POST LICENSURE SURVEILLANCE OF HUMAN PAPILLOMAVIRUS VACCINE, VACCINE ADVERSE EVENT REPORTING SYSTEM, 2010-2017

BY

PUVAINDRAN RAJANDRAN

2021

A Research Project submitted for the degree of Master of Philosophy

School of Pharmacy, University of Nottingham

ABSTRACT

Currently, there are three approved and commercially available Human Papillomavirus (HPV) vaccines. These are Gardasil®, a quadrivalent HPV, Cervarix®, a bivalent vaccine, and Gardasil®9, a nonvalent HPV and they were first approved in 2006, 2009, and 2014, respectively for use in females. Approvals for use in males followed a few years later for Gardasil® and Gardasil®9. The acceptance of HPV vaccination has been a challenge, including cost, cultural views, parent's acceptance, safety, and adverse events of the vaccine. Vaccination acceptance is mainly influenced by safety reports and, unfortunately, also by misinformation from social media. The United States (US) Food and Drug Administration (FDA) collects and maintains post-marketing products' safety data, including vaccines. These safety data or adverse event data are collected through several methods, including chart reviews and reporting systems. The use of data mining has shown to be useful in extracting critical information from a large dataset. The adverse event datasets associated with commercially available HPV vaccines for years 2010-2017 from the Vaccine Adverse Event Reporting System (VAERS) were analyzed using SAS Text Analytics. The results showed that most of the detected adverse events were commonly reported, and many are non-serious associated with teenage and young adult patients. In the 7-year data analyzed, authors found that most adverse events terms were associated with nervous system disorders (n=1251) followed with general disorders and administration site conditions (n=1192). In addition, death, and serious terms (Guillain-Barre syndrome, seizure, anaphylactic shock) were also identified. In conclusion, this study did not detect safety signals associated with HPV vaccines between 2010 to 2017. Big data analysis will serve as a baseline for analysis of this ongoing surveillance in the pharmacovigilance field in the future.

Keywords: Data mining, predictive text analytics, human papillomavirus vaccine, vaccine, vaccination, adverse events, pharmacovigilance

Declarations

Ethical approval: Ethical approval was not required

Funding: No funding has been received

Conflict of interests: No conflict of interests to declare

Code Availability: SAS Text Miner

ACKNOWLEDGEMENT

Firstly, I would like to express my sincere gratitude to my supervisors Prof. Ting Kang Nee, Professor, and Head of School of Pharmacy, Prof. Dr. Khong Wei Kok, Executive Dean, Faculty of Business and Law, Taylor's University, and Dr. Amr Ahmed, Associate Professor of School of Computer Science for their continuous support of my MPhil study and related research, for their diligent and motivation and immense knowledge. Both Prof Ting, Prof Khong, and Dr. Amr Ahmed have been guiding and supporting me to complete this study even giving me time to rest during my hospitalization in early 2018 and I could not have imagined having better advisors for my Mphil study. I had the opportunity to learn new skills in data analytics using SAS Software. Prof Khong was helpful and his advice on the use of the software helped me accomplish this research.

Besides, I would like to thank all the Professors and the Staff of The University of Nottingham for their kind help and guidance. Very special gratitude goes out to The University of Nottingham for enrolling me in this program.

To one of the greatest, my late grandfather Gopal, I owe this to you. Many Thanks!

I am grateful to my parents and close friends, who have provided me with moral and emotional support in my life. I am also grateful to my other family members who have supported me along the way.

I am extremely thankful to my managers, Nirva Eugene, Betty Delise, and Jackie Grissinger from Johnson & Johnson. They were very supportive of my MPhil study, encouraging me to complete it despite the busy workload at work.

TABLE OF CONTENTS

Chapter 1: INTRODUCTION

1.1 Human Papillomavirus

The human papillomavirus is characterized as small double-stranded DNA oncogenic viruses of about 8kbp (Ashrafi et al., 2016). Over 200 HPV genotypes have been identified, and they are classified by high-risk and low-risk types (Sanjose et al.,2017). There are 12 types of high-risk HPV types, and these have been classified as carcinogenic meanwhile low-risk types such as HPV 6 and 11 normally causes benign disease like genital warts (Sanjose et al., 2017). HPV strains are classified by their risk of causing cervical cancer, for example, HPV-6 and -11 are low risks meanwhile HPV-16 and -18 are classified as high risks (Serrano et al.,2017). It is believed the molecular evidence and oncogenic feature of HPVs are reasons behind their role in association with cancers (Ashrafi et al., 2016). Besides cervical cancers, high-risk HPVs also associated with many other anogenital cancers such as anal, penile, vaginal, and vulvar, tonsil cancer, head and neck cancers, the base of tongue cancer, and other oropharyngeal cancer sites (Serrano et al.,2017). Besides cancer, HPV infection is also linked to other skin and mucosal lesions such as warts and benign papilloma (Sanjose et al.,2017). Although the burden of disease is much larger in women, HPV infects both men and women (Sanjose et al.,2017). As shown in Table 1, International Agency for Research on Cancer classified 12 HPV types as carcinogenic to humans, mainly HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 (Group 1). Among them, HPV16 and HPV18 are the most carcinogenic to humans (Serrano et al.,2017).

Risk classification	HPV types
High-risk	16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probably high-risk	26, 53, 66
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
Undetermined risk	34, 57, 83

Table 1: Cervical oncogenicity classification of HPV types

1.2 Mechanism of HPV Infection

The papillomavirus family shares a similar genome structure and organization (Sanjose et al., 2017). The low-risk HPV subtypes clinical manifestations of infection may progress from asymptomatic to developing many types of benign papillomas or warts (Bordignon et al., 2017). HPVs escape host immune surveillance and can remain inactive for decades (Bordignon et al., 2017). The life cycle of HPVs depends on epithelial differentiation. HPVs depend on the host since HPVs can't encode their DNA polymerases and other factors needed for replication. In order to replicate, HPVs depend on the host including microRNAs (miRNAs), transcriptional factors, kinases, epigenetic enzymes, apoptotic caspases, and DNA damage signaling (Bordignon et al., 2017).

As shown in Figure 1, the circular double-stranded DNA genome is structured into three main regions. The early (E) region is where the encodes genes required for the viral cycle which is crucial in cell transformation (E1, E2, E4, E5, E6, and E7). The second late region (L) encodes the L1 and L2 capsid proteins. The third upstream regulatory protein (UPR), also referred to as the long control region (LDR), contains the origin for replication and transcription factor-binding sites which contribute to DNA replication regulation by controlling the viral gene transcription. For viral genome replication, virion synthesis, and release to occur, the E6 and E7, along with E1,

E2, E4, and E5 expression play an important role. They also play a key role in cell transformation (Sanjose et al., 2017).

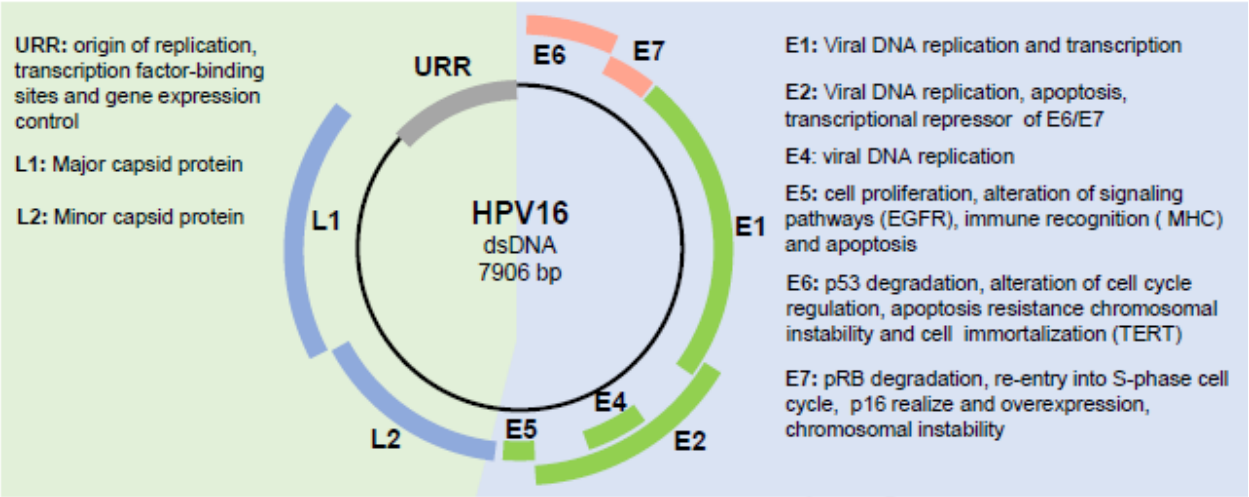


Figure 1 (Sanjose et al., 2017): The structure of HPV 16 and its viral proteins

The HPV life cycle starts with infection of the basal layer through tissue injury (microtrauma) that compromises the epithelial barrier (Sanjose et al., 2017). The human immune system usually clears HPV infections; however, progression to a malignant lesion in the presence of other risk factors gets triggered by the persistence of HPV (Ashrafi et al., 2016). Initiation of benign or cancerous lesions depends on the HPV types where the HPV virus infects cutaneous or mucosal epithelial cells (Ashrafi et al., 2016). Upon infecting host basal cells, the HPV genome is maintained a low-copy number (Sanjose et al., 2017). The capsid genes (L1 and L2) are expressed once the virus begins replicating to high copy number upon differentiation of epithelial cells (Sanjose et al., 2017). This is followed by the release of new progeny virions production from the epithelial surface (Sanjose et al., 2017). HPV needs to infect basal cells showing stem cell-like features that can proliferate (Sanjose et al., 2017). High-risk HPV is more likely to activate cell proliferation in basal and differentiated layers promoting the transition from a productive infection to an infection, which cannot complete the viral life cycle but activate several pathways essential for the epithelial transformation (Sanjose et al., 2017). The increased oncogenic capacity of high-risk types particularly the HPV16 type resides in the activity of the E6 and E7 oncoproteins (Sanjose et al., 2017). Even though low-risk types have E6 and E7 oncoproteins, the role of these oncoproteins is limited to viral production and unable to trigger the growth of pre-neoplastic lesions and cancer (Sanjose et al., 2016). Figure 2 below describes the mechanism of HPV infection.

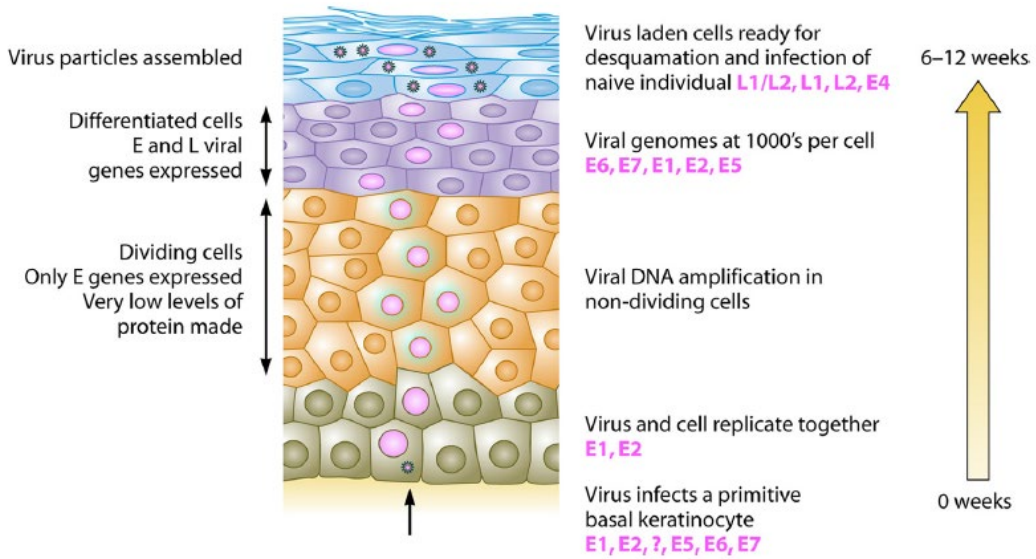


Figure 2 (Stanley., 2012): The infectious virus cycle of HPV is a complex process. HPV only infects and replicates in a fully differentiating squamous epithelium, therefore the papillomaviruses are considered species and tissue-specific. The infection cycle of HPV involves both temporal and spatial separation of viral protein expression. Infection of HPV virus starts with keratinocytes within the basal layer of the epithelium due to microtraumas such as abrasion of the epithelium that exposes the basement membrane and basal cells. The plasmid maintenance phase occurs in the proliferative compartments of the epithelium where the virus and cell replicate together. During this phase, the viral copy number is maintained at between 50 to 100 copies in the daughter cells. Also, during this phase, the gene expression of the high-risk HPV virus is tightly controlled. The expression of the viral proteins occurs very tightly while under control of high-risk HPVs as long the cell continues to divide. Thus, the E6 and E7 oncogenes are expressed at very low levels. Activation of its genes occurs once signals are sent to the virus when the host cell stops dividing and starts differentiating into mature keratinocyte. This then increases the viral genome copy number to the thousands. If a situation if malignancies occur, the gene expression in the cell gets deregulated due to loss of control of E6 and E7 expression. All the viral genes (including those encoding the L1 and L2 proteins) are then expressed through the top layers of the epithelium. About thousands of viral genomes are encapsulated, and infectious virus particles then exit the cell. It takes about three weeks from the time of infection to the generation of an infectious virus; therefore, the infection cycle of HPV is a long process, it has no blood-born phase, and do not cause cell death.

1.3 HPV Infection and Human Immune System

HPV viruses can break away from the human immune system (Bolhassani et al., 2018). Viral oncogenes expressions are kept at a low level throughout the initial life cycle, and highly immunogenic products (including L1 and L2 capsid proteins) are only synthesized in superficial layers of the epithelium (Bolhassani et al., 2018). This is a replication strategy where viral DNA replication and virus assembly occur in a cell that will terminally differentiate and die by natural causes therefore there is no inflammation as there is no viral-induced cytolysis or necrosis (Bolhassani et al., 2018). Throughout most HPV infectious cycle duration, there will be little or no release into the local milieu of pro-inflammatory cytokines, which is crucial for antigen-presenting cells (APC) activation and migration (Bolhassani et al., 2018).

The infectious cycle of HPVs is customized to the differentiation of the keratinocyte. This raises several significant issues with respect to immune identification (Stanley et al., 2012). HPV can circumvent the host immune response in many ways. Low levels of viral protein production and potential molecular mimicry mechanism may decrease the immunogenicity of HPV proteins (Hebner et al.,2006). The infection and vegetative growth fully depend on the program of keratinocyte differentiation, from basal cell to terminally differentiated superficial squames (Stanley et al., 2012). It takes about 3 weeks from infection to virus release, as this is the time for basal keratinocytes to move up through the epithelium, goes through complete differentiation, and desquamate (Stanley et al., 2012). On average, it takes 8-14 months to clear high-risk HPV types, particularly HPV 16, and about 5-6 months are required for low-risk HPV types. However, in certain hosts, the immune system fails to control and clear the infection, then a persistent infection is established with high levels of high-risk HPV DNA replication (Stanley et al.,2006). The time between infection and appearance of lesions may range from weeks to months, promising the virus effectively evade host defenses (Stanley et al., 2012). There are several factors for the failure of the immune system fails to detect HPV infection. First, there is no cytolysis or cytopathic death because of virus replication and assembly (Stanley et al., 2012). Virus episodes occur in the fully differentiating keratinocyte, a cell destined for death and desquamation far from the sites of immune activity, therefore no virus-induced cell death and inflammation (Stanley et al., 2012). Second, even in the absence of viral-induced cytolysis and cell death, HPV-infected keratinocytes should activate the powerful antiviral defense system, type 1 interferon secretion. The type 1 interferons, IFN-α and IFN-β, have antiviral, antiproliferative, antiangiogenic, and immunostimulatory properties that bridge innate and adaptive immunity which activates the immaturely dendritic cells. High-risk HPV viruses downregulate IFN-α inducible gene expression, and the HPV-16 E6 and E7 oncoproteins directly interact with components of the interferon signaling pathways abrogating these pathways (Stanley et al., 2012). HPV is effective at evading the innate immune response and delays the activation of the adaptive immune response. The host dendritic cells are exposed to low levels of viral proteins in a noninflammatory milieu for a protracted time, and as a result, local immune non-responsiveness may be established in the infected mucosa. HPV antigen-specific effector cells are either not recruited to the infected area, or their activity is downregulated or both once the host defenses become unrepairable. Hence, during constant infection by the HPV virus, there is increased protein expression of high risk E6 and E7. This does not cause an effector cell-mediated immune response. Due to this, the progression of HPV-mediated to high-grade squamous intraepithelial lesions and invasive carcinoma is unrestricted (Stanley et al., 2012).

As seen in Figure 3, HPV is an intraepithelial pathogen with no blood-borne or viremic phase of the life cycle, and only minimal amounts of virus are exposed to the immune defenses (Stanley et al., 2012). HPV is invisible to the host defenses, which remain uninformed of the presence of the pathogen (Stanley et al., 2012)

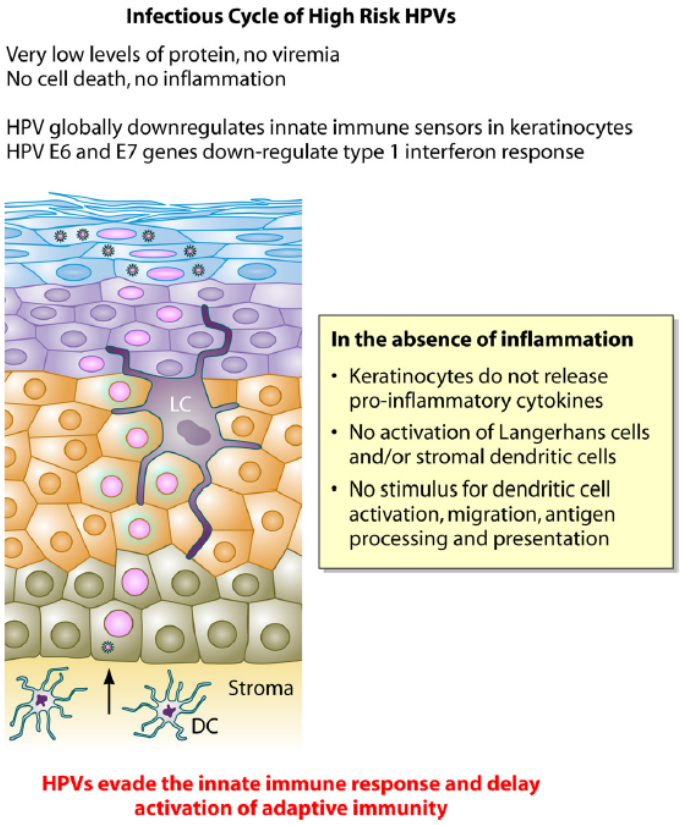


Figure 3 (Stanley et al., 2012): HPV virus efficiently evades recognition. It can down-regulate keratinocyte innate immune sensors and suppresses the type 1 interferon responses, which is important for the control of viral infection.

1.4 Epidemiology of HPV Infection

Globally, HPV is the most prevalent sexually transmitted infection (Boda et al., 2018). HPV is associated with a profound social and economic burden (Boda et al., 2018). Most sexually active individuals contract at least one type of HPV at some point in their lives. However, most HPV infections are transient, asymptomatic, and resolved spontaneously (Boda et al., 2018). Most of HPV infection occurs through anogenital contact mainly during vaginal and anal sex. Infection of HPV also occurs without penetration and oral, and genital-to-genital contact (Boda et al., 2018). Besides, the transmission of HPV could also occur through non-sexual routes, this includes casual physical contact via fomites or inoculation, also through HPV-infected pregnant women to their newborns during delivery or *in utero* (Boda et al., 2018). Among adults aged 18-69 years between 2013-2014, approximately 45% of men and 40% of women had genital HPV infection (Boda et al., 2018). Furthermore, 25% of men and 20% of women had high-risk genital HPV infections (Boda et al., 2018). As for oral infection prevalence, the HPV infection rate among adults aged between 18-69 years in 2011-2014 was approximately 7%, and the prevalence

of high-risk oral HPV infection was 4% (Boda et al., 2018). Most HPV infections (about 90%) get resolved within 1 or 2 years, being cleared by the immune system (Boda et al., 2018).

In recent studies, it was proven HPV infection also increases morbidity associated with other sexually transmitted diseases even at an asymptomatic stage (Boda et al., 2018). Evidence has also shown that HIV infection could potentially increase the number of infection HPV particles carried on a single individual (Boda et al., 2018). This could result from the negative impact of HIV on the immune system functionality (Boda et al., 2018). Although about 90% of HPV infection are likely to disappear within approximately two years post-infection and causes no harmful effects, high-risk HPV strains have a chance of causing persistent infection (Boda et al., 2018). Persistent infection due to high-risk HPV strains coupled with host including behaviors such as smoking, alcohol abuse, environmental co-factors, other associated viral infection such as HIV, which leads to neoplastic transformation (Boda et al., 2018). HPV infection has specific localization sites where the virus requires a stratified epithelium to complete the HPV infection generation cycle (Boda et al., 2018). This explains the reason behind cancers associated with HPV occurring in areas with intermediate epithelia towards cubic mucosal epithelia such as the lip, cervix, oral cavity, or the rectum (Boda et al., 2018).

As shown in Table 2, black and Hispanic women have higher rates of HPV-associated cervical cancer than women of other races. Penile cancer is rare, but about 1,300 new cases of HPV-associated penile cancers are diagnosed each year in the United States. The rates of anal and rectal HPV- related cancers is higher in women as compared with men (Centre for Disease Control and Prevention, 2019)

		Race									
		All Races Combined		White		Black		American Indian/Alaska Native		Asian/Pacific Islander	
Cancer Site	Sex	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases
Cervix	Female	7.2	12,015	7.1	9,227	8.3	1,840	5.9	118	5.8	609
Vagina	Female	0.4	862	0.4	697	0.6	128	0.3	5	0.2	24
Vulva	Female	21	4,009	2.2	3,567	1.5	340	1.4	25	0.5	44
Penis	Male	0.8	1,303	0.8	1,114	0.8	132	0.6	9	0.4	29
Anus	Overall	1.8	6,810	1.9	5,942	1.7	709	1	38	0.3	55
	Female	2.3	4,539	2.5	4,057	1.7	381	1.2	24	0.4	38
	Male	1.3	2,270	1.3	1,885	1.7	328	0.8	14	0.2	18
Oropharynx	Overall	4.9	19,000	5.3	16,921	3.7	1,582	3	113	1.3	241
	Female	1.7	3,460	1.8	3,021	1.4	335	0.9	18	0.6	63
	Male	8.5	15,540	9.1	13,900	6.6	1,247	5.4	96	2.1	179
All HPV-associated cancers	Overall	12.2	43,999	12.6	37,467	11.5	4,731	8.2	307	5.3	1,002
	Female	13.7	24,886	14	20,568	`3.5	3,025	9.7	189	7.5	777
	Male	10.6	19,113	11.2	16,899	9.2	1,707	6.7	118	2.7	225

Table 2 (Centre for Disease Control and Prevention,2019): Annual Number and Rate of HPV-Associated Cancers by Cancer Site, Gender, and Race and Ethnicity, United States, 2012-2016.

