

8.1 Appendix 1

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

SUMMARY ON HPV VACCINES (1 AUGUST 2011): REPORT FROM NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB)

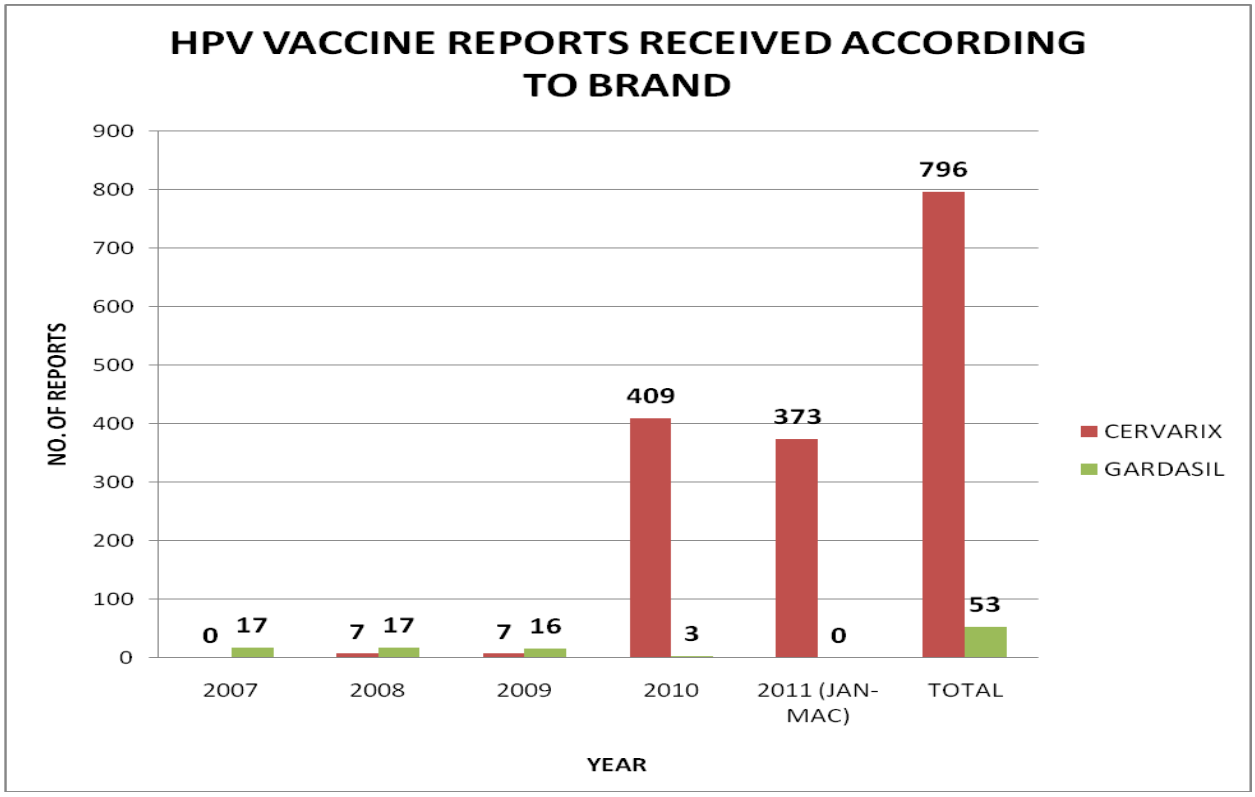

Figure 1: Number of ADRs Reports of HPV Vaccine Since 2007 to 2011

No	Adverse Event	Total*	Percentage** (%)
1	Injection Site Pain	266	15.13
2	Headache	227	12.91
3	Nausea	181	10.30
4	Injection Site Swelling/Erythema	170	9.67
5	Dizziness	153	8.70
6	Vomiting	135	7.68
7	Fever	102	5.80
8	Weakness Generalized	63	3.58
9	Limb Weakness	45	2.56
10	Giddiness	34	1.93
Total		**1376**	**78.26**