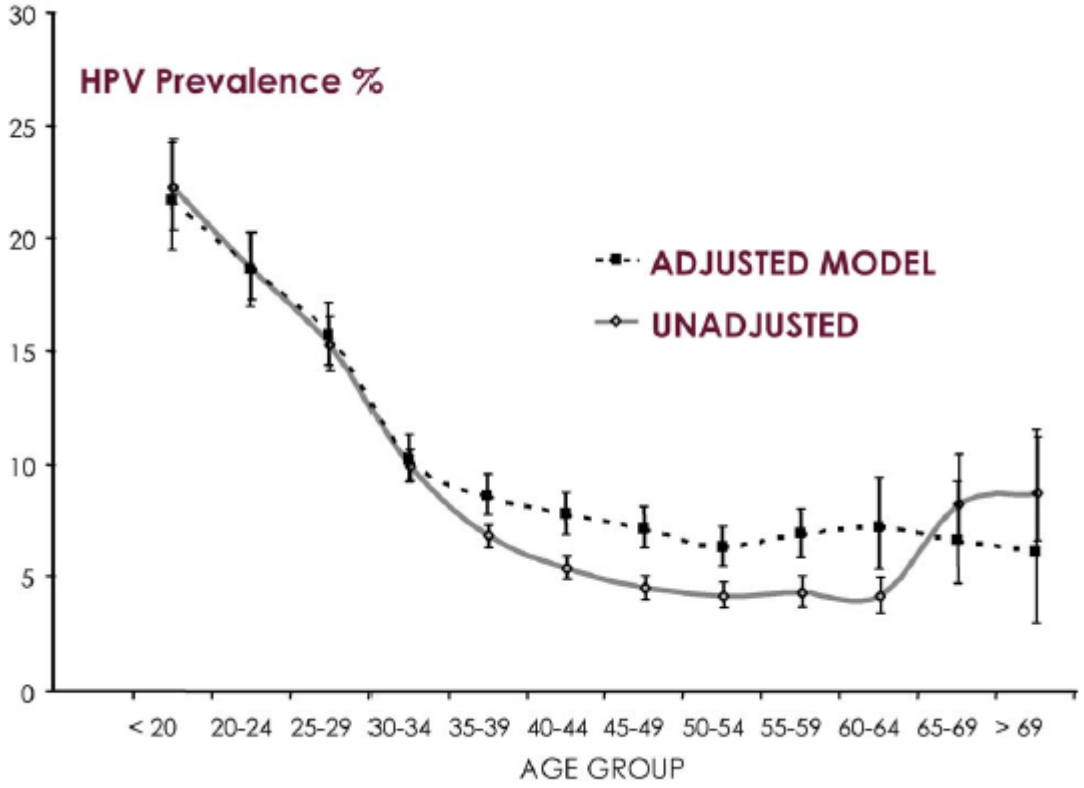


Figure 4 (Burchell et al.,2006): Prevalence of HPV among women

HPV infection is related to the burden of many cancers, as shown in Table 3. In 2012, is it estimated that about 4.5% (640,000) of new cancer cases were related to HPV infection. HPV was linked to 29.5% of infected-related cancers worldwide in 2012 and, was found to be associated with infection-attributable cancers in women (570,000), in which cervical cancer accounts for more than 80% of cases (Serrano et al., 2017).

Type of HPV Infection	Prevalence HPV Infection	Type of cancers	Disease burden
Cervical precancerous lesions	Prevalence of HPV increases with the severity of the lesion. HPV is detected in 52.5% of ASCUS lesions, 74.8% of low-grade cervical lesions (including low-grade squamous intraepithelial lesion and cervical intraepithelial neoplasia grade 1, and 88.9% of high-grade cervical lesions worldwide. HPV16 is detected in 19.3% of low-grade cervical lesions and 45.1% of high-grade cervical lesions	**Cervical cancer**	Among women, cervical cancer is the fourth most frequent cancer and the fourth leading cause of cancer deaths worldwide. It is estimated at 528,000 new cases and 266,000 new deaths in 2012. Asia accumulates most cervical cancer cases, 285,000 cases, and 144,000 deaths.
Infection in other anogenital sites	As compared with women, the prevalence of genital HPV is higher in men. Among men, HPV prevalence is highest at the penis and lowest at the urethra. Meanwhile, HPV prevalence is common among women at the cervix and vagina and lower at the vulvar epithelium. Anal HPV infection is also detected in both males and females, with differences by gender and sexual orientation.	**Anogenital cancer**	HPV causes various cancers of the vulva, vagina, penis, and anus. As compared to cervical cancer, estimation of anogenital sites cancer incidence rates are much lower. Globally, 115,000 cases are diagnosed, with 68,500 cases related to HPV. In men, 30,000 cases are diagnosed (in anus and penis); meanwhile, 38,5000 cases in women are diagnosed (in anus, vulva, and vagina). The prevalence of HPV16 is 71.4% for anal, 43.6% for vaginal, 19.4% for vulvar, 22.8% for penile cancer.
Oral Infection	The oral infection of HPV is rare a condition and differs by gender. Oral infection of HPV is higher in men as compared with women.	**Head and neck cancers**	Part of head and neck cancers are caused by HPV, especially the oropharynx, oral cavity, and larynx. Head and neck cancers are more common in men, with 30,000 cases, 50% of HPV-related cancers in men. About 456,000 head and neck cancer cases are diagnosed globally and 37, 2000 cases attributable to HPV, 29,000 in the oropharynx, 4,400 in the oral cavity, and 3,800 in the larynx respectively.

Table 3 (Serrano et al., 2017): Types of HPV Infection and HPV Associated Cancers

Statistics by Centre for Disease Control and Prevention showed median age at diagnosis of HPV-Associated cancer diagnosis are as below (Figure 4, 5 and 6):

- 49 years of HPV-associated cervical cancer
- 68 years for HPV-associated vaginal cancer
- 66 years for HPV-associated vulvar cancer
- 69 years for HPV-associated penile cancer
- 62 years among women and 59 among men for HPV-associated anal cancer
- 63 years among women and 61 among men for HPV-associated oropharyngeal cancers

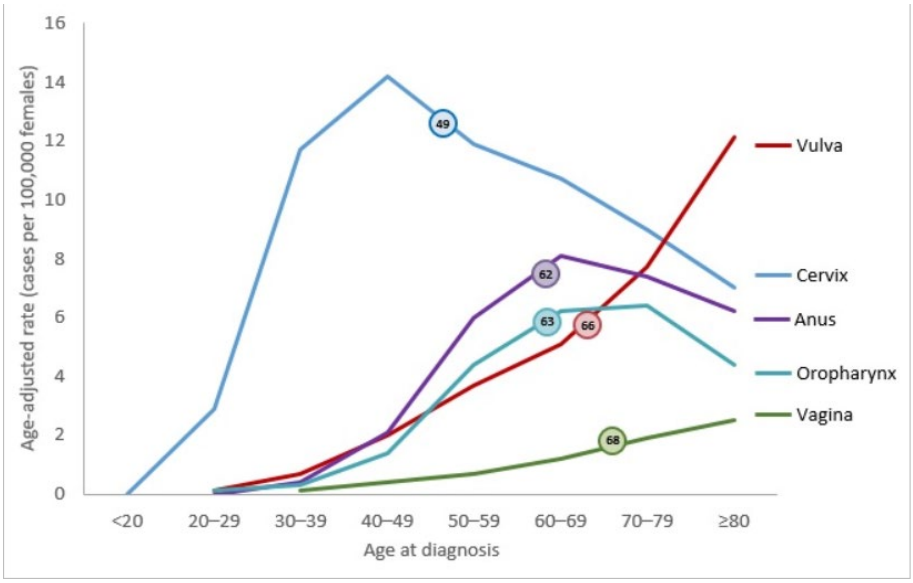


Figure 5 (Centre for Disease Control and Prevention, 2019): HPV-Associated Cancers Rates and Age at Diagnosis Among Women in the United States per year, 2012-2016. The chart shows the number of diagnosed women with HPV-associated cancer for every 100,000 women in each age group. For some cancer sites and age groups, the rates weren't shown as they were fewer than 16 cases.

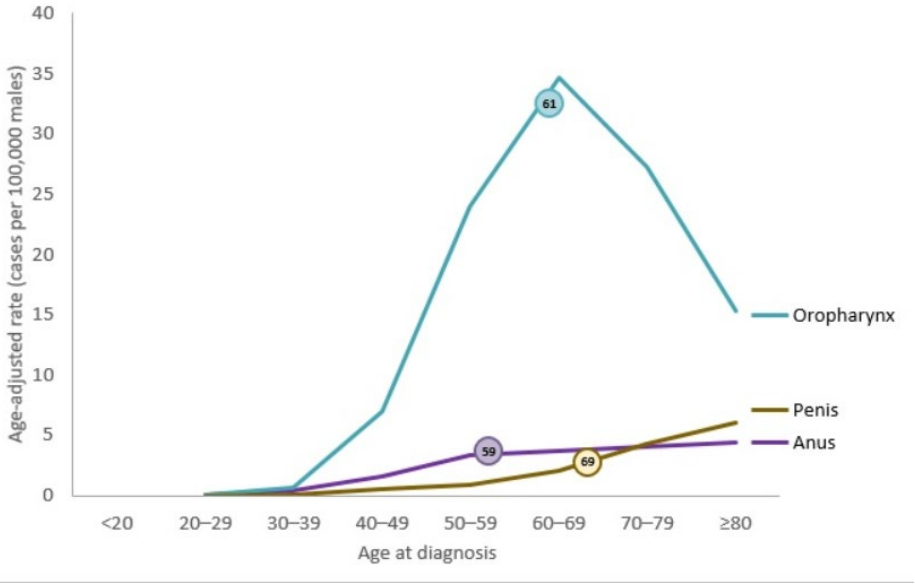


Figure 6 (Centre for Disease Control and Prevention, 2019): Rates of HPV-Associated Cancers and Age at Diagnosis Among Men in the United States per year, 2012-2016. The chart shows the number of men diagnosed with HPV-associated cancer. For some cancer sites and age groups, the rates weren't shown as they were fewer than 16 cases.

1.5 HPV in Malaysia and Prevalence of HPV Infection in Malaysia

As shown in Figure 31, HPV is responsible for all cervical, head and neck, and other anogenital cancer in Malaysia (www.hpvcentre.net., 2019). About 1682 cervical cancer cases are diagnosed annually in Malaysia, and it occurs mostly in women aged between 15 to 44 years (www.hpvcentre.net., 2019). In 2018, data extracted from the cancer registry showed that cervical cancer incidences between 2008-2010 were higher among the Chinese, followed by Malay and Indian women (www.hpvcentre.net., 2019). Among the incidence rates, squamous carcinoma is higher among all races, followed by adeno, other, and unspecified carcinoma histology (www.hpvcentre.net, 2019). As shown in Figure 32, the incidence of cervical cancer among women in Malaysia increases by age, where women aged between 40-64 years old have a higher number of cases than those aged between 15-39 years old and 65+ years old.

In 2018, data showed the annual number of deaths in Malaysia related to cervical cancer was 944 (www.hpvcentre.net., 2019). A high number of deaths were observed in women aged between 40-64 years old compared with 15-39 years old and women aged 65 and above (www.hpvcentre.net., 2019). However, as shown in Figure 33, cervical cancer mortality rates in Malaysia are lower than in South-Eastern Asia countries, where the death rates in Indonesia and Myanmar are relatively higher than in Malaysia (www.hpvcentre.net., 2019). HPV 16 and 18 were found to be the highest frequent HPV oncogenic types in Malaysia among women with and without cervical lesions (www.hpvcentre.net., 2019).

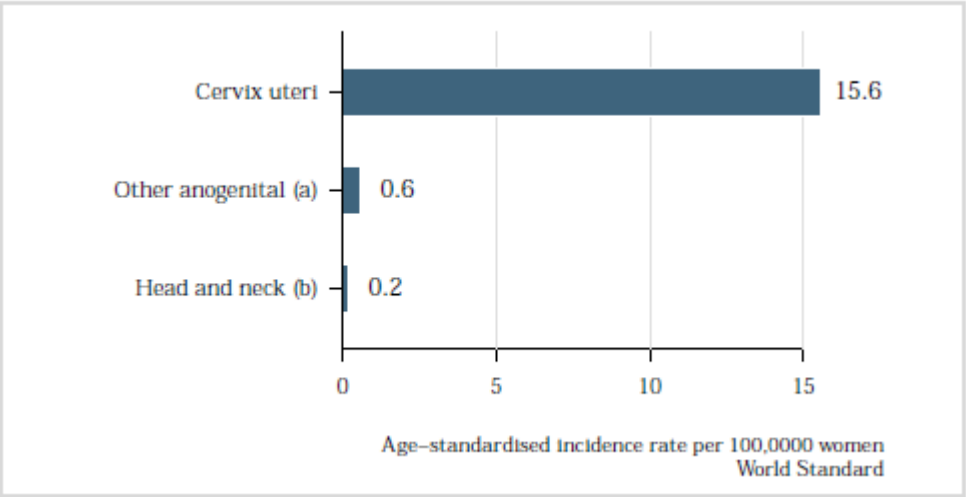


Figure 7 (www.hpvcentre.net., 2019): Incidence of HPV-related cancer in Malaysia (estimates for 2012)

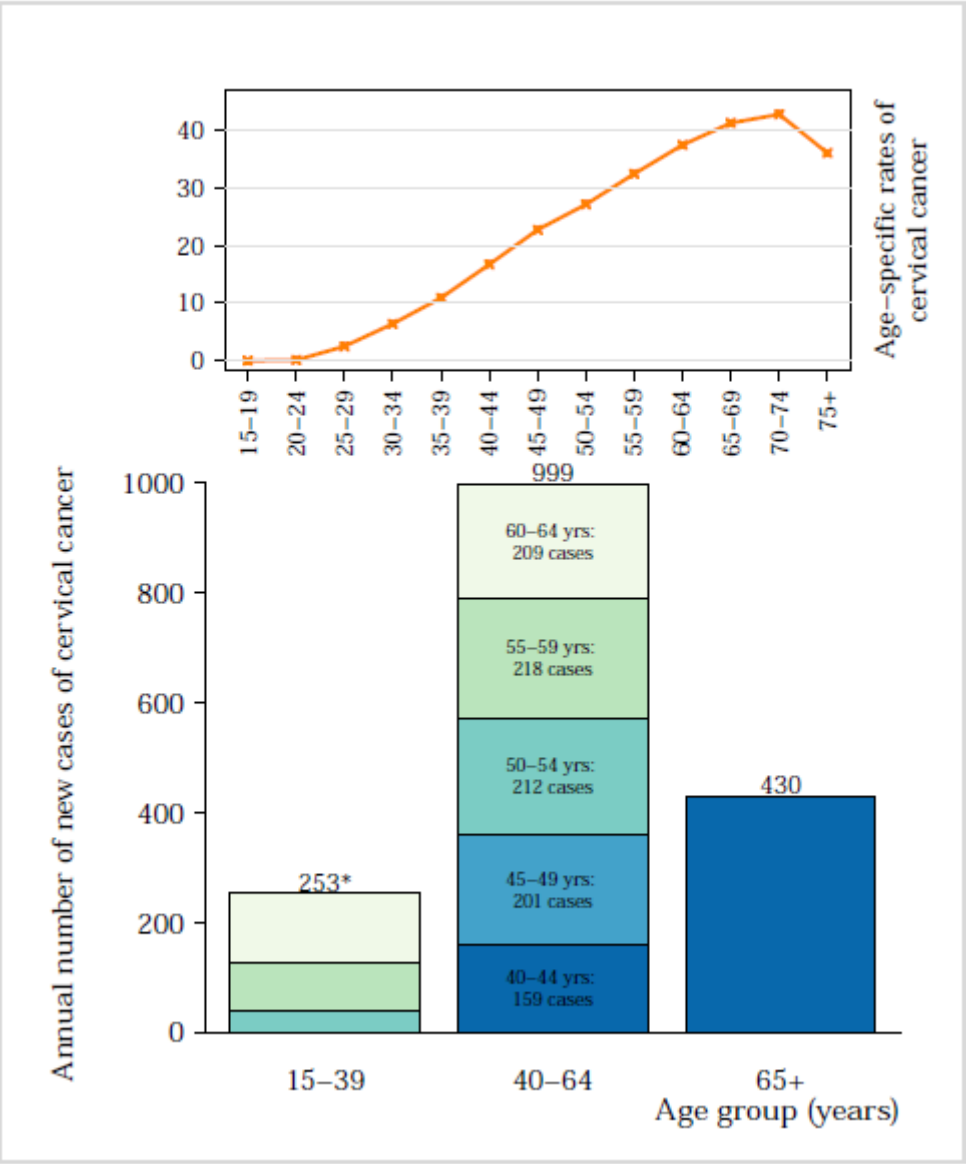


Figure 8 (www.hpvcentre.net., 2019): Incidence rates of cervical cancer in Malaysia, age-specific (estimates for 2018)

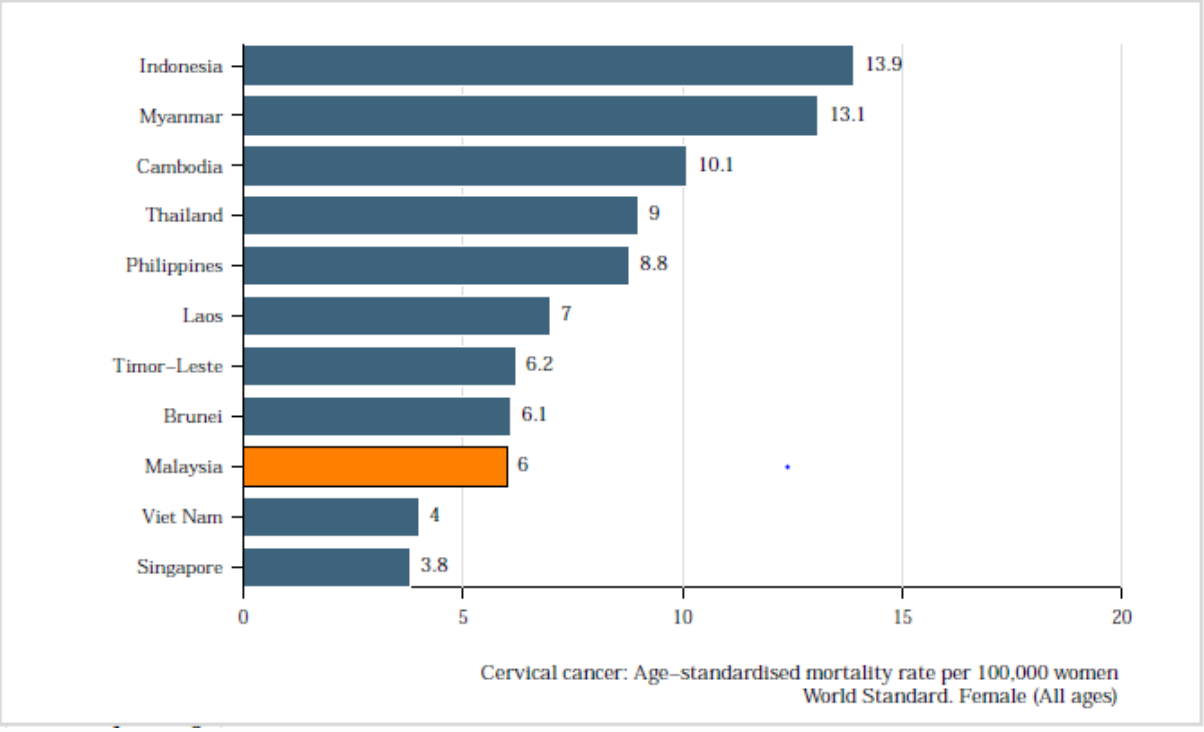


Figure 9 (www.hpvcentre.net., 2019): Mortality rates of cervical cancer in South-East Asia countries in comparison with Malaysia (estimates for 2018).

There are limited data on the prevalence of anogenital cancers linked to HPV in Malaysia. However, evidence links HPV DNA with cancers of the anus, vagina, vulva, and penis (www.hpvcentre.net., 2019). In Malaysia, women have higher incidences of anal cancer compared with men (www.hpvcentre.net., 2019). Incidence in men occurs mainly in men who have sex with men (MSM), women with a history of cervical or vulvar cancer, and immunosuppressed populations, including those infected with HIV and patients with a history of organ transplantation (www.hpvcentre.net., 2019). These cancers are mainly squamous cell carcinoma, adenocarcinoma, or basaloid and cloacogenic carcinomas (www.hpvcentre.net., 2019)

1.6 Factors of HPV Infection

The risk of HPV infection has been associated with many factors. Age is an underlying factor because biological age is associated with the risk of acquiring HPV infection. Adolescents and young adults aged 15 through 25 have a high risk because 75% of HPV infection occurs in this age group. The infection rate in this age group is high due to a lack of adaptive immune responses and a large area of cervical epithelium undergoing squamous metaplasia. The infection rate is also significantly high in women over 55 years old in some populations due to diminishing immune responses, birth-cohort effects, and reactivation of latent infection. Although the correlation between age, infection, and viral persistence is unknown and being investigated still, as age increases, the possibility of infection increases which could be due to waning immune responses and characteristics of the virus (Dempsey., 2008).

Individual behavior is also a risk factor of getting infected with HPV. The number of sex partners, partners' characteristics, consistency, contraceptive use, use of illicit drugs, alcohol, and cigarettes are considered behavior-based risk factors. A high number of sexual partners is associated with an increased risk of HPV infection. The relationship between oral contraceptive use, illicit drugs, and cigarettes with HPV infection is unclear, although previous studies have stated these connections (Dempsey., 2008).

1.7 HPV Vaccination

For many years, vaccines have been long acclaimed as the most successful achievement in the healthcare industry (McClure et al.,2017). Until now, vaccines have saved millions of lives, contributing to reducing and controlling infectious diseases worldwide. A remarkable feature of vaccines is that they prevent the vaccinated individual from serious illnesses and protect the entire community by reducing the spread of infectious agents, also known as herd immunity. Vaccines have prevented an estimation of 2.5 million deaths each year (Barnighausen et al., 2014). Vaccination has been implemented across different age groups, often infants, children, teenagers, and adults, including geriatrics (Di Pasquale et al.,2016).

Currently, there are three commercially available HPV vaccines. The Quadrivalent vaccine, Gardasil manufactured by Merck & Co was the first approved HPV vaccine for commercial use in 2006 by the United States Food and Drug Administration (FDA) (Cheng et al., 2020). The Bivalent HPV, Cervarix manufactured by GSK was approved by the European Medicines Agency (EMA) in 2007 and by the FDA in 2009 (Cheng et al., 2020). In 2014, Gardasil 9 manufactured by Merck & Co was licensed by the FDA (Cheng et al., 2020).

1.8 Importance of HPV Vaccination

According to the Central for Disease Control and Prevention (CDC), children between the age of 11-12 years should get two doses of HPV vaccines given six to twelve months apart (www.cdc.gov/hpv., 2021). HPV vaccines can be given starting at age nine years (www.cdc.gov/hpv., 2021). Everyone through age 26 should get vaccinated if they are not fully vaccinated (www.cdc.gov/hpv., 2021).

HPV vaccines are prophylactic vaccines that do not intend to treat pre-existing HPV infection and HPV-related conditions (Cheng et al., 2020). HPV vaccination prevents cancer-causing HPV-related cancers (www.cdc.gov/hpv.,2021). Since the introduction of HPV vaccines in 2006, the rate of HPV-related infection and cervical cancers has dropped in the United States alone (www.cdc.gov/hpv., 2021). Among teenage girls and young adult women, the rate of HPV infections that causes HPV cancers and genital warts has dropped 88 and 81 percent respectively (www.cdc.gov/hpv., 2021). Meanwhile, dropped in the percentage of cervical cancers caused by HPV types was also observed to be reduced by 40 percent (www.cdc.gov/hpv., 2021).

1.9 Vaccination Refusal

There are many reasons that influence the HPV vaccination update which include vaccination age, efficacy, awareness on the importance of HPV vaccination, geographical regions (Cheng et al., 2020). In a survey conducted among pediatricians, the results revealed parents of 19% of girls and 23% of boys ages 11 and 12 refuse the vaccine (www.cidrap.umn.edu., 2019). The result of the survey conducted among family physicians showed a higher percentage of refusal with 27% for girls and 26% for boys (www.cidrap.umn.edu., 2019). The study showed HPV vaccine is fully utilized (www.cidrap.umn.edu., 2019).

Another primary reason for vaccination refusal is concern about safety and adverse events (Chido-Amajuoyi et al., 2021). Concern about the safety of available vaccines is critical for confidence in the vaccines (Chido-Amajuoyi et al., 2021). The increase in the safety concern could impact HPV vaccine uptake negatively at the population level (Chido-Amajuoyi et al., 2021). Given the reason that concern on safety and the adverse events is shown to affect update of HPV vaccination, these concerns must be addressed and should be the highest priority of public healthcare (Chido-Amajuoyi et al., 2021).

1.10 Vaccine Adverse Event Surveillance

The safety of vaccines is important mainly because they are administered to healthy individuals and vulnerable populations such as children, elderlies, and pregnant women (Salmon et al., 2016). The safety of vaccines is evaluated at all stages during the development, including after the vaccines are approved by regulatory authorities and commercially available (Salmon et al., 2016). Post-marketing surveillance of vaccines is done to identify and monitor unseen serious complications that could not have been detected during prelicensure studies (Salmon et al., 2016). There are two types of post-marketing surveillance, which are passive and active surveillance (Salmon et al., 2016). In passive surveillance such as the VAERS, adverse event reports can be made by anyone, including physicians, other healthcare providers, and the public (Salmon et al., 2016).

Often, passive surveillance systems have large adverse event data which turns out to have a challenge in the quick detection of safety signals. The number of reports increases annually due to awareness in reporting by the public, increase in population, and availability of reporting tools. This is a challenge in adverse event surveillance as often the data is unstructured and complex.

Chapter 2: RESEARCH PURPOSE

This study aimed to focus on detecting and analyzing adverse events reported in Vaccine Adverse Event Reporting System (VAERS) using big data analytics between January 2010 and December 2017. This study contributes to the post-licensure surveillance of HPV vaccines. This duration coincided with the approval of the use in males. To date, detection of HPV adverse events through the computerized system by extracting from large unstructured text is limited. This methodology is still not frequently used in this regard. This exercise allows the analysis of how data mining can be performed through SAS Text Mining software to be useful in the field of pharmacovigilance.

This research also evaluated and classified adverse events identified by system organ class (SOC) to estimate the most affected organs by adverse events reported. This study provides meaningful insights and recommendations on improving the HPV vaccination acceptance rate among the public. This can better improve the vaccination acceptance rate and decision-making regarding vaccinating children with the HPV vaccine. Moreover, risk-assessment of HPV vaccines can be made through evaluation by system organ class, evaluation through several other factors including patient age groups, gender, and seriousness of the adverse events discovered.

2.1. Research Objectives

Prior to developing research objectives, four research questions were mapped out for the research purpose:

Research Question 1: What is the most affected organ associated with adverse events associated with HPV vaccines?

Research Question 2: What is the most identified adverse event associated with HPV vaccines?

Research Question 3: How serious are the adverse events associated with HPV vaccines?

Research Question 4: Which age group of patients is the available HPV vaccine indicated?

From the research questions, we highlighted the research objectives:

Objective 1: To detect and analyze adverse events of HPV vaccine from VAERS for the years 2010-2017 by using big data analytics.

Objective 2: To classify adverse events by system organ class (SOC).

Objective 3: To categorize adverse events by age groups, gender, and seriousness criteria.

2..2 Research Outline

The remainder of this dissertation is divided as follows: Chapter 2 brings a literature review, considering the research questions and highlighting the structure of this study. Chapter 3 present the methodology of this study detailing the data collection and analysis. Chapter 4 presents the results and analyzed findings where the dataset is described. Chapter 5 discusses the results and findings of Chapter 4 and elaborates them based on the literature review from Chapter 2. Chapter 6 focuses on the main conclusions and summarizes the research objectives from Chapter 1 through the addition of contributions and limitations.

Chapter 3: LITERATURE REVIEW

3.1 Introduction

This literature review is divided into four main sections. The first section is an introduction to current commercially available HPV vaccines. The second section focuses on the acceptance of HPV vaccination highlighting on the reasons behind the acceptance. The third section focuses on adverse event monitoring in both pre-marketing and post-marketing of vaccines. Finally, the fourth section explains the challenges in surveillance of adverse events.

3.2 HPV Vaccines

HPV vaccination is best given before exposure to the virus, before sexual debut and the target population are pre-pubertal girls and young adolescents (Stanley et al.,2006). It has been claimed that the effect of vaccines in pre-puberty is higher since the antibody responses by HPV vaccine and other vaccines are higher than post-puberty in both males and females (Stanley et al.,2006). There are several HPV vaccines available consisting of virus-like particles (VLP) gathered from the major coat proteins (L1) of HPV16 and HPV 18 only or of HPV16/18/6 and -11 (Stanley., 2012). These prophylactic HPV vaccines have shown high efficacy in randomized controlled trials (Stanley., 2012). HPV VLP produces a high concentration of neutralizing antibodies to L1, at least 2 to 4 logs higher than those in natural infections (Stanley et al., 2012). HPV vaccines are given intramuscularly which produces a quick entrance to the local lymph nodes and thus circumventing the immune avoidance strategies of the viral intraepithelial infectious cycle (Stanley., 2012). For the repeat structure of capsomers across the particle surface, VLPs are highly immunogenic, inducing potent antibody responses in the absence of adjuvant due to their ability to activate both innate and adaptive immune responses (Stanley., 2012). It is believed, the mechanism of protection by HPV vaccines to be through antibodies. VLP-induced serum antibodies can affect protection against an exclusively intraepithelial infection. Virus neutralizing antibody prevents virus entry into cells (Stanley., 2012).

As shown in Table 4, currently, there are three approved and commercially available HPV vaccines; these are Cervarix®, a bivalent vaccine, Gardasil®, a quadrivalent HPV, and Gardasil®9, a nonvalent HPV (Chabeda et al.,2018). Both bivalent and quadrivalent vaccines were first approved by the United States Food and Drug Administration (US FDA) in 2009 and 2006, respectively, and the nonvalent HPV was first approved in 2014 by the US FDA and 2015 by EMA. In October 2009, the quadrivalent HPV vaccine was approved by US FDA for use in males aged 9 through 26 years old, followed by the nonvalent HPV vaccine approved by US FDA in 2014. The Advisory Committee on Immunization Practices (ACIP) updated its recommendations on 19th June 2017; HPV vaccination is recommended in preteen boys and girls between 11 and 12 before exposure to the virus. In 2018, the US FDA approved nonvalent HPV for both females and males aged 27 through 45 years old.

Brand Name of HPV Vaccine	**Cervarix® (Bivalent)**	**Gardasil® (Quadrivalent)**	**Gardasil-9® (Nonvalent)**
Manufacturer	Glaxo Smith Kline	Merck & Co	Merck & Co
Type of HPV covered	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Approved gender and age by ACIP	Female patients aged 11-25 years	1. Female patients aged 11-26 years 2. Male patients aged 11-21 years	1. Female patients aged 11-26 years 2. Male patients aged 11-21 years 3. Female and male aged 27 through 45 years old
Dose and Schedule	3 doses of 0.5ml each at 0,1 and 6 months	3 doses of 0.5ml each at 0, 2, and 6 months	Age 9 through 14 years with regimen of either 2 doses of 0.5 ml (0, 6 to 12 months) or 3 doses (0,2, 6 months) Age 15 through 26 years with 3 dose regiments of 0.5 ml at 0, 2, 6 months

Table 4: Comparison of HPV Vaccines commercially available

Based on WHO guidelines, the immunological correlates of protection against the vaccine are unknown for the HPV vaccine because it takes more than ten years to develop the correlation for the most definitive clinical indicator, cervical cancer diagnosis, (Kim et al., 2018). The representative clinical trials evaluating the efficacy of both quadrivalent, and bivalent vaccines are FUTURE (The Women United to Unilaterally Reduce Endo/Ectocervical Disease) I, II, The Papilloma Trial Against Cancer in Young Adults (PATRICIA; HPV0008) and Costa-Rice vaccine trial (CVT) as multinational Phase III clinical studies, Figure 7 (Kim et al., 2018).

Title	FUTURE I	FUTURE II	PATRICIA	CVT
Vaccine	Gardasil®	Gardasil®	Cevarix®	Cevarix®
Funding source	Merck & Co., Inc.	Merck & Co., Inc.	GlaxoSmithKline	National Cancer Institute
No. of study sites	62	90	135	7
Countries included	16	13	14	1
No. of enrolled	5,455	12,167	18,644	7,466
Duration of trial, yr	4	4	4	4
Age, yr	16–24	15–26	15–25	18–25
Exclusion criteria	Pregnancy, history of abnormal Pap smear or genital warts	Pregnancy, history of abnormal Pap smear	Pregnancy, breastfeeding, history of colposcopy, autoimmune disease or immunodeficiency	Pregnancy, breastfeeding, history immunosuppression, hysterectomy, hepatitis A vaccination
Method	Anogenital examination, cervicovaginal sampling (Pap smear), anogenital swabs (for HPV), initial serology	Anogenital examination, cervicovaginal sampling (Pap smear), anogenital swabs, initial serology	Gynecological examination, cervical sampling (for HPV), cervical liquid-based cytology, blood sampling	Initial interview, pelvic exam, cervical secretion, cervical cell sampling (cervix brush), blood sampling
Primary endpoint	Incident HPV 6, 11, 16, 18-associated genital warts, CIN 1-3, VIN 1-3, VaIN 1-3, AIS and cervical, vaginal or vulvar cancer	Incident HPV 16, 18-associated CIN 2-3, AIS or cervical cancer	Incident HPV 16, 18-associated CIN 2+	Incident 12-month persistent HPV 16, 18 infection

Figure 10 (Kim et al., 2018): Phase III efficacy studies in young women

In three efficacy trials, the bivalent vaccine showed a consistent preventive efficacy of 61%-75% on cervical-associated lesions above CIN2. (Kim et al., 2018). These studies were performed in women aged between 15-25 years old (non-infected with HPV) in four continents (PATRICIA study 64.9%; CVT 61.4%; Japan Phase 2 trial 73.9%) (Kim et al., 2018). The PATRICIA study is a multinational clinical trial conducted in 18, 644 women aged 15-25 years, with no more than six-lifetime sexual partners in 14 countries in Asia, Europe, and North and South America (Kim et al., 2018). Following vaccination, CIN2+ associated with HPV 16 and 18 were observed after an average follow-up of 35 months (Kim et al., 2018). As a result, 98% had a preventive efficacy in the total

vaccinated cohort (TVC)-naïve vaccine, which had normal cytology and HPV DNA-negative and received at least one dose of vaccine (Kim et al., 2018). Meanwhile, the group who received three doses of vaccine with normal or low-grade cytology at baseline had preventive efficacy of 93% (Kim et al., 2018). Regardless of HPV DNA results, 53% of the TVC patients who received at least one dose of vaccine had a preventive efficacy (Kim et al., 2018). In the end, after 4 years of follow-up in the PATRICIA trial in 2012, the efficacy of bivalent HPV vaccine against HPV 16 and 18 associated CIN 3+ was 100% in the TVC-naïve group, and 45.6% in the TVC group; vaccine efficacy against all adenocarcinoma in situ (AIS) was 100% in the TVC-naïve group and 76.9% in the TVC group (Kim et al., 2018). The bivalent vaccine was also found to have general protection against other high-risk HPV strains even though bivalent vaccine was developed for protection against HPV 16 and 18 (Kim et al., 2018). The bivalent vaccine was also showed cross-protective vaccine efficacy against persistent infection, and CIN2+ was observed across cohorts for HPV 33, 31, 45, and 51 (Kim et al., 2018).

For the quadrivalent vaccine, vaccine efficacy was evaluated in FUTURE I and II clinical trials by analyzing the intention to treat (ITT) group (Kim et al., 2018). This clinical trial subjects consist mainly of randomly selected women for their HPV infection status and cervical disorders. The modified intention-to-treat (miTT) group include women who were uninfected by the target HPV genotypes as determined by serum or DNA analysis and had been vaccinated at least once, and the per-protocol (PP) group which include uninfected women by the target HPV genotypes as determined by serum or DNA analysis and had been vaccinated three times (Kim et al., 2018). In FUTURE I studies, a PAP test was done every year for women aged between 16-24 years old. and the incidence of anogenital disease was observed (Kim et al., 2018). The quadrivalent vaccine showed 100% effectiveness in preventing CIN 1,2,3, and AIS associated with 4 types of HPV 6, 11, 16, and 18 were observed (Kim et al., 2018). In the ITT group, the efficacy of the vaccine was 73% against external genital disorders associated with HPV 6, 11, 16, and 18 and 55% against cervical disorders; regardless of the HPV strain, vaccine efficacy was 34% against external genital disorders and 20% against cervical disorders (Kim et al., 2018). Meanwhile, in the FUTURE II clinical trial, women aged 15-26 years old were followed up with Pap and HPV tests to observe the incidence of CIN 2, 3, and AIS, and vaccination efficacy was observed at 98% three years post first vaccination administration (Kim et al., 2018). The vaccine was also shown to be 17% effective against all high-grade cervical lesions of the ITT group, regardless of the HPV strain (Kim et al., 2018).

Both FUTURE I and II (combined) clinical trials in women aged 15-26 years old showed protective efficacy of 100% against CIN 2,3 and AIS in the mITT group (Kim et al., 2018). The quadrivalent vaccine was shown to be effective against vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN) grade 2 or greater was 100% in the PP group and 95% in the Mitt group; effectiveness with 100% against genital warts in the PP group and 96% in the mITT group (Kim et al., 2018).

As for the nine-valent HPV vaccine, clinical trial showed prevention of 97% against high-grade cervical, vulvar, and vaginal disease associated with HPV 31, 33, 45, 52 and 58, eliciting non-inferior antibody responses to HPV 6, 11, 16, and 18 compared with quadrivalent HPV vaccine (Guiliano et al., 2019). In a study conducted, a nine-valent HPV vaccine showed 94.9-100% efficacy with reference to HPV 6, 11, 16 and 18, compared with an unvaccinated population (Guiliano et al., 2019). A nine-valent HPV vaccine reduces the risk of therapeutic procedures (97.8%) following the detection of cervical abnormalities associated with HPV types compared with unvaccinated women (Guiliano et al., 2019). Robust efficacy was observed (95.8%-100%) among women who

tested positive for one or more HPV types at trial enrollment against other targeted HPV types (Guiliano et al., 2019).

3.3 Vaccination Acceptance

Vaccine hesitancy is defined as a delay in accepting or refusing vaccines despite available vaccination services (Marti et al., 2017). Vaccine hesitancy and acceptance are complex and rapidly changing global phenomena that vary across the place, time, and vaccines (Marti et al., 2017). Currently, there are many contributing factors with access to vaccine supply, domestic financing, pricing, and an increase in anti-vaccination beliefs (Gualano et al., 2018). Many countries face challenges with a group of individuals refusing available recommended vaccinations either for themselves and/or their children (Gualano et al., 2018). By vaccines losing public confidence, international organizations such as the World Health Organization (WHO) are concerned over the increased occurrence of vaccine hesitancy and its effect on decreasing vaccine coverage trends (Gualano et al., 2018).

Vaccination hesitant individuals are between either without a doubt accept or refuse all vaccines, wherein this group, some accept only certain vaccines, and others delays vaccination on purpose or do not accept recommended scheduled vaccination (Sato., 2018). Such behavior relates to several factors including confidence in available vaccines, satisfaction, and convenience, a 3Cs model as defined by the WHO in 2011 (Sato., 2018). Confidence concerning the effectiveness and safety of vaccines, the healthcare centers delivering them, and the public administrators' motivations for recommending vaccines (Sato., 2018). Satisfaction results from the low-risk perception of contracting diseases, so vaccination would be unnecessary (Sato., 2018). Moreover, convenience considers physical availability, ability to understand, willingness to pay, and access to health information (Sato., 2018).

Strategy Advisory Group of Experts on Immunization classified the following influences on vaccine hesitancies: socioeconomic, political, geographical, cultural, and religious views, gender aspects, communication and media, influence by leaders, and perception over the pharmaceutical industry (Sato., 2018). Individual influences depend very much on prior experiences with vaccination, beliefs, and attitudes towards health, confidence in the health system, connection with healthcare professionals, risk perception of available vaccines, and perception of immunization as a social norm against that in which vaccination is not required or is harmful (Sato., 2018). Besides vaccine influences include risks and benefits, vaccination schedule, method of administration, the introduction of a new vaccine or formulation, costs, and supply of vaccine (Sato., 2018).

In 2014, the Joint Reporting Form (JRF) sent a questionnaire to all 194 WHO/United Nations Children's Fund (UNICEF) member states (Marti et al., 2017). The survey intends to collect data on immunization coverage, reported cases of vaccine-preventable diseases, immunization schedules, and indicators related to immunization program performance, such as establishing a national technical immunization advisory group, and this survey was completed by national immunization managers mostly (Marti et al., 2017). As shown in Figures 8, 9, and 10, the main factors influencing vaccine hesitancy were analyzed using quantitative and qualitative methods. The responses were categorized according to the factors developed by the SAGE Working Group on Vaccine Hesitancy (Marti et al., 2017). The matrix of determinants shows the specific drivers influencing the behavioral decision to accept, delay or reject some or all vaccines in three different categories; contextual influences, individual and group influences, and vaccine and vaccination-specific influences (Marti et al., 2017).

CONTEXTUAL INFLUENCES **Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors**	**a. Communication and media environment** Media and social media can create a negative or positive vaccine sentiment and can provide a platform for lobbies and key opinion leaders to influence others; social media allows users to freely voice opinions and experiences and it can facilitate the organization of social networks for or against vaccines.	**b. Influential leaders, gatekeepers and anti- or pro-vaccination lobbies** Community leaders and influencers, including religious leaders in some settings, celebrities in others, can all have a significant influence on vaccine acceptance or hesitancy.	**c. Historical influences** Historic influences such as the negative experience of the Trovan trial in Nigeria can undermine public trust and influence vaccine acceptance, as it did for polio, especially when combined with pressures of influential leaders and media. A community's experience isn't necessarily limited to vaccination but may affect it.	**d.Religion/culture/gender/socio-economic** A few examples of the interplay of religious/cultural influences include: Some religious leaders prohibit vaccines Some cultures do not want men vaccinating children Some cultures value boys over girls and fathers don't allow children to be vaccinated),	**e. Politics/policies** (Mandates) Vaccine mandates can provoke vaccine hesitancy not necessarily because of safety or other concerns, but due to resistance to the notion of forced vaccination	**f.Geographic barriers** A population can have general confidence in a vaccine and health service, and be motivated to receive a vaccine but hesitate as the health center is too far away or access is difficult.	**g.Pharmaceutical industry** Industry may be distrusted and influence vaccine hesitancy when perceived as driven only by financial motives and not in public health interest; This can extend to distrust in government when perceived that they are also being pushed by industry and not transparent.

Figure 11 (Marti et al., 2017): Contextual influences of vaccination hesitancy

INDIVIDUAL and GROUP INFLUENCES Influences arising from personal perception of the vaccine or influences of the social/peer environment	**a. Experience with past vaccination** Past negative or positive experience with a particular vaccination can influence hesitancy or willingness to vaccinate. Knowledge of someone who suffered from a VPD due to non- vaccination may enhance vaccine acceptance. Personal experience or knowledge of someone who experienced an AEFI can also influence hesitancy.	**b. Beliefs, attitudes about health and prevention** Vaccine hesitancy can result from 1) beliefs that vaccine preventable diseases (VPD) are needed to build immunity (and that vaccines destroy important natural immunity) or 2) beliefs that other behaviors (breastfeeding, traditional/alternative medicine or naturopathy) are as or more important than vaccination to maintain health and prevent VPDs.	**c. Knowledge/ awareness** Decisions to vaccinate or not are influenced by a number of the factors addressed here, including level of knowledge and awareness. Vaccine acceptance or hesitancy can be affected by whether an individual or group has accurate knowledge, a lack of awareness due to no information, or misperceptions due to misinformation. Accurate knowledge alone is not enough to ensure vaccine acceptance, and misperceptions may cause hesitancy, but still result in vaccine acceptance.	**d. Health system and providers-trust and personal experience** Trust or distrust in government or authorities in general, can affect trust in vaccines and vaccination programmes delivered or mandated by the government. Past experiences that influence hesitancy can includes system procedures that were too long or complex, or personal interactions were difficult.	**e. Risk/benefit (perceived, heuristic)** Perceptions of risk as well as perceptions of lack of risk can affect vaccine acceptance. Complacency sets in when the perception of disease risk is low and little felt need for vaccination. E.g. Patient's or caregiver's perceptions of their own or their children's risk of the natural disease or caregivers' perceptions of how serious or life threatening the VPD is.	**f. Immunization as a social norm vs. not needed/harmful** Vaccine acceptance or hesitancy is influenced by peer group and social norms

Figure 12 (Marti et al., 2017): Vaccine hesitancy among individuals and groups

VACCINE AND VACCINATION – SPECIFIC ISSUES Directly related to vaccine or vaccination	**a. Risk/ Benefit (scientific evidence)** Scientific evidence of risk/benefit and history of safety issues can prompt individuals to hesitate, even when safety issues have been clarified and/or addressed e.g. suspension of rotavirus vaccine due to intussusception; Guillain-Barre syndrome following swine flu vaccine (1976) or narcolepsy (2011) following (A)H1N1 vaccination; milder, local adverse events can also provoke hesitancy.	**b. Introduction of a new vaccine or new formulation** Individuals may hesitate to accept a new vaccine when they feel it has not been used/tested for long enough or feel that the new vaccine is not needed, or do not see the direct impact of the vaccine (e.g. HPV vaccine preventing cervical cancer). Individuals may be more willing (i.e. not complacent) to accept a new vaccine if perception of the VPD risk is high.	**c. Mode of administration** Mode of administration can influence vaccine hesitancy for different reasons. E.g. oral or nasal administrations are more convenient and may be accepted by those who find injections fearful or they do not have confidence in the health workers skills or devices used.	**d. Design of vaccination program/Mode of delivery** Delivery mode can affect vaccine hesitancy in multiple ways. Some parents may not have confidence in a vaccinator coming house-to-house; or a campaign approach driven by the government. Alternatively if a health center is too far or the hours are inconvenient	**e. Reliability and/or source of vaccine supply** Individuals may hesitate if they do not have confidence in the system's ability to provide vaccine(s) or might not have confidence in the source of the supply (e.g. if produced in a country/culture the individual is suspicious of) ; health workers may also be hesitant to administer a vaccine (especially a new one) if they do not have confidence that the supply will continue as it affects their clients trust in them. Caregivers may not have confidence that a needed vaccine and or health staff will be at the health facility if they go there.	**f. Vaccination schedule** Although there may be an appreciation for the importance of preventing individual vaccine preventable diseases, there may be reluctance to comply with the recommended schedule (e.g. multiple vaccines or age of vaccination). Vaccination schedules have some flexibility that may allow for slight adjustment to meet individual needs and preferences. While this may alleviate hesitancy issues, accommodating individual demands are not feasible at a population level.	**g. Costs** An individual may have confidence in a vaccine's safety and the system that delivers it, be motivated to vaccinate, but not be able to afford the vaccine or the costs associated with getting themselves and their child(ren) to the immunization point. Alternatively, the value of the vaccine might be diminished if provided for free.	**h. Role of healthcare professionals** Health care professionals (HCP)are important role models for their patients; if HCPs hesitate for any reason (e.g. due to lack of confidence in a vaccine's safety or need) it can influence their clients' willingness to vaccinate

Figure 13 (Marti et al., 2017): Vaccine and vaccination-specific issues influencing vaccine hesitancy

Data in Figure 11 shows vaccine hesitancy. These were mapped against three groups from Figures 8,9, and 10.

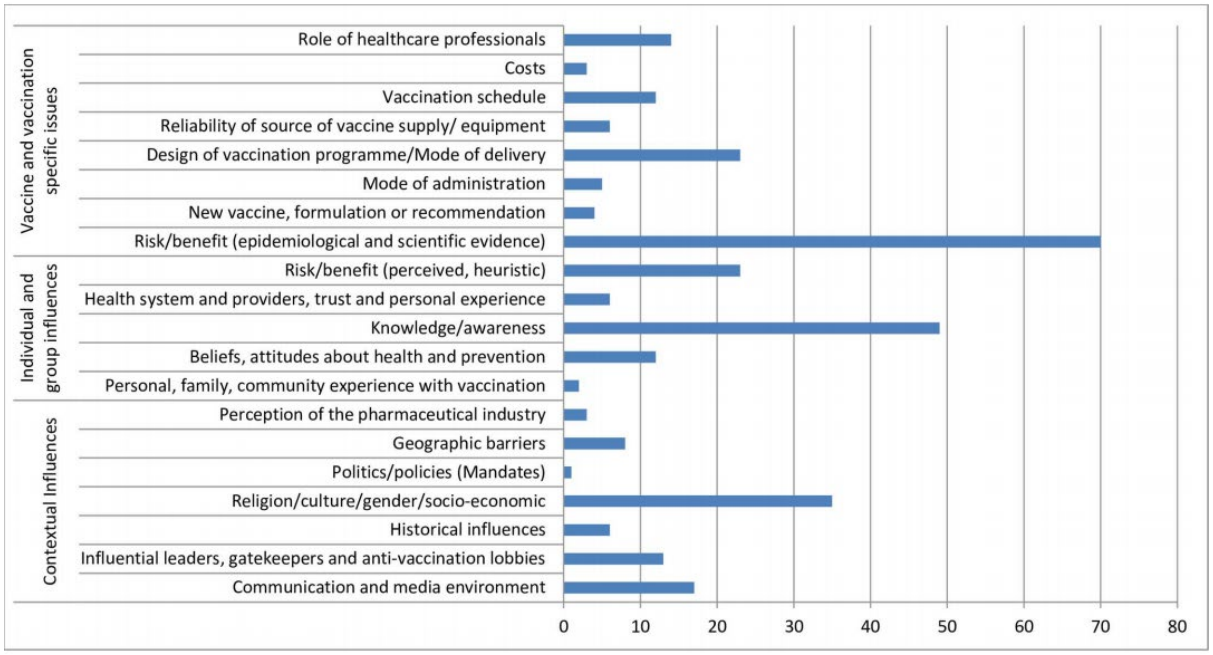


Figure 14 (Marti et al., 2017): Three main reasons for vaccine hesitancy by frequency within all WHO regions

When compared by regions (Figure 12), the top three reasons were consistent; however, in America's region was communication and the media environment (Marti et al., 2017). According to the vaccination managers, misinformation in media is a factor for vaccination hesitance which led to increase in anti-vaccination individuals. (Marti et al., 2017). In African and Eastern Mediterranean regions, knowledge, and awareness issues such as lack of knowledge or information on vaccines and their benefits and low awareness of the need for immunization were cited frequently (Marti et al., 2017). By income analysis (Figure 13), countries with low and middle incomes, lack of knowledge and awareness cited as most contributed to vaccine hesitancy (Marti et al., 2017). Meanwhile, in upper-middle-income countries, the reasons revolved around the risk/benefit (epidemiological and scientific evidence) of immunization, particularly issues related to AEFI and vaccine safety (Marti et al., 2017). The main reason for vaccination acceptance in high-income countries is vaccine safety issues (Marti et al., 2017).