Table 1: Ten most Common Adverse Effects Following Immunization

*Total indicates the total events reported from 2007 – March 2011

**Percentage is calculated based on total number of events reported until March 2011 i.e. 1758 events

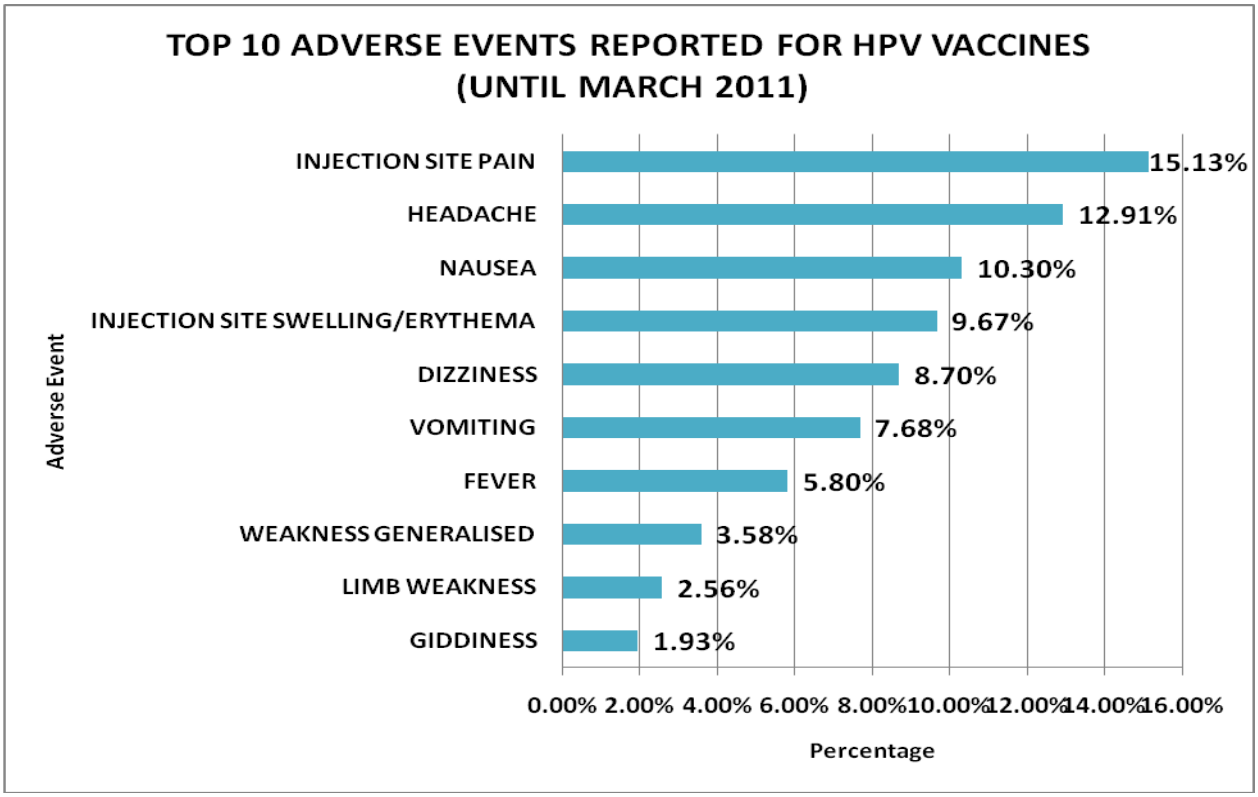

Figure 2: Ten Most Adverse Events Reported for HPV Vaccines

NO	SYSTEM ORGAN CLASS	TOTAL	PERCENTAGE (%)
1	Central & Peripheral Nervous System Disorders	453	25.8
2	Application Site Disorders	491	27.9
3	Gastro-Intestinal System Disorders	329	18.7
4	Body As A Whole - General Disorders	212	12.1
5	Musculo-Skeletal System Disorders	113	6.4
6	Others	160	9.1
TOTAL		**1758**	**100**