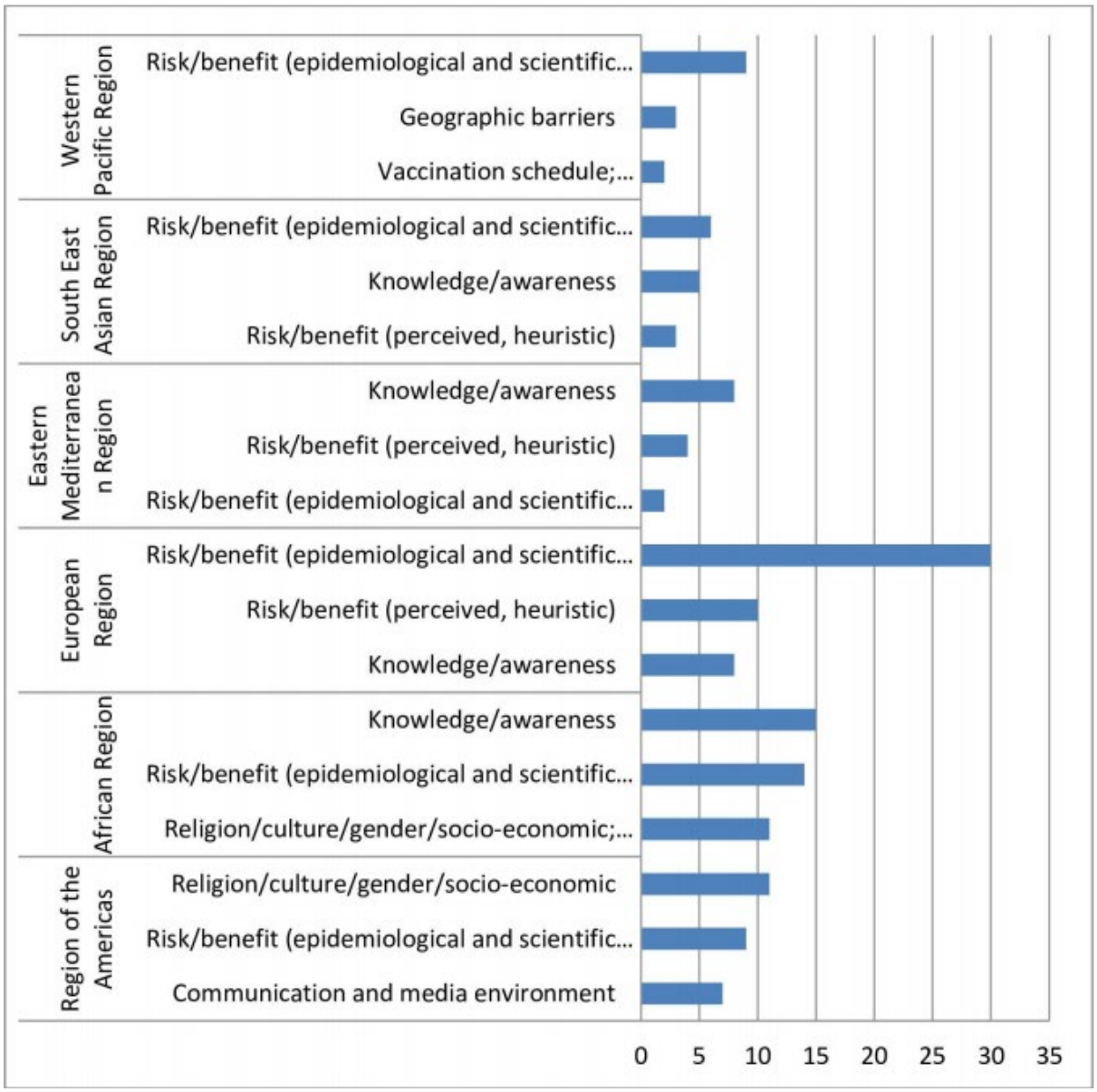


Figure 15 (Marti et al., 2017): Reasons for vaccine hesitancy by region

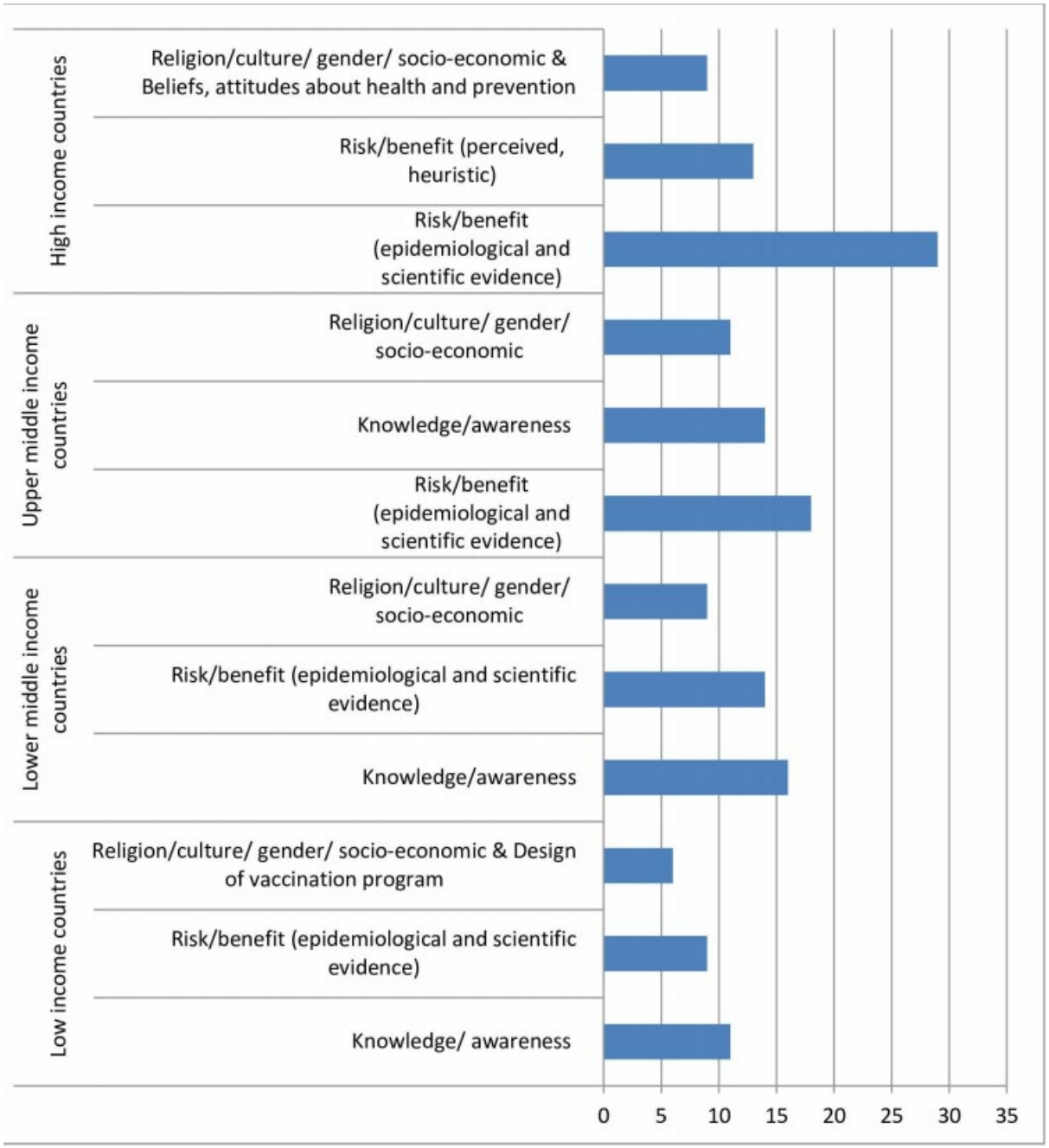


Figure 16 (Marti et al., 2017): Reasons for vaccine hesitancy by global level of income

3.4 Reasons of HPV Vaccination Acceptance and Refusal

The HPV vaccination is regrettably low worldwide, and only 1.4% of all eligible females have received a full course of HPV vaccination (Lobao et al., 2018). Intake of HPV vaccine is higher in high-income regions than lower-income regions, with approximately 33.6% females aged 10-20 years having received full vaccination in higher-income regions compared with 2.7% in lower-income regions (Lobao et al., 2018). In the United States, HPV vaccination rates fall below the 80% national objective (Westrick et al., 2016). In 2014, national vaccination rates in the US for adolescents aged between 13-17 years who had gotten at least one dose were 60% for girls and 41.7% for boys (Westrick et al., 2016). The low completion rate of HPV vaccines worldwide is concerning (Westrick et al., 2016).

Looking at Figure 14 below, there are various reasons for acceptance and refusal of HPV vaccination (Lobao et al., 2018). Parents are an important factor in the rate of HPV vaccination. Many parents perceive HPV vaccination as not recommended for their teenage children fearing adverse events, disbelief in vaccination, religion, and society's view (Lobao et al., 2018). Parents are also willing to accept HPV vaccination if it is recommended by a physician after knowing the importance of HPV and HPV vaccination and cost factor (Lobao et al., 2018). Apart from lack of knowledge and cost factor (Figure 15), physician recommendation and concern about the safety of the HPV vaccine remains a factor in the HPV vaccination rate (Verma et al., 2020).

	Parents accepting vaccination of daughters and sons (n = 687)		Parents accepting vaccination of daughters but not of sons (n = 68)		Parents refusing vaccination (n = 49)	
	Reported as the primary reason	Reported as one of the reasons	Reported as the primary reason	Reported as one of the reasons	Reported as the primary reason	Reported as one of the reasons
Reasons for acceptance of HPV vaccination						
Vaccination is good/important	90	96	82	88	NA	NA
HPV vaccination prevents cervical cancer [a]	7	10	15	22	NA	NA
The HPV vaccine is included in the national immunization programme	3	3	1	4	NA	NA
HPV vaccination prevents genital warts [b]	1	2	1	1	NA	NA
My doctor recommended the HPV vaccine	0.3	0.6	0	0	NA	NA
Reasons for refusal of HPV vaccination						
The HPV vaccine is not recommended for boys	NA	NA	74	78	0	0
Fear of reactions or adverse effects	NA	NA	3	10	51	61
I don't like/believe in vaccines	NA	NA	0	2	12	18
My daughter/son is too young	NA	NA	4	4	12	14
My daughter/son doesn't need the HPV vaccine	NA	NA	6	6	8	8
My religion doesn't approve the HPV vaccine	NA	NA	0	0	6	6
My doctor didn't recommend the HPV vaccine	NA	NA	2	2	4	4
Other reason(s) not specified	NA	NA	12	12	6	6

Figure 17 (Lobao et al., 2018): Distribution frequency of the reason for acceptance or refusal of HPV vaccination. The responses are from parents, collected during a survey

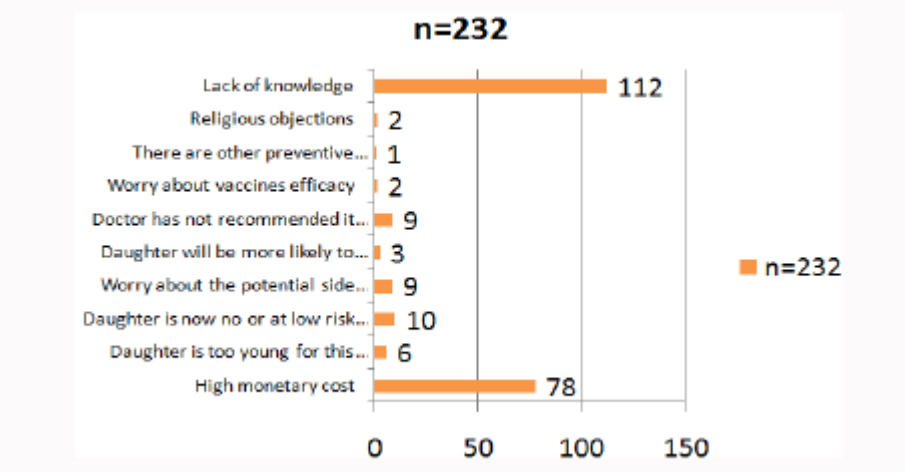


Figure 18 (Verma et al., 2020): Distribution of cases according to reasons for not receiving the HPV Vaccine

3.4.1 Public and Parents Perceptions on HPV and HPV Vaccine

Parents play a crucial role in the decision-making process regarding the HPV vaccination for their child (Grandahl et al., 2018). Parents decide if their children should be vaccinated against HPV, and the decision depends on attitudes, knowledge, beliefs, subjective norms, religious aspects and cultural views, and socio-demographics. (Grandahl et al., 2018). Studies indicate differences in gender on decision and knowledge about HPV and HPV vaccination (Grandahl et al., 2018). Among the many sources, the study found that individuals perceive HPV infection through media, physicians, and religious or social gatherings (Okunade et al., 2017). Primarily, mothers are primary decision-makers for their daughters due to awareness and knowledge of the HPV vaccine and cancer (Grandahl et al., 2018). Knowledge of HPV and HPV vaccine plays an important factor in the vaccination rate (Lobao et al., 2018). Although HPV is linked with several types of cancers, most men and women had never heard of HPV (Brewer.,2007). In a study conducted by Chan et al. (2007), a survey conducted among parents showed the knowledge of HPV and HPV vaccination remains low, which is one of the reasons for accepting the vaccine. This finding is like a study conducted by Grandahl et al. (2018), where parents of adolescent daughters aged between 10 – 12 years responded that information regarding the HPV vaccine was insufficient and the reason for vaccination is unclear.

Among the Asian mothers, although 98% heard of cervical cancer, only 58% claimed to know about cervical cancer, and some do not agree that cervical cancer is preventable or the fact that a person is at risk of developing cervical cancer while sexually active (Chow et al., 2010). As shown in Figure 16 below, some Asian mothers believe cervical cancer is linked with promiscuity poor personal hygiene and very few know of HPV infection (Chow et al., 2010).

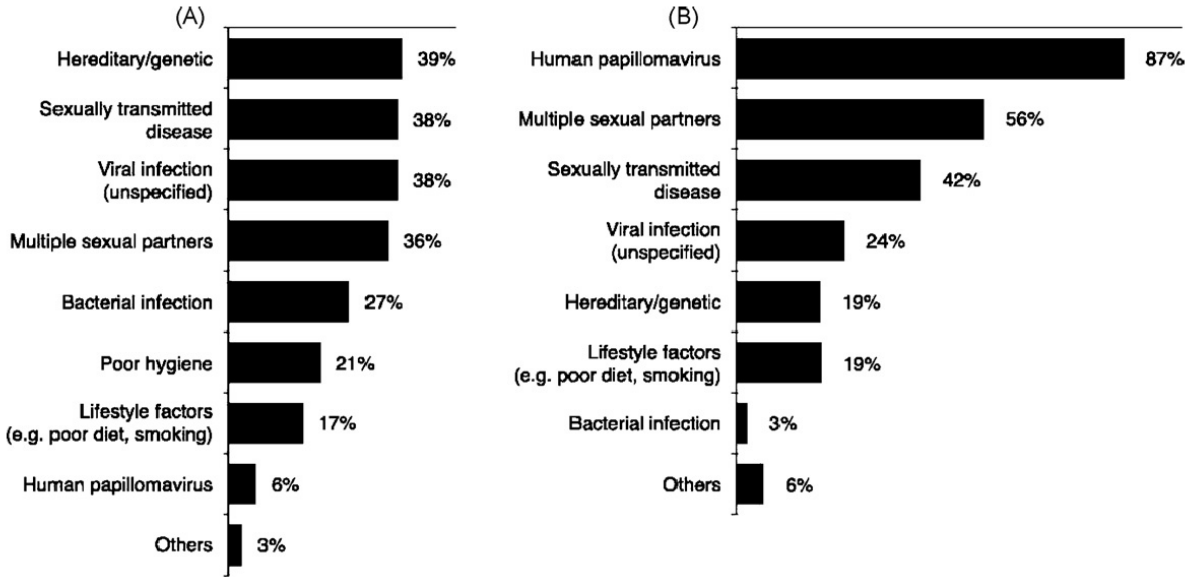


Figure 19 (Chow et al., 2010): Perceptions about cervical cancer among Asians. Chart A and B shows an understanding of the causes of cervical cancer among mothers and physicians respectively.

Many parents are unaware of prophylactic HPV vaccines that could prevent genital warts and very few acknowledge that condoms do not protect from HPV infection fully (Lobao et al., 2018). The likelihood of parents accepting HPV vaccination is relatively higher than those who refuse, not knowing HPV is sexually transmitted, it can cause genital warts, the advantage of taking HPV vaccine before sexual debut and most common adverse events are non-serious (Lobao et al., 2018). Knowledgeable parents of HPV are aware of HPV and its severities and how the HPV vaccine helps provide immunity against the HPV vaccine (Grandahl et al., 2018). Therefore, parents with greater knowledge are likely to accept and vaccinate their children (Grandahl et al., 2018).

Socio-demographics is a factor in parents' knowledge and acceptance of the HPV vaccine (Grandahl et al., 2018). Parents in the higher-income group are shown to have higher knowledge of the HPV vaccine than parents in the lower-income groups (Grandahl et al., 2018). Often, lower-income parents had never undergone pap smear, cervical cancer screening tests (Grandahl et al., 2018). Knowledge and information on HPV and HPV vaccine trigger individual behavior and uptake of the vaccine (Grandahl et al., 2018). Often parents and vaccinees hear or receive information from friends and family, media/advertisements, and healthcare professionals (Grandahl et al., 2018). Many parents lack confidence in the HPV vaccine, usually due to the false belief that the immunization is unjustified because the adolescent is not sexually active (Cipriano et al., 2017). Parents mostly delay vaccination due to concerns on sexual nature, including that the vaccine may encourage adolescents to engage in risky sexual behaviors (Cipriano et al., 2017). As shown in Figure 17 below, the most common reason for parents' acceptance of HPV vaccination is a recommendation by a physician followed by advertising on the importance of the vaccine (Brown et al., 2016). The barriers to parents' acceptance of HPV vaccination are safety issues, adverse events, concern about the increased risk of sexual behaviors among children, availability of HPV vaccination in immunization programs (Juntasopeepun et al., 2018). Meanwhile, the reason for parents' acceptance of HPV vaccination is knowledge about the vaccine and children's age (Brown et al., 2016). In some societies, due to clashes with religious and cultural views, the aim to prevent sexual transmission of HPV may potentially trigger

moral judgements (Bonanni et al., 2017). This is much more of a concern in society that considers sexuality taboo and girls and women do not receive adequate sexual education (Bonanni et al., 2017). The more parents are negative towards the HPV vaccine, the less they accept it (Degarege et al., 2019).

Reasons for accepting vaccine:*	**Total (n=164) N (%)**	**Male (n=109) N (%)**	**Female (n=55) N (%)**
My doctor felt it was important to protect against future HPV infection	138 (84.1)[a]	94 (86.2)	44 (80.0)
I have read or heard that this is an important vaccine to give my child	104 (63.4)[b]	70 (64.2)	34 (61.8)
I am very pro-vaccine and this is a recommended vaccine by the American Academy of Pediatrics and the Centers for Disease Control	74 (45.1)[c]	55 (50.5)	19 (34.5)
My insurance covers all or most of the cost of the vaccine	42 (25.6)	31 (28.4)	11 (20.0)
I have had or know someone that had HPV disease or cervical (female organ) cancer.	23 (14.0)	14 (12.8)	9 (16.4)
Other	9(5.5)	5 (4.6)	4 (7.3)
Reasons for refusing vaccine*	**Total (n=36) N(%)**	**Male (n=14) N(%)**	**Female (n=22) N(%)**
I want to research the vaccine more	19 (52.8)[a]	9 (64.3)	10 (45.5)
My child is too young for this vaccine	9 (25.0)[b]	4 (28.6)	5 (22.7)
I do not think the vaccine is safe	6 (16.7)	1 (7.1)	5 (22.7)
My spouse/partner/child's other parent does not want this child vaccinated against HPV	5 (13.9)	0	5 (22.7)
I worry that vaccinating against HPV may make my child more likely to engage in sexual activity	4 (11.1)	2 (14.3)	2 (9.1)
My child does not want to get this vaccine	4 (11.1)	0	4 (18.2)
My child is not likely to get disease from the HPV virus	1(2.7)	0	1 (4.5)
I do not think the vaccine is effective	1 (2.7)	0	1 (4.5)
Other	6[c] (16.7)	3 (21.4)	3 (13.6)

Figure 20 (Brown et al., 2017): Parental reasons for accepting and refusing HPV vaccine

As for knowledge and perception among target HPV vaccine candidates, HPV knowledge among females is generally higher than males (Grandahl et al., 2018). This is supported by Cipriano et al. (2017), in a study conducted showed female has higher knowledge on HPV and HPV vaccine since female patients routinely screen for HPV strains and may have gotten basic information during medical examinations. In general, the female has higher knowledge on HPV and HPV vaccine since female patients routinely screen for HPV strains and may have gotten basic information during medical examinations (Cipriano et al., 2017). In a recent study conducted in China (Figure 18), females have significantly better knowledge of HPV infection and types of HPV high and low risks strains (Deng et al., 2020). Many young female and male teenagers understand HPV is a sexually transmitted disease; however, many are unaware of the risk factors of HPV vaccination (Deng et al., 2020).

Questions	Overall	Female	Male	P
Q1 HPV is divided into high-risk and low-risk types	268 (26.2%)	220(29.1%)	48(18.0%)	.000
Q2 Which types of HPV are the riskiest	38 (3.7%)	32(4.2%)	6(2.3%)	.139
Q3 Whether HPV requires regular screening	292 (28.6%)	248(32.9%)	44(16.5%)	.000
Q4 HPV transmission	0 (0.0%)	0(0.0%)	0(0.0%)	/
Q5 HPV infection can be asymptomatic	183(17.9%)	149(19.7%)	34(12.8%)	.010
Q6 The connection between the occurrence of cervical cancer and HPV infection	302(29.6%)	254(33.6%)	48(18.0%)	.000
Q7Where you think HPV can be infected	2(0.2%)	2(0.3%)	0(0.0%)	.400
Q8 You think the lesions caused by low-risk HPV are	247(27.2%)	193(25.6%)	54(20.2%)	.080
Q9 HPV infection can cause genital herpes	269(26.3%)	217(28.7%)	52(19.5%)	.003
Q10 Which of the following do you think is a risk factor for HPV infection	18(1.8%)	11(1.5%)	7(2.6%)	.214
Q11Almost everyone gets HPV	135(13.2%)	111(14.7%)	24(9.0%)	.018
Q12 There is no cure for HPV itself	94(9.2%)	78(10.3%)	16(6.0%)	.035
Q13 HPV infection is sure to cause cancer	234(22.9%)	196(26.0%)	38(14.2%)	.000
Q14 Taking birth control pills can prevent HPV	188(18.4%)	153(20.3%)	35(13.1%)	.009
Q15 HPV does not harm male	282(27.6%)	226(29.9%)	56(21.0%)	.005
Q16 In your opinion, the impact of HPV infection on male reproductive health	113(11.1%)	92(12.2%)	21(7.9%)	.053
Q17 In your opinion, the impact of HPV infection on female reproductive health	181(17.7%)	146(19.3%)	35(13.1%)	.022
Q18 What types of HPV vaccines you know	134(13.1%)	91(12.1%)	43(16.1%)	.092
Q19 HPV vaccine vaccination cycle	79(7.7%)	72(9.5%)	7(2.6%)	.000
Q20 The suitable age for vaccination of tetravalent HPV vaccine in China is	60(5.9%)	53(7.0%)	7(2.6%)	.009
Q21 The suitable age for vaccination of nine-valent HPV vaccine is promoted in China	98(9.6%)	85(11.3%)	13(4.9%)	.002
Q22 HPV vaccine can effectively prevent cervical cancer and other cancers caused by HPV infection	235(23%)	199(26.4%)	36(13.5%)	.000
Q23 'If you don't have sex, you don't need the HPV vaccine'. do you think this statement is correct	395(38.7%)	324(42.9%)	71(26.6%)	.000
Q24 The most appropriate time for HPV vaccination	265(25.9%)	216(28.6%)	49(18.4%)	.001
Q25 You can get lifelong immunity from the HPV vaccine	180(17.6%)	156(20.7%)	24(9.0%)	.000
Q26 Whether women need routine gynecological examination after receiving the HPV vaccine	327(32.0%)	271(35.9%)	56(21.0%)	.000

Figure 21 (Deng at al., 2020): Knowledge of HPV and HPV Vaccination among Chinese College Students

A recent study showed parents who initially rejected HPV vaccination for their children and accepted vaccination due to secondary reasons (Kornides et al., 2018). Almost half of the parents who initially declined the HPV vaccine eventually accepted it for their children at a later visit and some in the next 12 months largely due to after learning about HPV and the vaccine (Kornides et al., 2018). Besides, as shown in Figure 19, parents tend to accept vaccination upon receiving counseling from their child's healthcare service provider accepted vaccination at later visits (Kornides et al., 2018).

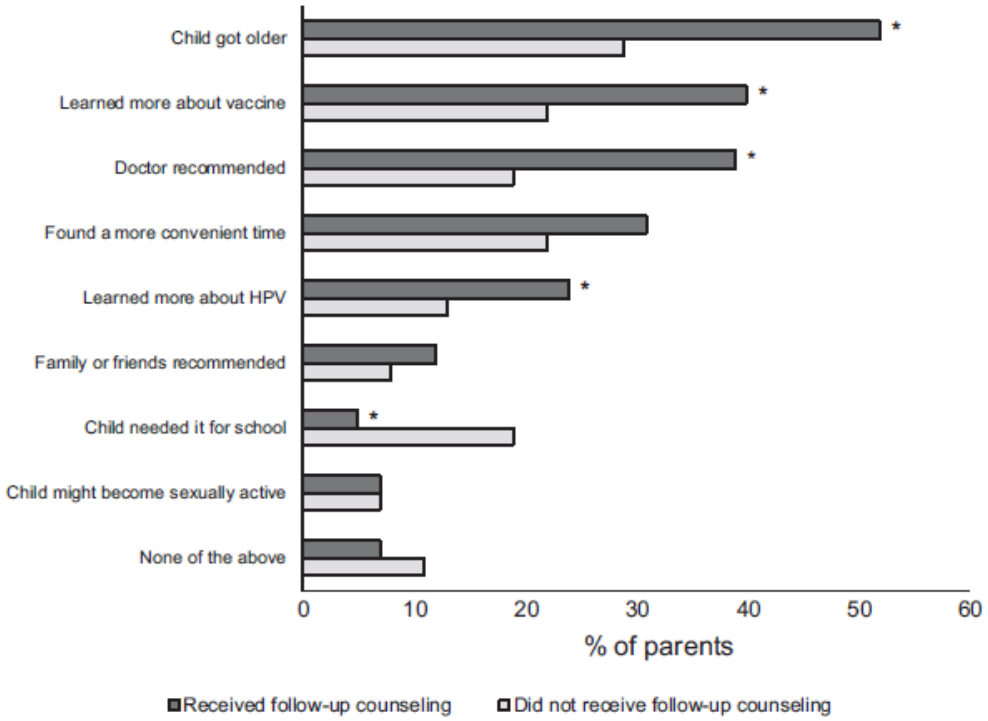


Figure 22 (Kornides et al., 2018): Reasons for secondary acceptance of Human Papillomavirus Vaccination

Apart from parents, knowledge of HPV and HPV vaccination among teenagers are not well versed (Ndikom et al., 2017). As shown in Figure 20, most individuals are not aware of the HPV virus, HPV related cancers and the availability of HPV vaccines (Ndikom et al., 2017). In certain countries, teenagers are unaware HPV can be transmitted sexually and many are unaware that having multiple sexual partners is an infection risk factor (Ndikom et al., 2017). Perception about HPV vaccination is relatively low among teenagers, where many of them are unaware HPV vaccine prevents genital warts and cervical cancer (Ndikom et al., 2017). Adolescents are willing to accept the HPV vaccine if they are at high risk of getting HPV (Ndikom et al., 2017). Apart from parents' decisions and approvals, religious beliefs and ethnic background play a significant role in accepting HPV vaccination (Ndikom et al., 2017). In certain countries, religion, and ethnic background play a significant role in an individual decision. Teenagers in those countries are willing to accept HPV vaccination if they are encouraged by religious and ethnic organizations (Ndikom et al., 2017).

Perceptions	Yes	No	Don't know
The HPV vaccination can prevent cervical cancer	68 (23.0)	19 (6.4)	209 (70.4)
HPV is the main cause of cervical cancer	43 (14.5)	34 (11.5)	219 (74)
Cervical cancer is a sexually transmitted disease	48 (16.2)	71 (24.0)	177 (59.8)
The HPV vaccine increases the occurrence of cervical cancer	28 (9.5)	43 (14.5)	225 (76)
HPV vaccine prevents against contacting genital warts	59 (19.9)	26 (8.8)	211 (71.3)
HPV is the main cause of genital warts	42 (14.2)	27 (9.1)	227 (76.7)
HPV is transmitted sexually	40 (13.5)	35 (11.8)	221 (74.6)
Having multiple sex partners reduces risk of HPV infection	35 (11.8)	57 (19.3)	206 (68.8)
Sex at an early age increases risk of HPV infection	72 (24.3)	26 (8.8)	198 (66.9)
HPV infection can easily be noticed	44 (14.9)	35 (11.8)	217 (73.3)
HPV can survive for a long time within the body	45 (15.2)	27 (9.1)	224 (75.7)
The virus can clear from the body without treatment in some individuals	36 (12.2)	46 (15.5)	214 (72.3)

Figure 23 (Ndikom et al., 2017) : Respondents' perception about HPV vaccine and cervical cancer

3.4.2 Public Perception of HPV and Acceptance of Vaccination in Malaysia

In a study conducted among Malaysian 13-year-old students, knowledge of HPV and HPV vaccine was low (Wong et al., 2018). Many young females presumed HPV vaccination helps get rid of the need for Pap smears (Wong et al., 2018). Besides, many also believe that HPV infection occurs mainly in women (Wong et al., 2018). Among those who are aware of HPV and HPV vaccination, most young females heard of HPV from various sources prior to vaccination, including teachers, media (television/radio), and parents (Wong et al., 2018). In another study conducted, healthcare professional influence appears to be an important influence in accepting HPV vaccination (Widjaja., 2019). As shown in Figure 34, vaccine recipients agreed to be vaccinated following healthcare professionals' suggestion followed by parental or partner's force and self-awareness regarding HPV infection (Widjaja et al., 2019). When comparing the level of knowledge across gender, females scored higher than males (Widjaja et al., 2019). This could be because most of the disease prevalence, campaigns, and social assumptions are inclined towards the female population (Widjaja et al., 2019). Many men presume HPV affects females primarily, and vaccinating females would be sufficient in controlling disease transmission with the assumption of normal sexual behavior (Widjaja et al., 2019).

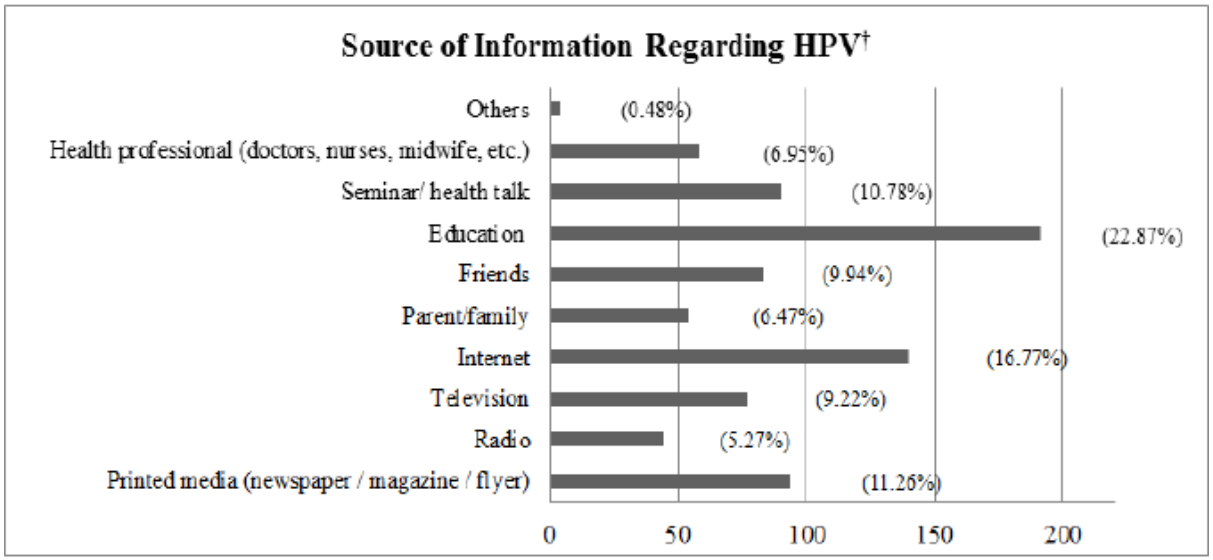


Figure 24 (Widjaja., 2019): Sources of information regarding HPV. The figure shows the summary of the respondent's source of information. (40.245).

Many Malaysians refuse HPV vaccination mainly due to pricing, awareness of vaccine availability, concern on safety and efficacy, self-embarrassment, and inability to bear 3 injections at a different time frame (Widjaja et al., 2019). As shown in Figure 35, parental refusal remains another burden to get vaccine recipients vaccinated (Widjaja et al., 2019).

Statements	Frequency
Acceptance statements†	
Suggested by healthcare professional.	217 (27.4%)
Benefits of vaccination regardless of the pricing.	118 (14.9%)
I can be sexually active to everyone after the injection.	64 (8.1%)
Forced by parent / partner.	179 (22.6%)
Self-awareness regarding HPV infection.	178 (22.5%)
Discounted price of vaccination.	35 (4.4%)
Others.	1 (0.1%)
Refusal statements†	
I feel shy to talk about it to my parent/healthcare professional.	99 (14.6%)
I don't have time to bare 3 injections to the hospital.	87 (12.8%)
My parents do not allow me to take the vaccine.	29 (4.3%)
Safety and efficacy regarding the vaccine.	108 (15.9%)
Price.	186 (27.2%)
I'm not sure where to get the vaccination.	133 (19.6%)
Others	39 (5.7%)
Intentional Attitudes	
Willing to be more educated.	377 (88.7%)
Not interested with further elaboration.	48 (11.3%)

Figure 25 (Widjaja et al., 2019): Participant's Attitude Towards HPV Vaccination

3.4.3 Cost of Human Papillomavirus Vaccine

The cost and affordability of HPV vaccine remain the top reasons for not accepting the HPV vaccine (Verma et al., 2020). Many parents refuse vaccination, preferring to have HPV vaccine included under insurance coverage or national immunization program (Brown et al., 2016). In a study conducted, parents who viewed HPV vaccination cost as expensive or very expensive were more likely to refuse to pay for vaccination (Dinh Thu et al., 2017). Among those willing to pay for vaccination for children are parents who were previously diagnosed with cervical cancer (Dinh Thu et al., 2017). HPV vaccination cost is an important determinant of parents' willingness to pay for their daughter's vaccination (Dinh Thu et al., 2017). The price range of HPV vaccines was made between the US $0.20 per dose to 20% of the Gavi purchase since 2013 by the Vaccine Alliance (Gavi). (LaMontagne et al., 2017). Currently, low-income countries and lower-middle-income countries are currently eligible to access vaccines at these discounted prices through Gavi (LaMontagne et al., 2017). Figure 21 shows the average price paid per HPV vaccine dose (in USD) by countries (Mark Jit., 2021). In a cost-effectiveness study conducted, the number of HPV vaccination introductions in high- and middle-income countries increased each year steadily (Figure 21). The number of HPV vaccine introductions in these countries increased until 2016, which then plateaued (Mark Jit., 2021). Putting vaccination costs aside, the introduction of HPV vaccination will also reduce HPV-related incidences and mortality (De La Fuente et al., 2019). Uptake of HPV vaccination reduces cost related to the treatment of HPV-related genital warts and cancers (Burger et al., 2020). It was found, with an estimation of 70% HPV vaccination coverage in 48 Gavi-eligible countries, the nonvalent HPV vaccine averted cervical cancer cases (Burger et al., 2020).

WHO region	World Bank country income classification			
	High	Upper-middle	Lower-middle	Low
Africa	27.87	15.25	4.60	4.59
Americas	10.75	9.35	7.18	No data
Eastern Mediterranean	No data	No data	No data	No data
Europe	48.86	50.04	4.75	No data
Southeast Asia	No data	9.59	5.73	No data
Western Pacific	56.31	20.17	8.31	No data

Figure 26 (Mark Jit., 2021): Average price paid per HPV vaccine dose (in US) by countries from 2013-2018.

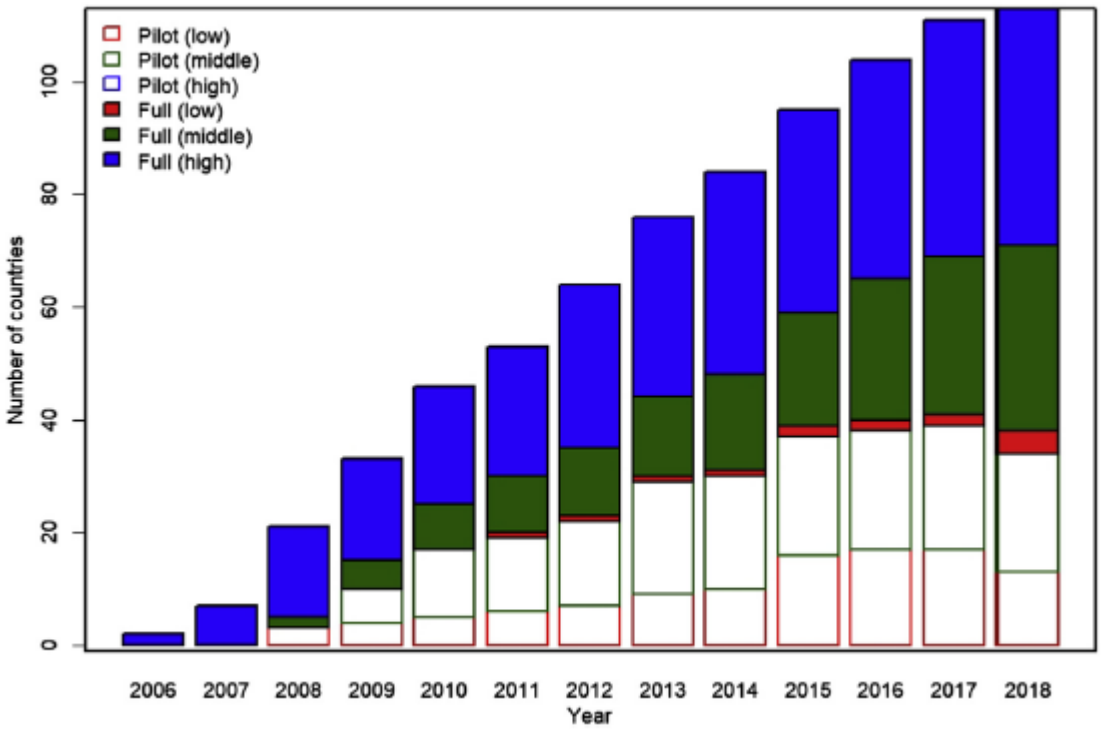


Figure 27 (Mark Jit., 2021): Number of countries each year with introductions of HPV vaccination

In April 2009, the World Health Organization recommended that the HPV vaccination be included in national immunization programs, emphasizing that cervical cancer prevention should be a priority in every country (LaMontagne et al., 2017). In 2014, the World Health Organization (WHO) reiterated its support to include HPV vaccination in the national immunization program. In the United States (US), the Advisory Committee on Immunization Practices recommended HPV vaccination since 2006 (Brandt et al., 2016). Since 2006, about 42 states and territories in the US have introduced legislation to require the HPV vaccine, fund the vaccine or educate the public or school children about the HPV vaccine (NCSL.2019). However, the uptake of HPV vaccination was lower due to concerns about side effects, lack of health care provider recommendations, concerns about safety, and general knowledge on HPV vaccination. Both Australia and Rwanda have proven the ability to increase the update of HPV vaccination among girls in school through policy. In Rwanda, the government worked together with vaccine manufacturers for school-based vaccination and community-based for non-schooling girls. Meanwhile, in Australia vaccination program was introduced at the national level through policy and financing for girls aged 12 through 26 years old (Brandt et al., 2016).

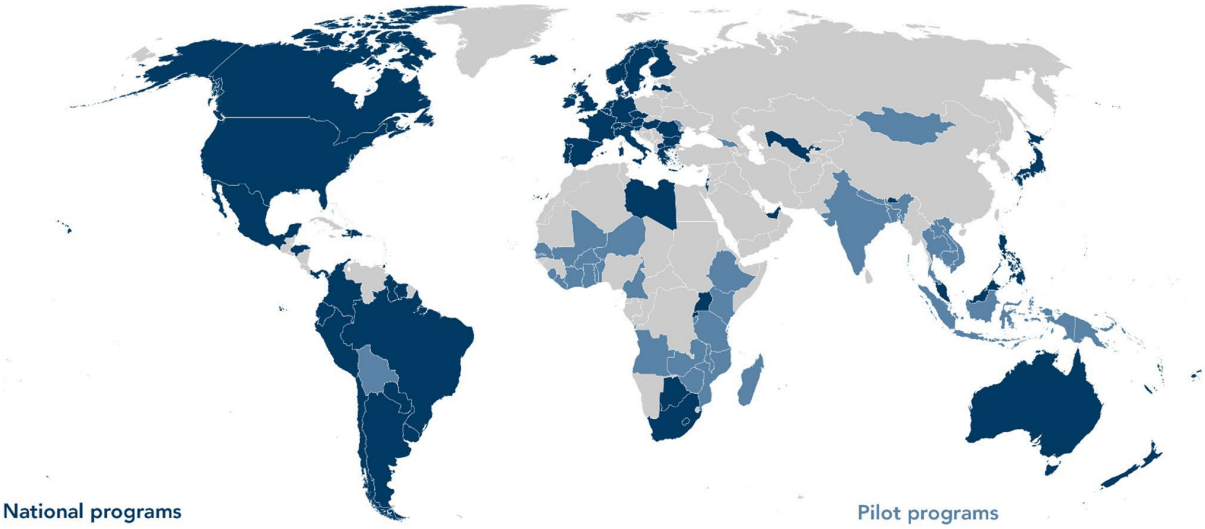
HPV vaccine uptake rates have been varied widely not only by country to country but also within the same country or jurisdiction, Figure 24 (Perez et al., 2018). This is due to different programs, access to services, and the acceptance and beliefs towards HPV vaccination of the citizens, policymakers, or community leaders in different areas and regions (Perez et al., 2018). As shown in Figure 23, in Australia and Denmark, a significant reduction in CIN or genital warts was observed after the quadrivalent HPV vaccine was added as part of the National Immunization Program (NIP) (Kim et al., 2018). The quadrivalent vaccine was introduced as a NIP for women aged 12-26 years old in the year 2007 in Australia (Kim et al., 2018). Australia then introduced HPV vaccination for free for boys in 2013 (Perez et al.,2018). This program showed a decline of up to 92% in cervical HPV types

among women aged 18-35 years. It also showed a 54% reduction in the incidence of high-grade cervical abnormalities in girls under 18 years of age, and a 90% reduction in genital warts in heterosexual men and women under 21 years of age (Perez et al., 2018). Incidence of genital warts then decreased by 89.7% in women under 21 years old compared to before vaccination (Kim et al., 2018). Meanwhile, in Denmark, a significantly lower risk of cervical lesions was observed in 247,313 women vaccinated with the quadrivalent HPV vaccine in 2006 (Kim et al., 2018). This observation was clear in women born between 1993 and 1994, where the risk of CIN 3 reduced up to 80% compared to unvaccinated women (Kim et al., 2018). The HPV vaccine was introduced in the United States NIP in 2006, and infection rates of HPV 6, 11, 16, and 18 were reduced by 56% between 2007 and 2010 compared to 2003-2016 before the introduction of the quadrivalent HPV vaccination program (Kim et al., 2018).

Programs	Australia	France	Germany	UK	Denmark	Sweden	USA	Japan
NIP introduction (male)	2007 (2013)	2007	2007	2008	2009	2012	2006 (2011)	2013
Routine vaccination	12–13	11	12–17	12–13	12	10–12	11–12	12–16
Catch-up vaccination	13–26	12–20	-	13–17	13–15	13–17	13–26	-
NIP vaccine	2HPV	2HPV	2HPV	4HPV	9HPV	2HPV	9HPV	2HPV
	4HPV	4HPV	4HPV			4HPV		4HPV
	9HPV	9HPV	9HPV			9HPV		

Figure 28 (Kim et al., 2018): Introduction of HPV vaccines into the NIP by country

In the United States (US), the HPV vaccine is funded nationally by the Vaccines for Children program private insurance and must be covered by the Affordable Care Act (Perez et al., 2018). In 2017, in the US, 48.6% of adolescents (53.1% of females; 44.3% of males were up to date with the HPV vaccination series of recommendations, which was the same increase from the year prior) (Perez et al., 2018). The vaccination program in Canada is different from the US because it is predominantly administered through publicly funded school-based provincial programs throughout the country (Perez et al., 2018). Meanwhile, in Europe, all 28 European Union (EU) countries have implemented HPV vaccination, where vaccine uptake rates have been reported as low as 10% (Perez et al., 2018). Meanwhile, disparities were seen across central and South America due to variations in funding (whether the Pan American Health Organization supported funding), such as Haiti, Brazil, and Bolivia (Perez et al., 2018).



National programs

American Samoa
Andorra
Anguilla
Argentina
Aruba
Australia
Austria
Bahamas
Barbados
Belgium
Belize
Bermuda
Bhutan
Bonaire
Botswana
Brazil
Brunei
Bulgaria
Canada
Cayman Islands
Chile
Colombia
Cook Islands
Curacao
Czech Republic
Denmark
Dominican Republic
Ecuador
Fiji
Finland
France
French Polynesia
Germany
Greece
Guam
Guyana
Honduras
Hungary
Iceland
Ireland
Israel
Italy
Japan
Kiribati
Latvia
Lesotho
Libya
Lichtenstein
Luxembourg
Macedonia
Malaysia
Malta
Marshall Islands
Mexico
Micronesia
Monaco
Netherlands
New Caledonia
New Zealand
Niue*
Northern Marianas
Norway
Palau
Panama
Paraguay
Peru
Philippines
Portugal
Puerto Rico
Rwanda
Samoa*
San Marino
Seychelles
Singapore
Slovenia
South Africa
Spain
St. Eustatius
Suriname
Sweden
Switzerland
Trinidad and Tobago
Uganda
United Arab Emirates
United Kingdom
United States
Uruguay
US Virgin Islands
Uzbekistan
Vanuatu

Pilot programs

Angola
Bangladesh
Benin
Bolivia
Burkina Faso
Burundi
Cambodia
Cameroon
Cote d'Ivoire
Ethiopia
Gambia
Georgia
Ghana
Haiti
India
Indonesia
Kenya
Lao PDR
Liberia
Madagascar
Malawi
Mali
Moldova
Mongolia
Mozambique
Nepal
Niger
Papua New Guinea
Sao Tome
Senegal
Sierra Leone
Solomon Islands
Tanzania
Thailand
Togo
Vietnam
Zambia
Zimbabwe

Figure 29 (Perez et al., 2018): Global Progress in HPV vaccine introduction (June,2017).