Table 2: Five Most Organ Classes with Most AEFIs Report

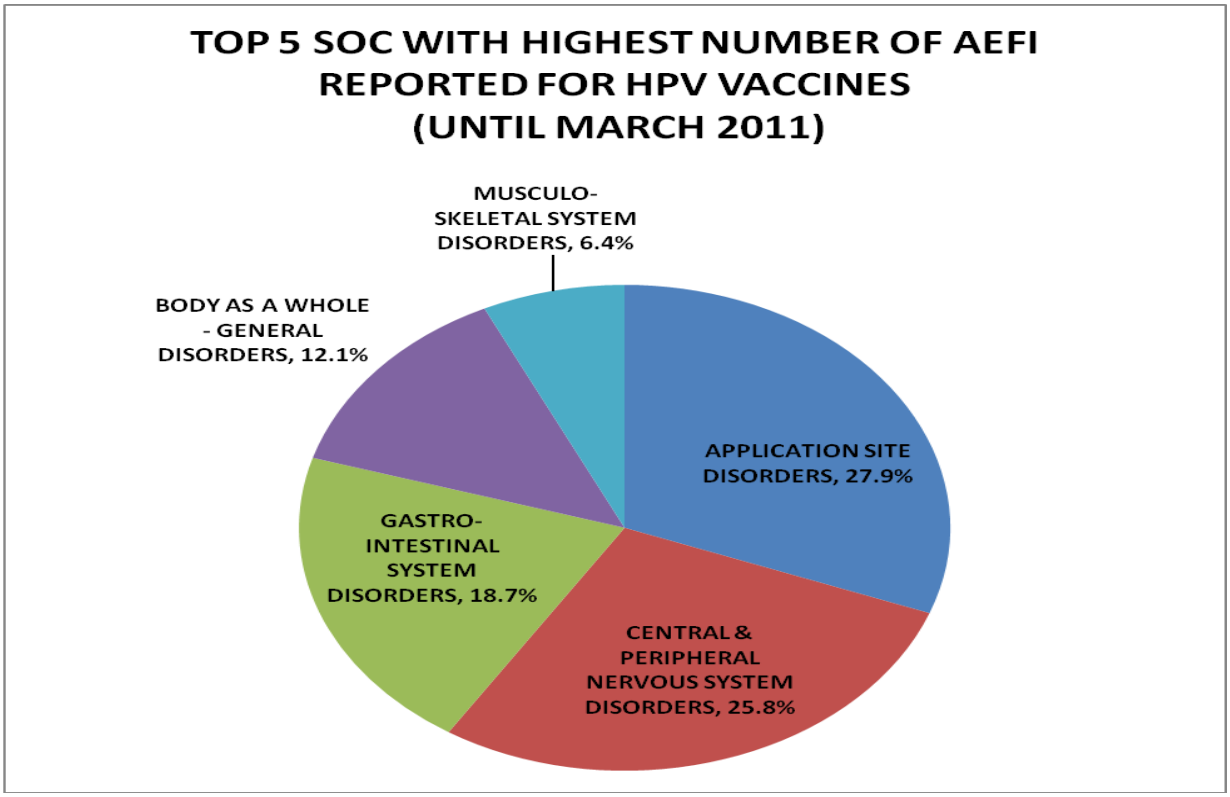

Figure 3: Five Most Organ Classess Reported for AEFIs

GARDASIL	TOTAL	CERVARIX	TOTAL
Injection Site Pain	9	Injection Site Pain	260
Fever	5	Headache	228
Syncope	5	Nausea	181
Pruritus	3	Dizziness	153
Rash	3	Injection Site Swelling	134
Sweating Increased	3	Vomiting	133
Injection Site Swelling	3	Fever	91
Pyrexia	3	Weakness Generalised	62
Giddiness	3	Limb Weakness	45
Hypoaesthesia	3	Injection Site Erythema	34
Vomiting	3	Body Aching	33