3.4.4 Role of Physicians in HPV Vaccination

Apart from other barriers to HPV vaccination, such as parental attitudes and financial concerns, many parents include physician recommendations as the primary reason for not vaccinating (Rutten et al., 2017). Lack of a strong recommendation is one of the important barriers to the HPV vaccination rate (Kempe et al., 2021). Most teenagers follow through with vaccination following physician recommendations (Rutten et al., 2017). In a study conducted among physicians, it was found that most clinicians recommend HPV vaccination to their female patients compared to male patients (Rutten et al., 2017). Meanwhile, a significantly high number of pediatricians recommend HPV vaccination to both female and male patients compared to those practicing in other primary care specialities (Rutten et al., 2017). Most physicians found rates of vaccination among females are higher than in males, which could be due to initial public awareness efforts of the vaccine were focused on females focusing on the prevention of cervical cancer (Rutten et al., 2017). As shown in Figure 25, similar results were obtained where female patients' recommendations are higher than male patients (Kempe et al., 2021). Many parents are confident in vaccinating their children depending on the physician's recommendation's quality, which is defined as the strength of recommendation along with a message on cancer prevention and support for the same-day vaccination (Rutten et al., 2017). This has proven to be a significant association with vaccination association and completion (Rutten et al., 2017). Parents expect physicians to provide a clear and strong recommendation when parents' hesitancy is high (Rutten et al., 2017). Physicians need to provide targeted and scientifically sound recommendations regarding HPV and HPV benefits to parents (Anderson et al., 2017).

Despite high recommendations by physicians, Figure 26 shows many parents refuse to vaccinate their children following information received from the internet or social media, concerned about the safety of the vaccine. Parents feel vaccine is unnecessary for their daughters or sons and opposition to moral and religious reasons (Kempe et al., 2021). According to physicians, parents are concerned that vaccination may encourage their children to have early sexual behavior or risky behavior, may cause infertility in their children, concern about side effects, efficacy, and waning immunity if the vaccine is given too early, too many doses of the vaccine, some belief risk of HPV infection-related cancers and diseases are not high enough to receive vaccination, insurance coverage and pricing is also a concern. (Kempe et al., 2021).

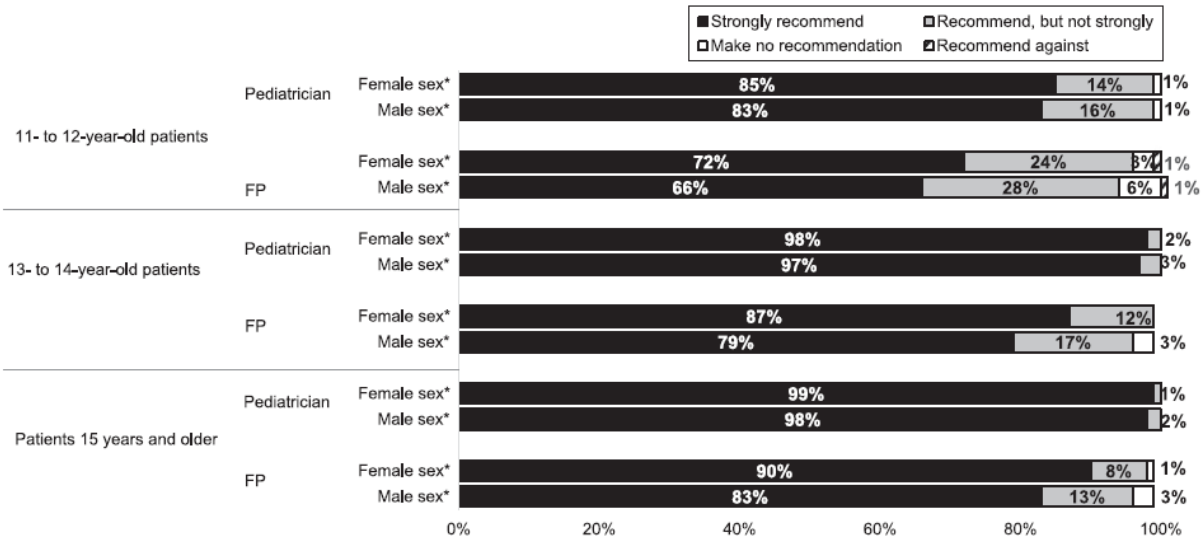


Figure 30 (Kempe et al., 2021): Recommendation of HPV vaccine by physician by patient age and gender

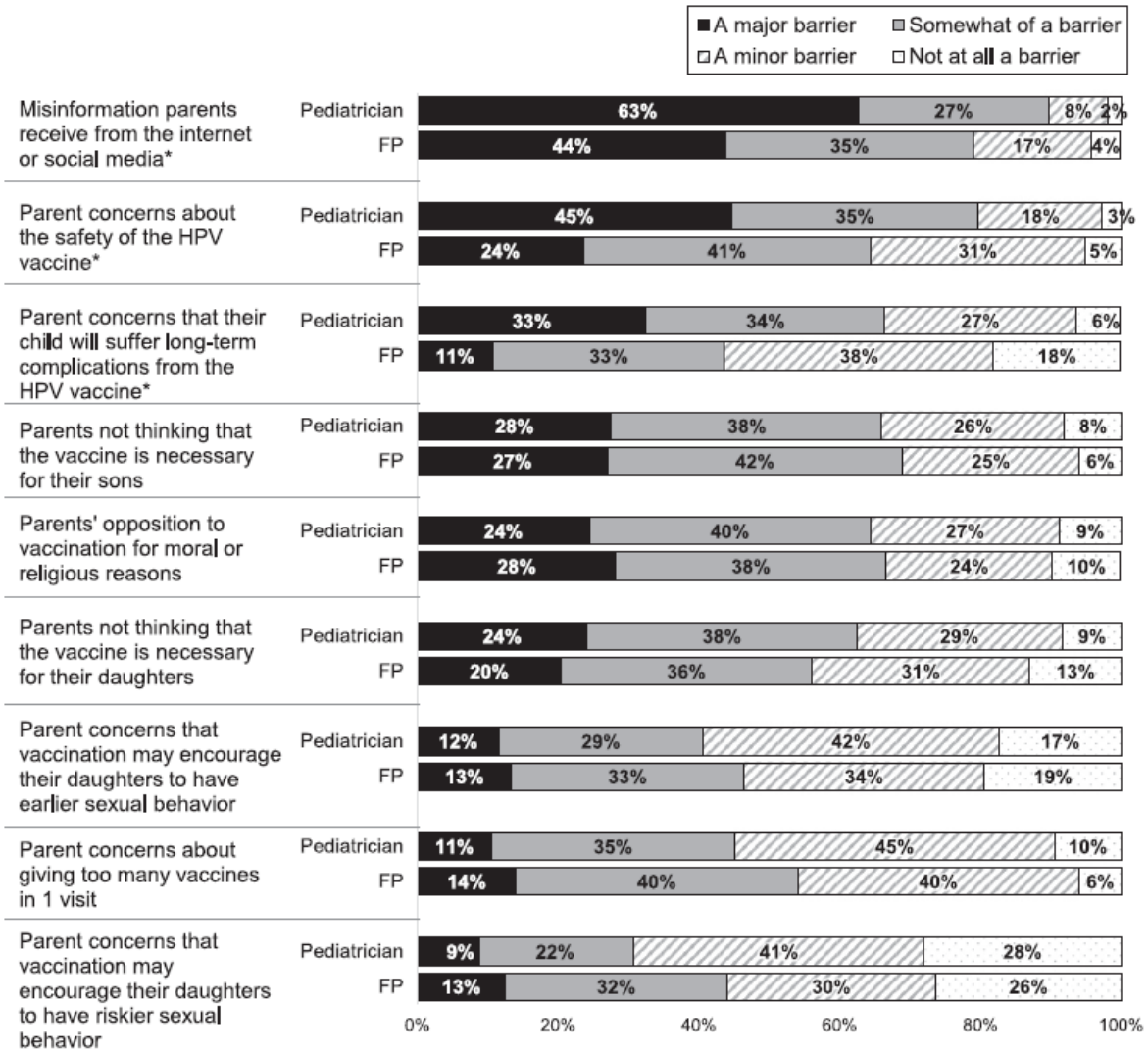


Figure 31 (Kempe et al., 2021): Barriers to HPV vaccination according to physicians

3.4.5 Role of Media in HPV Vaccination Uptake

Deception about vaccines is a concern because vaccine misinformation is growing in the media, leading to vaccine hesitancy and juridical or political decisions (Agergaard et al., 2020). The current use of the internet and social media allows social media users to share vaccine information across the globe and possibly affect the vaccination acceptance rate (Agergaard et al., 2020). Social media has enabled the previously unprecedented public sharing of health information, including health problems and outcomes and patients' experiences concerning medications (Ventola CL.,2018). Patients and caregivers consult the internet and participate in online interactions to obtain medical or drug information to supplement the guidance provided by their healthcare professionals (Ventola CL., 2018). As a result, social media, including, social networks, chat rooms, health blogs, and patient community websites, provide a more patient-centered model of adverse event reporting (Ventola.,2018). Vaccine communication is safe if everyone communicating about vaccines recognizes based on scientific evidence about efficacy and safety (Agergaard et al., 2020). The issue arises when information shared and introduced to the public on social platforms has little or no scientific evidence, this concerns group of parents in deciding on the vaccination their children (Agergaard et al., 2020). In the past decade, vaccine-related conspiracy theories have been prevalent on the internet (Chen et al., 2020). For example, vaccine websites and pages on social media not only question the reliability of vaccines and link vaccinations with specific adverse reactions, but they also consistently make untruthful claims such as that vaccines contain mercury and that vaccine provides temporary protection (Chen et al., 2020). As shown in Figure 27, many parents and adolescents in the United States are exposed to stories about HPV vaccination and its harm on various communication channels, including social media. Negative information tends to influence higher in shaping perceptions and decisions than positive information (Margolis et al., 2017). Most of the time, people attend to, trust, and share negative information greater than positive information (Margolis et al., 2017). Stories of HPV vaccine harms may be more negative, sensational, and controversial than stories of HPV vaccine-preventable diseases (Margolis et al., 2017). Therefore, parents may give more attention to and more fully process stories of harm than stories of HPV vaccine-preventable diseases (Margolis et al., 2017). This eventually impacts public health where stories of HPV vaccine could be a blockade to communication promoting vaccination in a timely manner (Margolis et al., 2017).

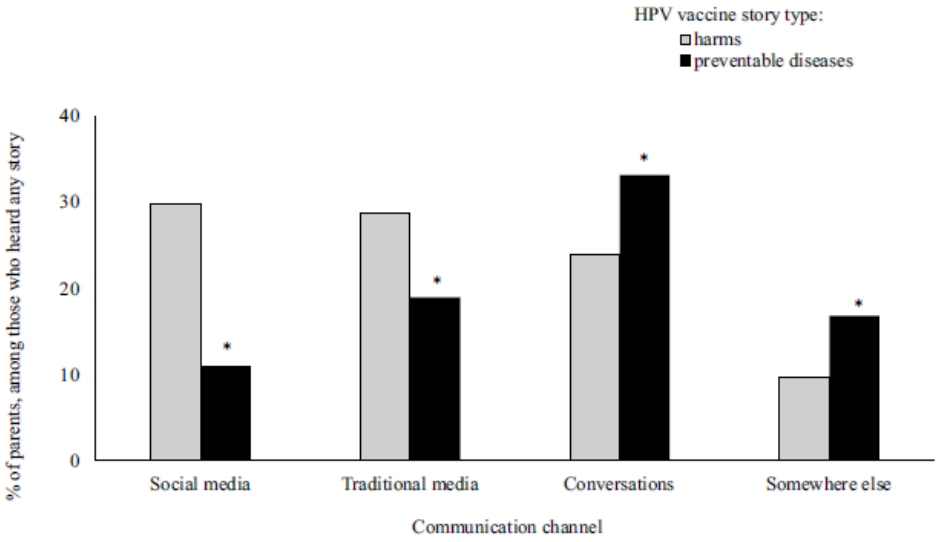


Figure 32 (Margolis et al., 2017): Sources of HPV vaccine information, among parents, United States 2017

Media coverage of the HPV vaccine has changed over time (Chen et al., 2020). In the early 2000s, when the HPV vaccine was under research and development, it received huge media attention (Chen et al., 2020). Between 2003 to 2005, about 285 newspapers in the United States released media content about the HPV vaccine providing information on the experimental status, the efficacy of the vaccines, and the association between the HPV vaccine and the prevention of HPV-related cancers (Chen et al., 2020). The rise of HPV antivaccine sentiment on social media has been a concern that is on the rise (Du et al., 2020). In a study conducted, a total of 258,418 tweets using the Twitter platform related to HPV vaccines in the United States were identified with estimating a total number of global Twitter users who may have been exposed to one or more of these tweets (Dunn et al., 2017). The topics vary, where it contains positive information on scientific evidence or educating on the use of HPV vaccine, debates on HPV vaccination, and sharing of concerns such as safety and political influences (Dunn et al., 2017). Meanwhile, on Instagram, it was discovered that antivaccine posts received, on average more likes than pro-vaccine (Massey et al., 2020). Similarly, YouTube pro-HPV vaccine content relied heavily on information and evidence; meanwhile, antivaccine content on YouTube focused on side effects and conspiracy theories (Massey et al., 2020).

3.5 HPV Vaccination in Males

The quadrivalent HPV vaccine was not licensed for males by the FDA until 2009 (Ackerson et al., 2017). In 2010, ACIP published a recommendation for permissive use of the quadrivalent HPV vaccine to prevent genital warts in males aged 9-26 years of age. Meanwhile, FDA added prevention of anal cancer to the indication of quadrivalent vaccine in 2010 (Ackerson et al., 2017). Currently, there are no methods for the detection of HPV in males, however, it's recommended for males to receive HPV vaccination (Cooper et al., 2018). At the same time, healthcare system does not encourage males for routine screening for anal, penile, or throat cancers (Copper et al., 2018). Overall, males aged 14-59 years have a high prevalence of high-risk HPV compared with females aged 25 and 29 years (Copper et al., 2018).

Vaccinating the male population does benefit the females through herd immunity (Ackerson et al., 2017). Herd immunity can be achieved through the efficacy of the HPV vaccine in males and the maximum vaccination rate in females (Ackerson et al., 2017). Besides, vaccination in males also plays an important role in reducing cancers (Ackerson et al., 2017). The HPV vaccination in men reduced the risk of HPV causing diseases in men and reduced transmission of HPV to females (Allison et al., 2013). HPV vaccination in males prevents many HPV-related conditions such as penile, anal, neoplasia's, head and neck, genital warts, recurrent respiratory papillomatosis. Significant morbidity can be reduced in boys and men to live a healthier lifestyle by preventing these life-threatening diseases (Ferris et al., 2009). Extending HPV vaccination in males has a positive impact on public health and economic benefits. In a mathematical model study, vaccination with the HPV vaccine reduces incidences of all HPV-6/11/16/18 related diseases in both females and males. The inclusion of males in the HPV vaccination program provides both direct and indirect benefits (lowering the incidences of disease) by reducing the prevalence of HPV infection in a population. Vaccination of HPV in men can reduce genital wart cases, CIN 2/3 cases, cancer cases, and cancer death among women in 100 years following the introduction of the vaccine (Elbasha et al., 2010). The prevalence of HPV vaccine uptake is significantly higher in females than in females (Choi et al., 2018). Females are generally more aware of HPV and HPV vaccination than males (Choi et al., 2018).

The key barriers to HPV vaccination among male adolescents include the lack of perceived benefit or need to vaccinate males, lack of awareness that vaccine should or can be given to males, not receiving a healthcare professional's recommendation for the HPV vaccine, and the cost (Choi et al., 2018). Improving the HPV vaccine has been a challenge throughout the years, particularly in males (Ackerson et al., 2017). The HPV vaccine is often promoted as developed for females where HPV disease is labeled for females or females' disease, and the HPV vaccine is prone to be known as cervical cancer vaccine (Choi et al., 2018). People assumed that the HPV vaccine is not relevant to males (Choi et al., 2018). The most common barriers to getting boys vaccinated are cost, parents' attitudes towards vaccination, and infrequent office visits by male adolescents (Allison et al., 2013). The major barrier to getting boys vaccinated with HPV is finance due to lack of reimbursement and failure of insurance companies covering for boys. Parents are often concerned about the safety of the HPV vaccine and worried it might encourage the adolescent to engage in sexual behaviors (Allison et al., 2013)

Barrier	Major Barrier, %	Somewhat a Barrier, %	Minor Barrier, %	Not a Barrier, %
Vaccine financing issues				
Failure of some insurance companies to cover HPV4 for boys	56	27	8	8
Lack of adequate reimbursement for vaccination	49	27	12	11
Parents unable to pay the out-of-pocket cost for vaccine	48	28	13	11
The up-front costs for my practice to purchase the vaccine	24	27	23	26
Parental attitudes about HPV4 for boys				
Parents not thinking that HPV4 is necessary for their sons	19	45	29	7
Parents' opposition to HPV4 vaccination for moral or religious reasons	13	26	46	15
Parents' concern about the safety of HPV4 for their sons	11	33	43	13
Parents' concern that vaccination may encourage earlier sexual behavior	6	25	41	28
Parents' concern that vaccination may encourage riskier sexual behavior	5	25	42	28
Logistic barriers to HPV4 administration				
Infrequent office visits made by male adolescent patients	12	38	34	17
Difficulty ensuring completion of 3-dose vaccine series	11	35	41	13
The time it will take me to discuss HPV4	7	19	41	34
General administrative a burden to my practice	7	18	32	43
Providers' attitudes about the safety of HPV4 and effect of HPV4 vaccination on boys' behavior				
My concern about the safety of HPV4 for boys	4	7	21	69
My concern that vaccination may encourage riskier sexual behavior	1	5	13	82
My concern that vaccination may encourage earlier sexual behavior	1	4	11	85
My opposition to HPV4 vaccination for moral or religious reasons	1	1	3	95

Figure 33 (Allison et al., 2013): Barries to Quadrivalent HPV vaccine administration in Boys, according to physicians

3.5.1 Parental and Individual (Males) Knowledge on HPV and HPV Vaccination

In a study conducted, young adult men responded that they have heard of HPV from health education classes, television, or friends (Gerend et al., 2009). Men's intentions to get vaccinated with the HPV vaccine were moderately high and the acceptance of HPV vaccine by showing the benefits of vaccination to female partner(s) remained unchanged compared with presenting young male adults with benefits to the male alone (Gerend et al., 2009). However, awareness and knowledge of HPV vaccination are higher in women as compared with men. The reason is that women were probably familiar and exposed to the knowledge of HPV through frequent health checkups for cervical cancer and pap smear (Ferris et al., 2009).

In a survey conducted, out of 295 participants; 58% of men have heard of HPV through television, health education, and friend. Furthermore, about half have heard of the HPV vaccine. The knowledge of HPV was considered at baseline. Although, some men were confused between genital warts and genital herpes (Gerend et al., 2009). As shown in Figure 29, in comparison by gender, heterosexual males and bisexual/homosexual males had a lower prevalence of HPV vaccine uptake than heterosexual males (Choi et al., 2018). Although most of the males are aware of HPV vaccination, the overall prevalence of HPV vaccination is low (Choi et al., 2018). Although males who hear and attend college hear about HPV vaccination, the vaccine uptake remains low (Cooper et al., 2018). Having a formal education does not translate into having more knowledge about HPV (Cooper et al., 2018). Males have moderate knowledge of the HPV vaccine, and most do not intend to receive the vaccine (Cooper et al., 2018).

Response	All	Male	Female	Chi Square Test
	N = 888	*N* = 306	*N* = 582	*p*-Value
Vaccine uptake				
Q1: HPV vaccination, *n* (%), *n* = 876 ^				***<0.001***
Yes	242 (27.6%)	14 (4.7%)	228(39.7%)	
No	573 (65.4%)	260 (86.4%)	313 (54.4%)	
Unsure	61 (7.0%)	27 (9.0%)	34 (5.9%)	
Overall	876	301	575	
Knowledge				
Q2 I have heard about HPV vaccination, n (%), *n* = 879 ^				***0.002***
Yes	803 (91.4%)	263 (86.8%)	540 (93.8%)	
No	33 (3.8%)	19 (6.3%)	14 (2.4%)	
Unsure	43 (4.9%)	21 (6.9%)	22 (3.8%)	
Overall	879	303	576	
Q3: HPV vaccination is for females only, *n* (%), *n* = 879 ^				***0.005***
Yes	290 (33.0%)	109 (36.0%)	181 (31.4%)	
No	403 (45.8%)	117 (38.6%)	286 (49.7%)	
Unsure	186 (21.2%)	77 (25.4%)	109 (18.9%)	
Overall	879	303	576	

Figure 34 (Choi et al., 2018): Knowledge of HPV Vaccination by gender

The low uptake of HPV vaccination in males can be ascribed to the attitude and knowledge of parents because parents are the ones who decide a child's vaccination most of the time (Choi et al., 2018). Children vaccination uptakes are often influenced by the knowledge and attitude of parents (Choi et al., 2018). Parents are against HPV vaccination because of safety concerns, children are too young to have the risk of HPV infection, worry about the vaccine's effectiveness, and the vaccine is not widely used (Choi et al., 2018).

3.5.2 Concern on Cost of Vaccination

Cost is the most common barrier to HPV vaccination in boys (Allison et al., 2013). HPV vaccination for males is not included in the national immunization program in several countries (Choi et al., 2018). Parents are willing to vaccinate their sons if the vaccine is available for free (Tisi et al., 2013). In 2013, HPV vaccination was included in Australia's public fund, making it the first country in the world to make a move to protect boys against genital warts and anal, penile, and throat cancers. The national fund is a school-based program that includes three doses of quadrivalent HPV vaccine given to boys aged 12-13 years old. This scheme also includes boys aged 14-15 years old (Brill., 2013). The United States, Australia, and Canada are considered among the first countries to offer routine vaccination in boys (Tisi et al., 2013).

3.5.3 Recommendation by Physician

In a study conducted by Weiss et al. (2010), physicians agreed that vaccinated males have benefits as the vaccines not only prevent them from anal and penile cancers, but it also prevents them from getting genital and anal warts. This statement is also proven and agreed by physicians in a study conducted by Allison et al., 2013. Most physicians agreed that most male subjects with HPV infection are asymptomatic. Most physicians reported that they routinely recommend HPV vaccines for girls, while they almost do not recommend them for boys. Compared with girls, the percentage of physicians speaking about sexual activity in boys aged 11 and 12 years old is comparably less. However, physicians tend to discuss sexual activity topics with boys aged between 13-18 years old (Allison et al., 2013).

Besides, the prevalence of HPV-associated anal cancer is higher among men who have sex with men (Allison et al., 2013). However, there is a group of physicians who also claim the prevalence of HPV-associated cancers is not high, therefore is possibly no need to vaccinate males with the HPV vaccine (Weiss et al., 2010). In a study conducted by Allison et al., 2013; as shown in Figure 30, most physicians agreed that they routinely also recommend the HPV vaccine for boys apart from girls.

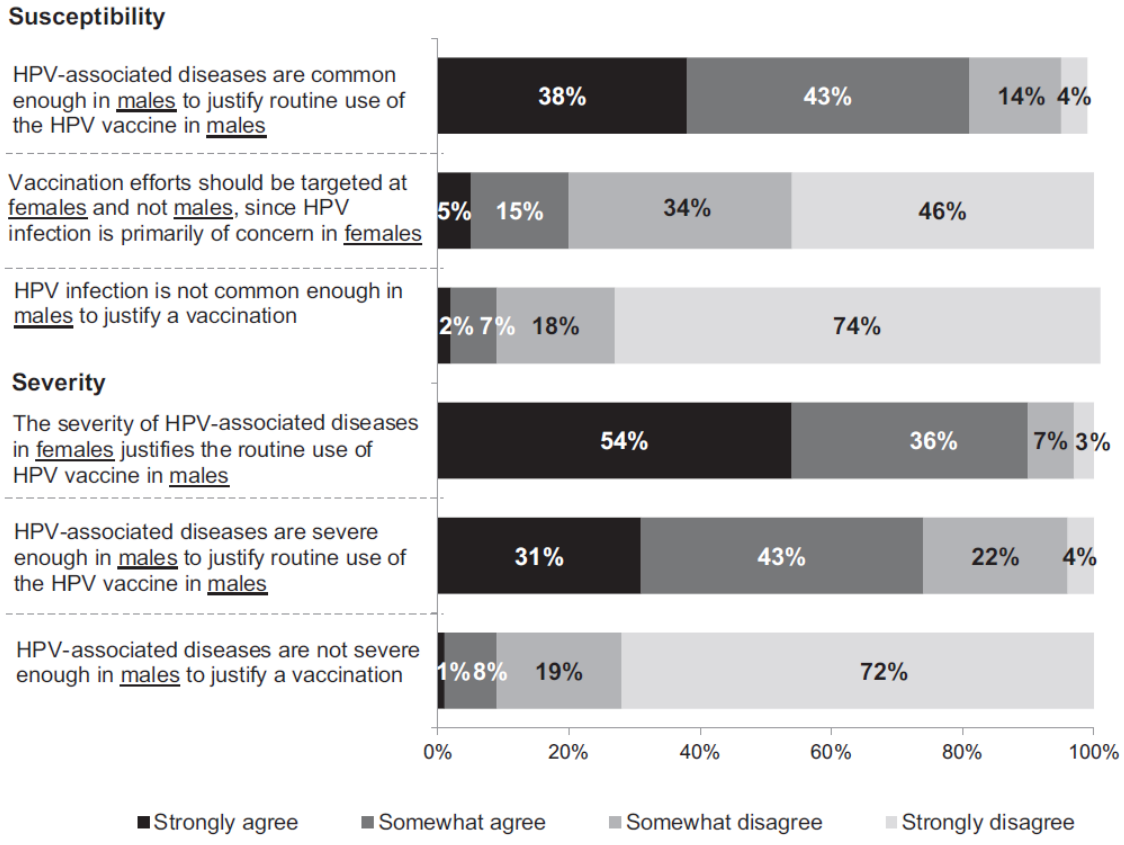


Figure 35 (Allison et al., 2013): Physicians attitudes about HPV4 for boys for paediatricians and family physicians combine. Physicians believe HPV infection is common in males and HPV vaccine should be given in males like females.

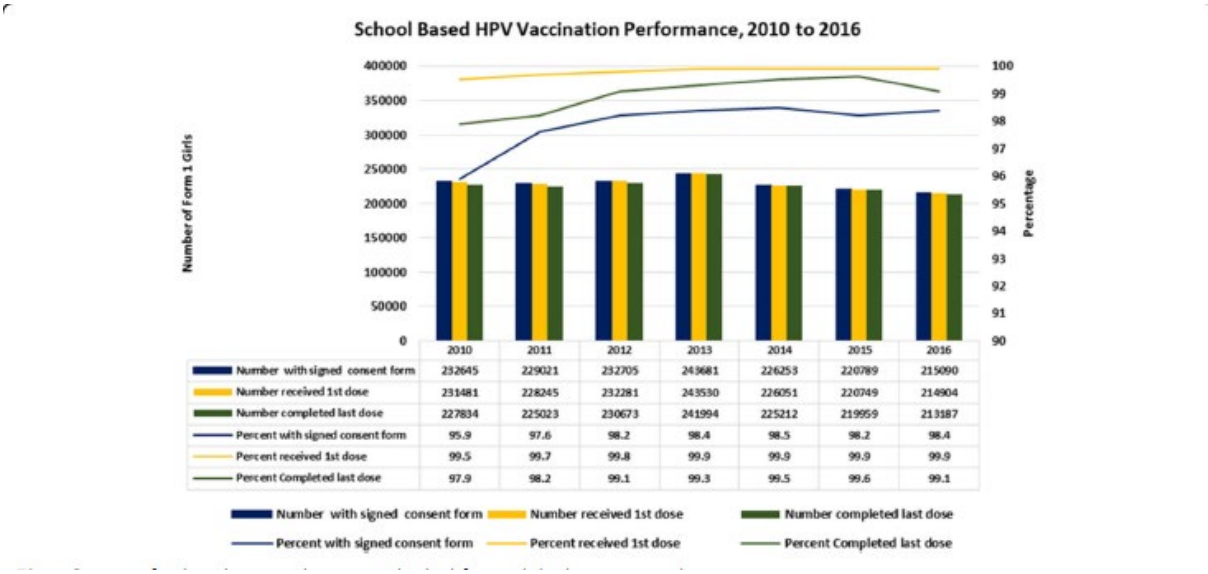
3.6. HPV Vaccines in Malaysia

The HPV vaccine was introduced in the National Immunization Programme (NIP) in 2010 only for females targeting 13 years old (www.hpvcentre.net., 2019). This was launched in 2010 by the Ministry of Health with a bivalent HPV vaccine and given upon getting parental consent (www.hpvcentre.net., 2019). The HPV vaccine is not included in Malaysia NIP for boys (www.lppkn.gov.my., 2019). HPV immunization has been widely accepted since it was introduced in Malaysia in 2010, with more than 95% of participants among female students each year (Wong et al., 2018). In a study conducted, many young women aged 13 years old have a better understanding of HPV infection and vaccination before and after vaccination (Wong et al., 2018). As shown in Figure 36, vaccinated females appear to be aware of HPV better post-vaccination (Wong et al., 2018). A significant change was observed in health beliefs regarding HPV infection and vaccination after receiving the vaccine (Wong et al., 2018). As the HPV vaccine is not introduced in NIP for males, pricing could be an issue to get males vaccinated (Widjaja et al., 2019). Unfordable pricing remains an issue due to their ineligibility towards government programs and the fact that they are yet to receive any income (Widjaja et al., 2019).

Knowledge Item	Correct Responses, n (%)		*P*
	Prevaccination	Postvaccination	
HPV infections are common and many have been infected	542 (27.0)	610 (30.4)	.012
Most people who become infected with HPV do not even know they have it	964 (48.1)	1264 (63.0)	<.001
Only females get HPV infection	164 (8.2)	78 (3.9)	<.001
HPV can cause cervical cancer	1077 (53.7)	1263 (63.0)	<.001
Genital warts are caused by HPV	249 (12.4)	298 (14.9)	.017
HPV is a sexually transmitted infection	467 (23.3)	614 (30.6)	<.001
HPV cannot be cured	236 (11.8)	305 (15.2)	.001
Vaccines are available to prevent HPV infection	1151 (57.4)	1540 (76.8)	<.001
The HPV vaccine gets rid of the need for Pap smear tests	359 (17.9)	530 (26.4)	<.001
Vaccinating boys with HPV can help protect girls against HPV infection	229 (11.4)	206 (10.3)	.214

Figure 36 (Wong et al., 2018) : Knowledge of HPV Infection and HPV Vaccination before and after vaccination

In Malaysia, when HPV vaccination was introduced in 2010, first dose vaccination completion for 2010 was 99.5% for recipients with parental consent, and it improved throughout up to the year 2015 (Muhamad et al., 2018). However, the rate dropped to 83% in 2016, and the main reason for not getting vaccinated was fear of side effects, absenteeism, claimed to have been vaccinated previously (Muhamad et al., 2018). As shown in Figures 37 and 38, the number of completion for doses and three dropped slightly compared with the first dose (Muhamad et al., 2018). The main reason female recipients did not continue second and third dosing was due to the side effects experienced post-first vaccination (Muhamad et al., 2018).



	2010	2011	2012	2013	2014	2015	2016
Number with signed consent form	232645	229021	232705	243681	226253	220789	215090
Number received 1st dose	231481	228245	232281	243530	226051	220749	214904
Number completed last dose	227834	225023	230673	241994	225212	219959	213187
Percent with signed consent form	95.9	97.6	98.2	98.4	98.5	98.2	98.4
Percent received 1st dose	99.5	99.7	99.8	99.9	99.9	99.9	99.9
Percent Completed last dose	97.9	98.2	99.1	99.3	99.5	99.6	99.1

Figure 37 (Muhamad et al., 2018): Percentage of girls with parental consent who had first and third dose vaccination dose, 2010-2016

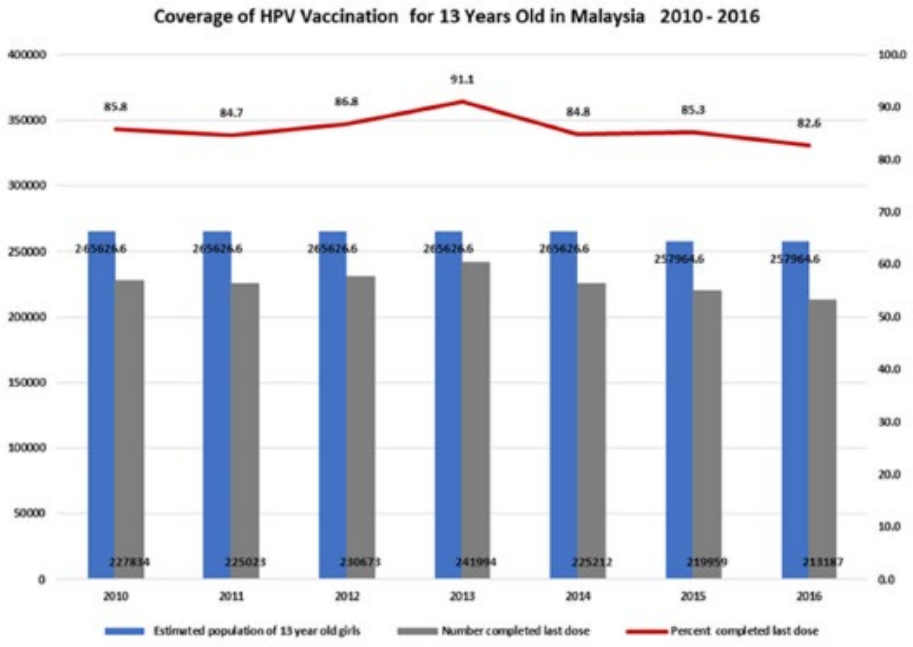


Figure 38 (Muhamad et al., 2018): Percentage of 13 year old girls vaccinated, 2010-2016

3.7 Concern on Safety of Vaccination and HPV Vaccines

Safety and adverse events have a strong relationship with vaccine preventable diseases (Chatterjee et al., 2010). The community has raised concerns on safety when it comes to getting themselves vaccinated with the HPV vaccine. Public concerns and news on adverse events, low confidence in safety findings by health authorities, and inaccurate information's available on websites are barriers to accepting HPV vaccination (Bonanni et al., 2017). While HPV vaccination coverage improves in many countries, a drop in vaccination rates has been observed (Perez et al., 2018). Significant reductions in vaccination rates were observed in countries like the Netherlands, Denmark, and Ireland where it dropped as low as below 50% in these countries (Perez et al., 2018). The reason for the drop-in vaccination rate is due to concern of parents over safety due to information spread by certain groups, often through media (Perez et al., 2018). The controversy or argument over the MMR vaccine and autism has caught attention all over the globe. Although this has been proven false, many American parents continue to refuse vaccination for their children, citing fear of safety, which resulted in a measles outbreak all over the US in 2014 (Bonanni et al., 2017). The controversy over the HPV vaccine in Japan is well-known (Okita et al., 2020). When the HPV vaccine was added to the Japan National Immunization program in April 2013, multiple reports of serious adverse events started circulating in the media, which prompted the suspension of recommendation only two months later (Okita et al., 2020). In countries like Austria, Columbia, Denmark, Ireland, and Japan, the circulation of unfavorable information's regarding the harm of the vaccines influences the vaccination uptake (Perez et al., 2018). In Ireland, a group called Reactions and Effects of Gardasil Resulting in Extreme Trauma (REGRET) demanded a ruling from the High Court to withdraw the vaccine across the country (Perez et al., 2018). As a result of the legal order, the vaccination rate dropped 51% (Perez et al., 2018). Meanwhile, over 700 women filed a class-action lawsuit in Colombia claiming they had been damaged by the HPV vaccine (Perez et al., 2018). In Japan, the Health Ministry withdrew its recommendation for the quadrivalent HPV vaccine though the vaccine is still available (Perez et al., 2018).

Pre- and post-licensure studies on bivalent and quadrivalent HPV vaccines proven that HPV vaccines are generally safe and well-tolerated, parents and patients are concerned about serious adverse events and unknown side effects that could lead to failure of HPV vaccinations (Bonanni et al., 2017). The most common reported adverse events in studies are injection site-related pain, redness, and swelling (Barboi et al., 2019). Meanwhile, systemic adverse events are fatigue, fever, gastrointestinal symptoms such as diarrhea, nausea and vomiting, headache, myalgia, and arthralgia (Barboi et al., 2019). According to physicians, many parents are concerned about the availability of safety data on vaccines (Chow et al., 2010). Certain groups have raised concerns on possible adverse events such as vaccination, which can lead to chances of multiple sclerosis, transverse myelitis, optic neuritis, optic neuromyelitis and encephalomyelitis (Bonanni et al., 2017). Besides, publications by media on the internet claiming adverse events and negative information associated with HPV such as the possibility of developing Complex Regional Pain Syndrome (CRPS) or Postural Orthostatic Tachycardia Syndrome (POTS) has created uneasiness among the public. POTS is characterized by orthostatic intolerance with variable symptoms of cerebral hypoperfusion upon standing, relieved by recumbency (Arana et al., 2017). Despite the lack of scientific and epidemiological data on causality assessment of POTS and HPV vaccine, POTS have raised public concern on safety of the HPV vaccine (Arana et al., 2017). In a study conducted, frequent symptoms associated with POTS

are chronic fatigue, asthma, and chronic headache (Arana et al., 2017). In June 2013, the Japanese Ministry of Health, Labor and Welfare (MHLW) suspended active recommendation of HPV vaccination due to unverified media information claiming more than 50 girls experienced CRPS, chronic pain, absenteeism from school, suffering to walk and seizure (Bonanni et al., 2017).

In a survey conducted, the safety concerns on side effects of HPV vaccines increased from 4.5% in 2008 to 7.7% in 2009 to 16.4% in 2010 and in 2010. The percentage of parents who do not intend to vaccinate their children with HPV vaccination increased dramatically from 4.5% in 2008 to 16.4% in 2010 (Darden et al., 2013). In particular, concerns on systemic reactions (such as fever, gastritis, nausea, vomiting, dizziness, myalgia, and diarrhea), serious AEs (such as syncope, anaphylaxis, allergic reaction, persistent headache, gastroenteritis, hypertension, bronchospasm, and venous thromboembolism), autoimmune disease (AD) (such as hypothyroidism, rheumatoid arthritis, Behcet's syndrome, Raynaud's disease, type 1 diabetes, and vitiligo) and neurological disorders (such as epilepsy, paralysis, Guillain-Barre syndrome, central demyelination, and multiple sclerosis) are parent's real concern, caught more attention compared with common injection-site reaction (De Vincenzo et al., 2014).

3.8 Adverse Events and Pharmacovigilance

Adverse events are defined as any undesirable experience associated with using medicine in a patient (Min et al., 2018). Adverse events also include lack of drug effect, unexpected side effects, administration of a drug in the wrong manner or incorrectly, and administration of manufacturing defect drug (Min et al., 2018). Adverse events range from mild side effects to serious illnesses or death (Min et al., 2018). Adverse events account for one million hospital emergency room visits and hospital admissions (Min et al., 2018). The clinical benefit of a drug depends not only on its efficacy in treating disease but also on its safety and tolerability in individual patients (Liu et al.,2014). The use of drugs must balance between expected therapeutic benefits and possible risks of adverse events (Liu et al.,2014). A drug is approved by regulatory authorities only after its efficacy and safety are proven in a series of clinical trialsVentola.,2018). The randomized, controlled phase three studies are considered important as they involve the study of drug efficacy and safety; however, only a small number of patients enrolled during phase three clinical trials (Ventola.,2018). The clinical trial also takes place within a short period making detecting adverse events difficult (Ventola.,2018). During the post-marketing phase, a drug will be taken by a large population over a prolonged duration, and adverse events may occur which could alter the risk-benefit relation of drugs and may require regulatory action in certain cases (Duval et al., 2014). Adverse events detected in the post-marketing phase help in updating drug labeling or prescribing practices to include or remove new indications or patient populations, off-label uses, or concomitant use with other drugs (Ventola.,2018). Each could result from adverse events detected in the post-marketing phase, which were not previously observed during clinical trials (Ventola.,2018).

Identification of adverse events or adverse drug reactions is a challenge due to the short and biased nature of the pre-marketing drug trials (Liu et al.,2014). Despite various research, tests, and time is taken for a drug to reach the marketing stage, the adverse events are not identified (Duval et al., 2014). During phase I to III of clinical trials, the number of patients is limited, and its selection and treatment often differ from methods used in post-marketing clinical practices (Duval et al., 2014). Early discovery of an adverse event during the post-marketing phase is the primary goal of the pharmacovigilance field (Duval et al., 2014). The primary goal of drug safety regulators and researchers is to identify and observe adverse events that could cause public harm (Ventola.,2018).

Pharmacovigilance (PhV) is defined as the science and activities related to detecting, assessing, understanding, and preventing adverse effects or any drug-related problem (Hauben et al., 2009). It is often used for post-marketing surveillance or drug safety monitoring (Hauben et al., 2009). The primary aim of pharmacovigilance is to improve patient care and safety regarding the use of medicines (Liu et al., 2014). Besides, pharmacovigilance also aims to improve the safety of the patient by benefit-risk and efficacy of medicines (Liu et al., 2014)

3.9 Pre-Marketing Safety Surveillance

The safety of a vaccine is monitored throughout all stages including the development phase, including post-approval by regulatory authorities, as shown in Figure 39 (Salmon et al., 2016). During the development phase of the vaccines, a trial will be conducted on animals to measure and identify potential toxicities (Salmon et al., 2016). Usually, approval is required prior to starting safety and efficacy studies in humans (Salmon et al., 2016). Prior to conducting human studies, vaccine developers are required to obtain Investigational New Drug (IND) applications (Salmon et al., 2016). The IND is submitted to the regulatory authorities such as the FDA and EMA and typically contains preclinical data about the vaccine, manufacturing methods, quality control testing, targeted study subjects, toxicology data, clinical trial protocol, and the list of investigators (Salmon et al., 2016). During the clinical trial phase, the manufacturer is responsible to report serious or unexpected adverse events and annual reports of adverse events to the regulatory authorities (Salmon et al., 2016). During clinical trials, the safety of a vaccine is either made randomized (some human subjects get the new vaccine that is being investigated and some do not) or double-blind (neither the patients nor the investigator knows who received the study product) (Salmon et al., 2016).

Once a vaccine has proven to be effective and safe in clinical trials, the vaccine manufacturer applies to the national regulatory authorities for licensure or registration of the vaccine (Salmon et al., 2016). In the United States, it is called a biological license application which is submitted to the FDA (Salmon et al., 2016). In Europe, the submission is made to the European Medicine Agency (EMA) which provides approval for European Union Member States as well as European Economic Area Countries (Salmon et al., 2016). Regardless, the manufacturers are required to obtain licensure from every country where it will be used prior to having it commercially available (Salmon et al., 2016). During licensure approval requests, respective regulatory authorities of countries will carefully review the clinical trial data including results, chemistry, manufacturing procedure, description of the manufacturing facility, test results, packaging, and labeling of the product (Salmon et al., 2016).

The recommendations for the use of vaccines are obtained by regulatory authorities from advisory committees such as the Advisory Committee on Immunization Practices (ACIP) in the United States (Salmon et al., 2016). For the European countries, the recommendations are made at the national level rather than across the European Union (Salmon et al., 2021). Meanwhile, the WHO provides guidance for use of vaccines in developing countries (Salmon et al., 2016). The role of the advisory committee is to provide recommendations and guidance on the use of vaccines in various ages, risk groups, and information's on the safety of the vaccine (Salmon et al., 2016). For example, recommendations may include the use of the vaccines in specific groups such as pregnant women or children who may have not been studied during the clinical trial (Salmon et al., 2016).

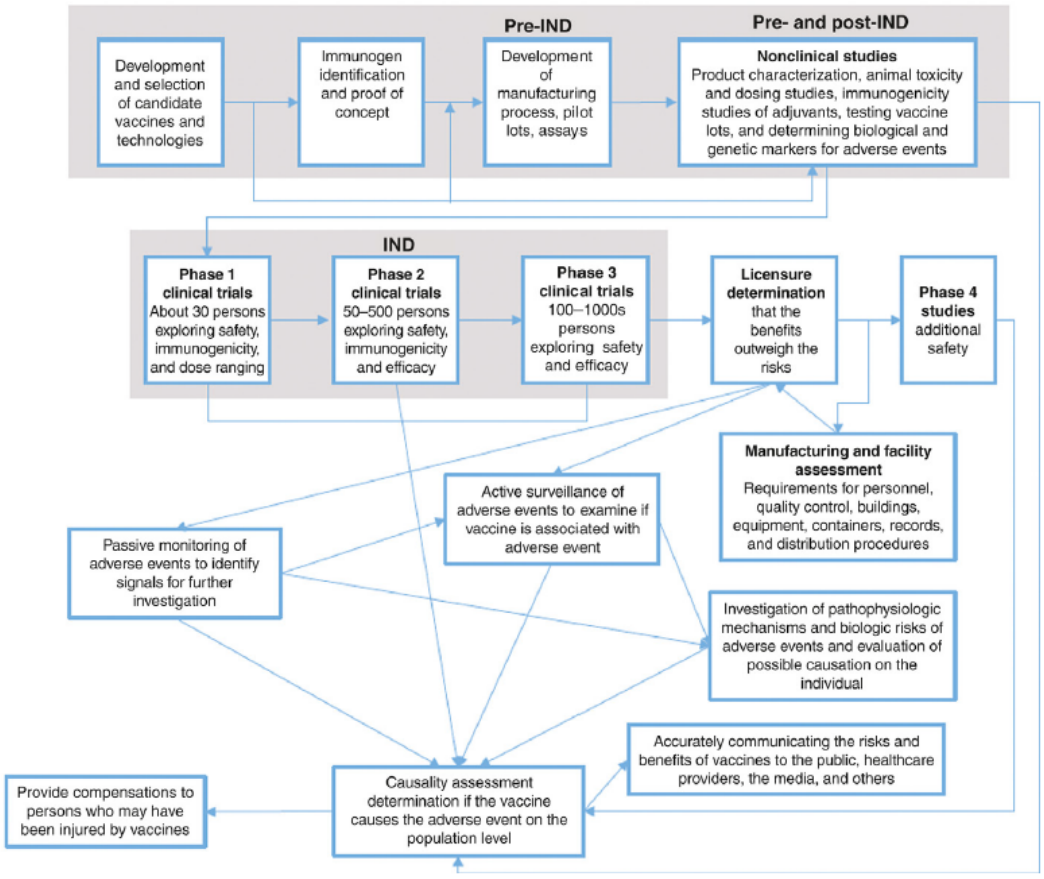


Figure 39 (Salmon et al., 2016): Vaccine safety activities throughout the product life cycle

3.10 Post-Marketing Safety Surveillance

The safety of vaccines is required to be monitored post-approval by the regulatory authorities (Salmon et al., 2016). The manufacturers are required to perform post-licensure active surveillance studies targeting defined populations to obtain further information on the vaccine safety and effectiveness (Salmon et al., 2016). An AEFI is defined as any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the use of the vaccine (Joshi et al., 2018). The main purpose of AEFI surveillance is to detect any undiscovered, unexpected, late-onset, and population-specific adverse events that were not discovered during the pre-marketing vaccine trials (Joshi et al., 2018).

There are two types of surveillance, which are passive and active surveillance (Salmon et al., 2016). Passive surveillance refers to adverse event reports received from anyone including physicians, healthcare providers, and the public (Salmon., 2016). In the United States, this system is called the Vaccine Adverse Event Reporting System (VAERS), which is maintained by both the FDA and CDC (Salmon et al., 2016). Other examples of passive surveillance include the Immunization Monitoring Program, ACTive (IMPACT) in Canada, yellow card in the United Kingdom which is administered by the Medicines and Healthcare Products Regulatory Agency, in Europe, they have surveillance systems integrated into drug safety surveillance (Salmon et al., 2016). Other examples include a passive system called SANEVA used by Argentina, Mexico, Brazil, Panama, and Venezuela (Salmon et al., 2016).

The Vaccine Adverse Event Reporting System (VAERS) is a system used to detect early signals in the United States licensed vaccines. A signal refers to the information's on the adverse or beneficial effects of a drug (WHO-UMC, 2019). VAERS is managed by the Centers for Disease Control and Prevention (CDC) and the United States Food and Drug Administration (FDA). The VAERS analyzes adverse event reports after a person received a vaccination. Apart from healthcare professionals and vaccine manufacturers, anyone can report on adverse events in VAERS including patients or family members. VAERS accepts all reports without judging whether the event was caused by the vaccine.

Being a passive reporting system, VAERS relies on individuals to submit reports of their adverse event experiences to CDC and FDA. VAERS is useful in detecting unexpected and unusual patterns of adverse event reports, observing an increase in a specific adverse event, assess the safety of newly approved vaccines that may indicate safety problems. With that, CDC and FDA get information from VAERS, and further evaluation will be performed to assess possible safety concerns. The number of adverse event data stored by the FDA increased by year due to several factors such as an increase in population, increase in the number of products, increase in adverse event reporting awareness, increase in reporting methods (example: online reporting tools). Various methods are used to detect adverse events, such as chart reviews and reporting systems (Chazard et al., 2011). Traditional methods are often inadequate for processing big data because the volume of data is so large and complex (Ventola.,2018).