Table 3: Comparison of Common ADRs Report Between Gardasil® and Cervarix®

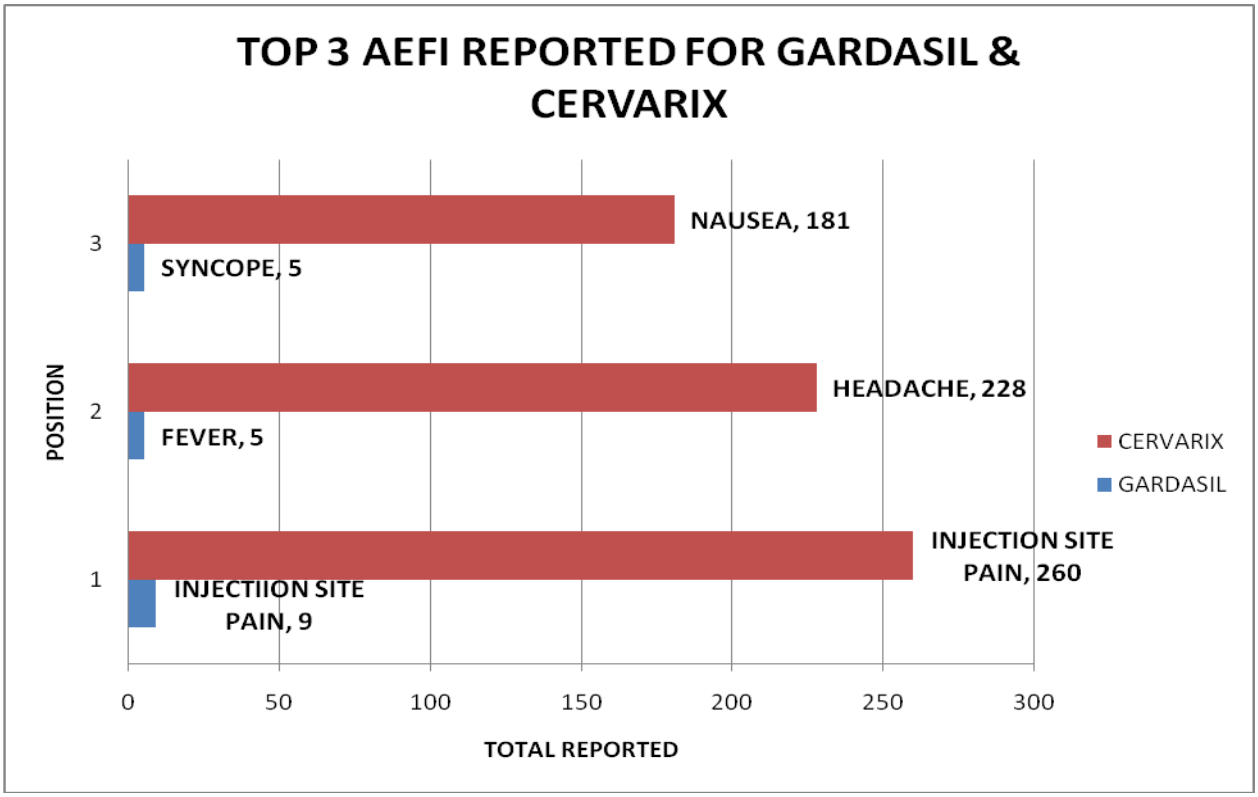

Figure 4: Three most Reported Adverse Events for Gardasil® and Cervarix®

NO	GARDASIL	TOTAL	CERVARIX	TOTAL
1	Body As A Whole - General Disorder	23	Application Site Disorders	476
2	Skin And Appendages Disorder	17	Central & Peripheral Nervous System Disorder	448
3	Application Site Disorders	15	Gastrointestinal System Disorder	324
4	Central & Peripheral Nervous System Disorder	12	Body As A Whole - General Disorder	197
5	Reproductive Disorders - Female	9	Musculo-Skeletal System Disorder	109
TOTAL AEFI		**101**	**TOTAL AEFI**	**1664**

Table 4: Comparison of Five Most Organ Classes with Most AEFIs Reported Between Gardasil® and Cervarix®

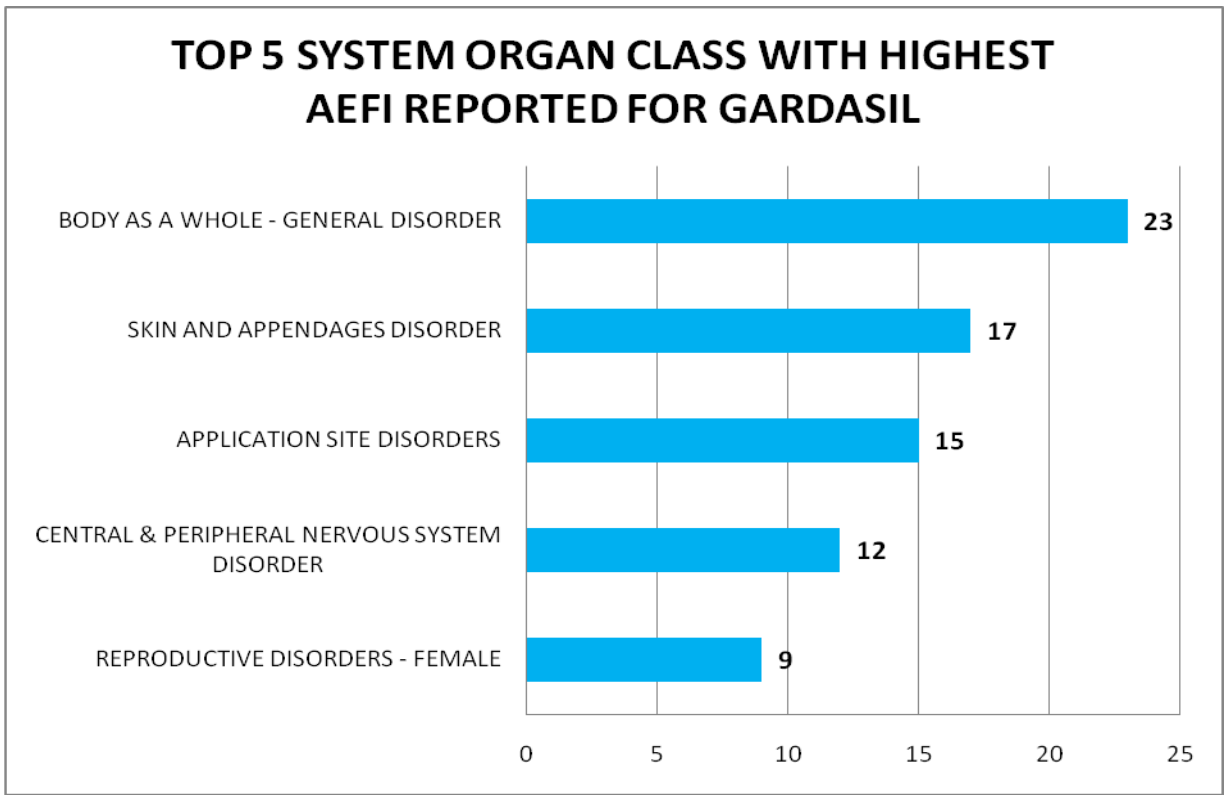

Figure 5: Five System Organ Class with Highest AEFIs Reported for Gardasil

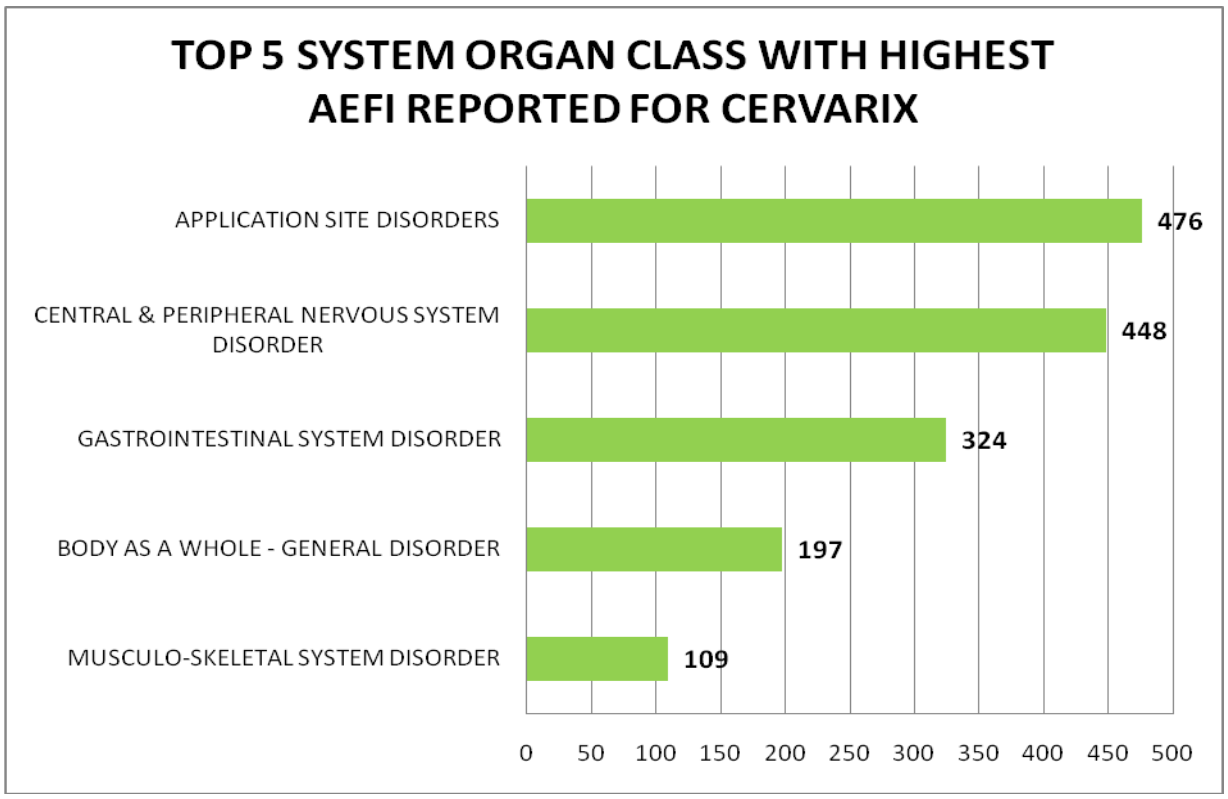

Figure 6: Five System Organ Class with Highest AEFI Reported for Cervarix

NO	REPORT NO.	VACCINE	BRAND	AEFI
1	10-05-2874A	Human Papillomavirus	Cervarix	Adenocarcinoma
2	10-09-5254A	Human Papillomavirus	Cervarix	1) Feeling cold 2) Spasms
3	10-12-6753A	Human Papillomavirus	Cervarix	Fits NOS

Table 5: Serious Cases for HPV Vaccine Reported in 2010