3.11 Use of Text Mining in Post-Marketing Safety Surveillance

The term big data refers to large volume and unstructured data (Ventola CL., 2018). Large unstructured data could be a challenge during interpretation due to its large size and complexity (Ventola CL., 2018). Improvements in computing power and speed have allowed the automation of drug safety surveillance signal detection in large complex databases (Ventola.,2018). The computational method, often referred to as 'signal detection' or 'tracking', allows drug safety evaluators to analyze large amounts of data to detect adverse event risks, proven to be extremely important in pharmacovigilance (Duval et al., 2014). Retrospective medical chart reviews include the main source of reliable epidemiological knowledge on adverse drug events, but the method is often time and resource consuming (Chazard et al., 2011). The reporting system has been useful for analyzing the analysis of contributing factors of adverse events, but reporting systems usually suffer from important under-reporting biases (Chazard et al., 2011). The use of big data for pharmacovigilance involves novel electronic methods that are applied to analyze the large and growing volume of information about adverse events in spontaneous reporting system databases and other digital sources (Ventola.,2018). Sources of adverse event data in spontaneous reporting databases are healthcare professionals, consumers, pharmaceutical companies, and other sources (Ventola CL.,2018). These methods are impossible to detect and analyze through a conventional manual search (Ventola CL.,2018).

Another method of detecting adverse events is through text mining (Chazard et al., 2011). Text mining is where a large volume of unstructured or narrative data is often present in the text submitted in adverse drug event reports, which requires analysis using 'text mining' (Ventola CL.,2018). Text mining is a critical approach to identifying novel facts, hypotheses, and new associations from the large amounts of free-text data (Liu et al.,2014). A text often contains large information and might be challenging for statistical modeling (Raja et al., 2008). Data or text mining provides an opportunity to extract critical information from textual data (Raja et al., 2008). Since the 1990s, the FDA has been using data mining to analyze the increasing number of reports, help in prioritizing potential safety issues, and rapidly identify potential safety issues (Duggirala et al., 2015). In the pharmacovigilance field, data mining can be used in the detection of unusual signals which was not detected previously, benefit-risk assessment of a product, drug-drug interactions detection, and detection of known signals (Martin et al., 2013).

The SAS Text Mining software helps in extracting patterns, meanings, and hidden structures in unstructured textual data (Chakraborty et al., 2014). Text mining converts text into the numeric form and allows it to be used for analysis (Raja et al., 2008). Text mining approaches count of words in documents (Tremblay et al., 2005). The algorithm works by eliminating specified words (stop list) or keeping specified words (start list) and words with common roots are stemmed and removed since they have little power in discriminating documents (Tremblay et al., 2005). SAS Enterprise Miner has algorithms to automate word stemming and provide synonyms (Tremblay et al., 2005). A term-by-document frequency matrix is created, with the row dimension of the matrix limited to the 100 most frequent terms (Tremblay et al., 2005). Text mining by using SAS Text Miner derives a quantitative representation of documents (Chakraborty et al., 2014). When a text is changed into a set of numbers, it captures patterns in the textual data, statistical model, or data mining algorithm that can be used on the numbers for predictive modeling (Chakraborty et al.,2014).

Chapter 4: METHODOLOGY

4.1 Data Source

VAERS report should contain the year of the report, age and sex of the patient, description of the adverse event, and any additional remarks from the reporter, e.g., the outcome of the adverse event following immunization (AEFI). The data in VAERS is available publicly in the form of raw data in comma-separated values (CSV). Data from the year 01st January 2010 – 31st December 2017 was downloaded by year, description of adverse events, type of vaccines (e.g., human papillomavirus vaccine), seriousness, and age. The data in VAERS is available publicly in the form of raw data in comma-separated values (CSV). Data from the year 01st January 2010 – 31st December 2017 was downloaded by year, description of adverse events, type of vaccines (e.g., human papillomavirus vaccine), seriousness, and age. The fundamental interest of this research was to classify adverse events identified by System Organ Class (SOC), age groups, sex, and seriousness.

The Bivalent vaccine, Cervarix® was licensed by FDA on 16th October 2009 in use for females aged 9 through 25 years of age. The Quadrivalent vaccine, Gardasil® was first licensed for use in females aged 9 through 26 years of age on 08th June 2006. Subsequently, with approvals of supplements in 2008, 2009, and 2010; the indication of Gardasil® expanded to boys and men aged 9 through 26 years of age. The non-valent, Gardasil 9® was approved in 2014 for use in both females aged 9 through 26 years of age and males aged 9 through 15 years of age. In 2016, Gardasil 9® was approved for use in males aged 9 through 26 years of age. Hence, this study focused on VAERS data from the year 2010-2017 to evaluate trends of adverse events following approvals in males and age groups.

4.2 Research Design

This research involved data mining of vaccine adverse events using predictive text analytics. Adverse event descriptions related to Human Papillomavirus (HPV) Vaccine from the year 2010-2017 downloaded from VAERS in CSV format was converted into SAS7bdat format by using IBM SPSS Statistics 24. The file then was loaded into SAS Enterprise Miner, where text parsing, filtering, topic finder, concept links, text clustering was applied. Identified adverse events then were classified by System Organ Class (SOC) by using Medical Dictionary for Regulatory Authorities (MedDRA) software.

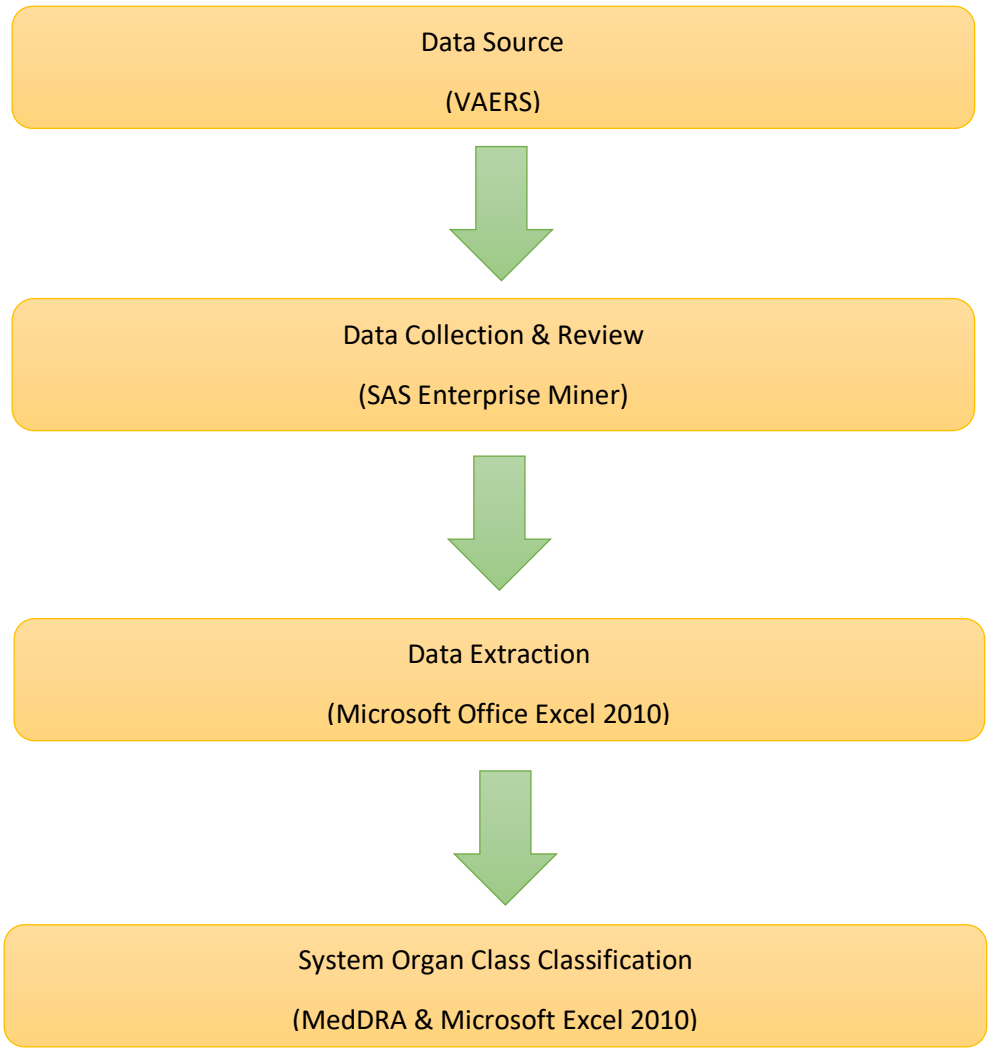


Diagram 1: Research Design – Data Mining Using Predictive Text Analytics

The second part of the research was to classify adverse events reported by age, gender, and seriousness criteria. Data downloaded from VAERS filtered in Microsoft Excel and classified as shown in results, Section 6.4, 6.4, and 6.5.

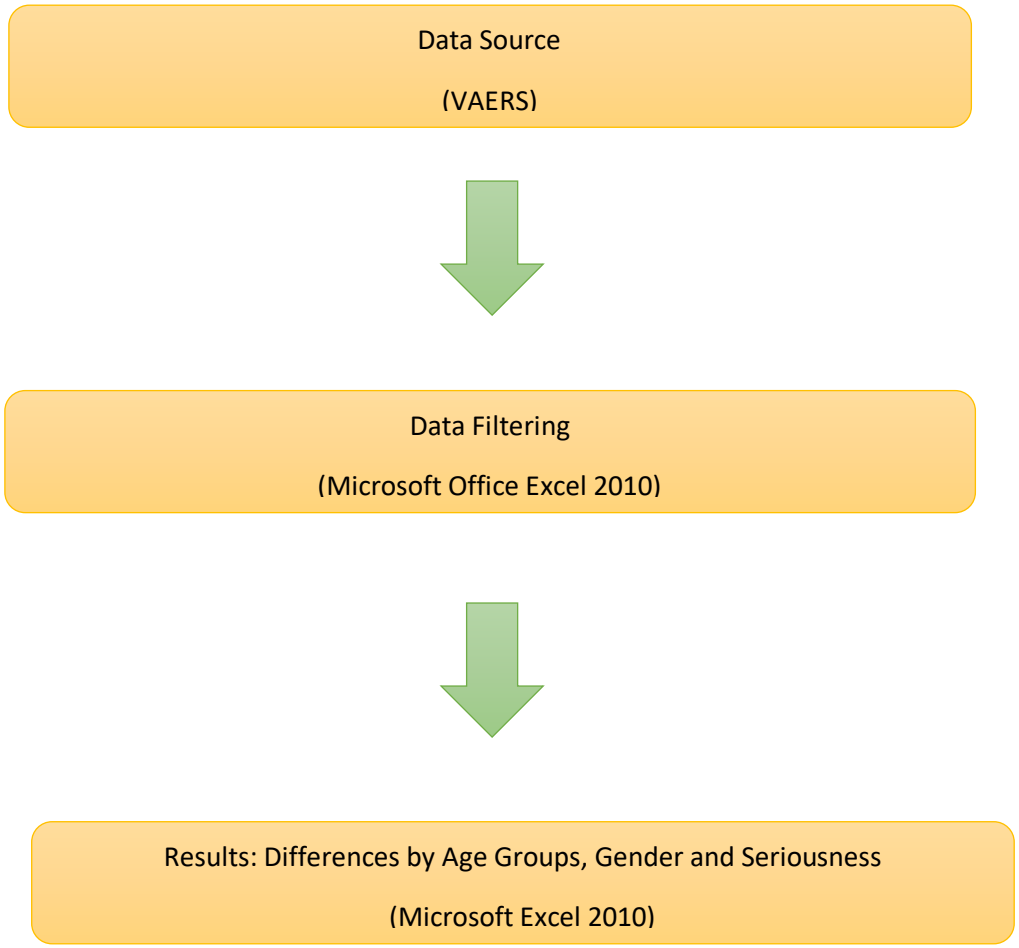


Diagram 2: Research Design: Classifying Adverse Events into Groups; Age, Gender and Seriousness

4.3 Data Analysis

4.3.1 Classification of Adverse Events by System Organ Class (SOC)

Predictive data analysis was used to extract key terms in textual documents (adverse event descriptions downloaded from VAERS). Each adverse event term was identified and assessed through SAS Text Miner, Text Filter (as shown in Diagram 1); were classified into System Organ Class by using the Medical Dictionary for Regulatory Authorities (MedDRA) web-based browser. Below are SOCs available in the MedDRA system:

1. Blood and lymphatic system disorders
2. Cardiac disorders
3. Congenital, familial, and genetic disorders
4. Ear and labyrinth disorders
5. Endocrine disorders
6. Eye disorders
7. Gastrointestinal disorders
8. General disorders and administration site conditions
9. Hepatobiliary disorders
10. Immune system disorders
11. Infections and infestations
12. Injury, poisoning, and procedural complications
13. Investigations
14. Metabolism and nutrition disorders
15. Musculoskeletal and connective tissue disorders
16. Neoplasm benign, malignant, and unspecified (incl cysts and polyps)
17. Nervous system disorders
18. Pregnancy, puerperium, and perinatal conditions
19. Product issues
20. Psychiatric disorders
21. Renal and urinary disorders
22. Reproductive system and breast disorders
23. Respiratory, thoracic, and mediastinal disorders
24. Skin and subcutaneous tissue disorders
25. Social circumstances
26. Surgical and medical procedures
27. Vascular disorders

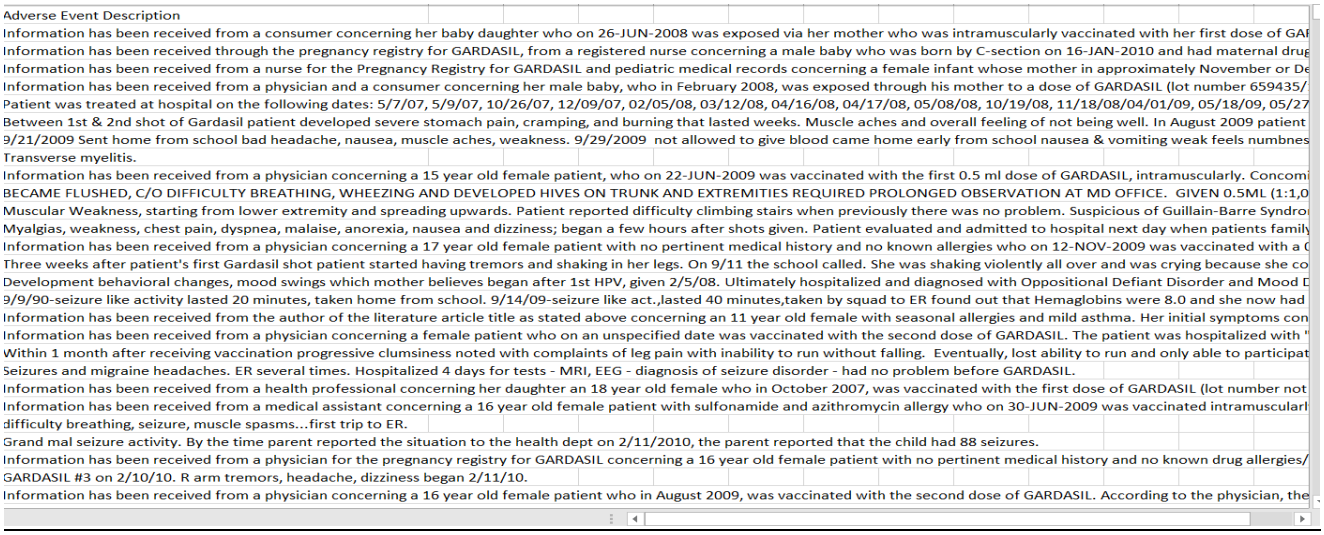


Figure 40: Adverse Event Description which was uploaded into SAS Text Miner before Text Parsing process

Terms

	TERM ▲	FREQ	# DOCS	KEEP	WEIGHT	ROLE	ATTRIBUTE
	confirmed vte	2	2	☑	0.896	Noun Group	Alpha
⊞	congenital anomaly	8	8	☐	0.0	Noun Group	Alpha
⊞	congenital defect	1	1	☐	0.0	Noun Group	Alpha
	conjunctival hyperemia	1	1	☑	1.0	Noun Group	Alpha
	conscious layed	1	1	☐	0.0	Noun Group	Alpha
	conscious loss	1	1	☑	1.0	Noun Group	Alpha
	consent form	1	1	☐	0.0	Noun Group	Alpha
	considered excess fluid	1	1	☑	1.0	Noun Group	Alpha
	considered incorrect storage	1	1	☐	0.0	Noun Group	Alpha
	constant fatigue	1	1	☑	1.0	Noun Group	Alpha
⊞	constant headache	2	2	☑	0.896	Noun Group	Alpha
	consulting doctor	1	1	☐	0.0	Noun Group	Alpha
	consumer's child	1	1	☐	0.0	Noun Group	Mixed

Figure 41: Terms generated from Text Parsing. These were then analyzed, and adverse events were selected. Adverse events terms are selected by analyzing the medical terms. As seen in the figure above, terms such as consulting doctor, consumer's child, considered incorrect storage, and consent form are non-medical terms. Terms such as congenital anomaly and congenital defect are medical terms, but the term selected by expanding the description of adverse event (as can be seen in Figure 41) to confirm if these were true adverse event terms or rather part of the description

4.3.2 Analysis of Text Cluster

Adverse Event terms identified through SAS Text Miner, Text Filter.

4.3.3 Assessment of Age Groups

Data downloaded from VAERS has categorized patients by the following age groups. These age groups were classified by the VAERS.

1. < 6 months
2. 6 – 11 months
3. 1 – 2 years
4. 3 – 5 years
5. 6 – 17 years
6. 18 – 29 years
7. 30 – 39 years
8. 40 – 49 years
9. 50 – 59 years
10. 60 – 64 years
11. > 65 years
12. Age Unknown

4.3.4 Assessment of Seriousness

In pharmacovigilance terminology, seriousness is based on the patient's outcome of the adverse event. Data downloaded from VAERS has categorized events by seriousness. Seriousness criteria were classified by the following: Yes, No and Unknown.

4.3.5 Assessment of Gender

Data downloaded from VAERS has categorized events by gender of patients who experienced the adverse events. Gender was classified by the following: Male, Female and Unknown

4.3.6 Statistics

Excel files (Microsoft Office Excel 2010) were used for statistical analysis. Charts for each assessment were done in an Excel file.

Chapter 5: RESULTS

The first sections summarize the result for text topic analysis of adverse events identified and classified into System Organ Class for human papillomavirus vaccine from the year 2010-2017. This is to explore and validate how themes and keywords are associated with each other. The second section summarizes adverse events reported by the system organ class.

A total of 6407 adverse events following immunization (AEFI) were identified through Text Filter from the year 2010-2017. A total of 22 802 terms were available after the text parsing process. The highest AEFI terms were identified in the year 2010 and the number of AEFI identified fluctuates between the years 2011-2017. Comparatively lower numbers of AEFI identified in the year 2012 as compared with previous and following years. The peak of adverse events identified in 2010 due to the introduction of HPV in 2008 for in the use of the girls aged 14 but decreased rapidly after the year 2010. It is unclear on the fluctuation of adverse events identified between 2011 – 2017 although a nonvalent HPV vaccine was introduced to boys in the year 2014. The adverse events detected in the year between 2015 - 2017 were higher probably due to the introduction of the nonvalent HPV vaccine in boys in the year 2014.

As shown in Table 8, most AEFI fell in SOCs of Nervous system disorders (n=1251), followed by General disorders and administration site conditions (n=1192), Skin and subcutaneous tissue disorders (n=911), and Musculoskeletal and connective tissue disorders (n=575). The number of AEFI fluctuates throughout the year from 2010 – 2017, with the year 2010 having the highest AEFI detected in SAS Text Miner and 2012 with the lowest AEFI detected.

5.1 System Organ Class

System Organ Class	2010	2011	2012	2013	2014	2015	2016	2017	Total
Blood and lymphatic system disorders	15	17	5	8	6	10	12	9	82
Cardiac disorders	25	11	7	7	3	19	3	3	78
Congenital, familial, and genetic disorders	9	4	4	1	2	1	3	9	33
Ear and labyrinth disorders	15	3	-	3	2	10	9	4	46
Endocrine disorders	3	1	1	2	3	10	3	2	25
Eye disorders	37	12	13	28	25	30	23	17	185
Gastrointestinal disorders	54	51	33	50	50	49	62	42	391
General disorders and administration site conditions	153	166	86	156	111	141	193	186	1192
Hepatobiliary disorders	10	-	2	3	-	-	-	-	15
Immune system disorders	13	15	8	9	9	13	15	20	102
Infections and infestations	45	29	12	23	31	20	21	21	202
Injury, poisoning and procedural complications	4	9	7	9	16	11	10	10	76
Investigations	27	14	6	16	20	19	30	30	162
Metabolism and nutrition disorders	9	2	2	2	4	1	5	3	28
Musculoskeletal and connective tissue disorders	101	68	48	55	70	70	81	82	575
Neoplasm benign, malignant, and unspecified (incl cysts and polyps)	10	14	4	88	12	19	19	16	182
Nervous system disorders	196	135	96	163	149	156	186	170	1251
Pregnancy, puerperium, and perinatal conditions	40	16	9	6	8	4	9	2	94
Psychiatric disorders	24	13	13	26	30	11	33	21	171
Renal and urinary disorders	9	10	1	7	2	1	7	7	44
Reproductive system and breast disorders	36	37	13	20	19	24	35	31	215
Respiratory, thoracic and mediastinal disorders	37	18	18	20	26	35	31	27	212
Skin and subcutaneous tissue disorders	127	153	64	99	120	134	109	105	911
Social circumstances	1	1	1	3	3	3	2	-	14
Surgical and medical procedures	2	1	2	-	-	2	-	-	7
Vascular disorders	21	18	5	19	12	13	13	13	114
AEFI (N)	1023	818	460	823	733	806	914	830	6407

Table 8: Numbers of AEFI Identified through SAS Text Miner, Text Filter and Classified under System Organ Class by year.

There was a total of 27 terms with 'death' identified between the year 2010 – 2017 (as shown below in Table 9). The cause of death and causality if the deaths are related to HPV vaccine were not able to be identified through SAS Text Miner.

Year	**Terms Identified**
2010 (Total of 5 terms identified)	1.Fetal death 2.sudden infant death syndrome 3.Sudden cardiac death 4. Death (2 terms identified)
2011 (Total of 4 terms identified)	1.Child death 2.Sudden cardiac death 3.Death (2 terms identified)
2012	None
2013 (Total of 2 terms identified)	1.Cause of death 2.Death unknown
2014 (1 term identified)	1.Cause of death
2015 (4 terms identified)	1.Cause of death 2.Fetal death 3.Infant death 4.Report considered death
2016 (7 terms identified)	1.Cause of death 2.Internal review death 3.Multiple unknown death 4.Patient experienced death 5.Patient's death 6.Reporter considered death 7.Sudden death
2017 (3 terms identified)	1.Cause of death 2.Daughter's death 3.Patient's death

Table 9: List of terms (death terms) identified through Text Mining between 2010 - 2017

Between 2010 – 2017, a total of 7 terms associated with Guillain-Barre Syndrome were identified. 1 term was found in year 2011 (brachial variant Guillain), 2013 (Guillain-Barre syndrome), 2014 [patient experienced GBS (Guillain-Barre syndrome)], 2015 (patient experience Guillain-Barre), and 2017 (patient experience Guillain). Meanwhile, 2 terms were identified in the year 2016 (Guillain-Barre and patient experienced Guillain-Barre). The severity and causality assessment of these terms were not able to be identified through SAS Text Miner. Causality assessment refers to the likelihood of an adverse event related to the medicinal product (www.who.int Assessed: 17th February 2022). Causality assessment is a routine pharmacovigilance practice, and it helps in classifying the relationship likelihood, assessing individual case reports, reducing disagreement between case assessors, and improving scientific evaluation (www.who.int Assessed: 17th February 2022). In most cases, the reported adverse event is likely to fall between certain, unlikely, possible, or probable (www.who.int Assessed: 17th February 2022).

A total of 6 terms of postural orthostatic tachycardia (POTS) were identified between 2010-2017. The causality assessment of these reports on the possibility of a causal relationship to preceding immunization (s) is unknown.

Besides, most identified terms identified in SAS Text Miner, Text Filter by year:

2010	1.Congenital anomaly 2.Sore throat 3.Abnormal pap smear 4.Exposure during pregnancy 5. Joint pain
2011	1.Abdominal pain 2.Chest pain 3.Syncopal episode 4.Joint pain 5.Allergic reaction
2012	1.Syncopal episode 2.Body ache 3.Lost consciousness 4.Abdominal pain 5.Stomach pain
2013	1.Abdominal pain 2.Body ache 3.Chest pain 4.Joint pain 5.Syncopal episode
2014	1.Anal condyloma 2.Syncopal episode 3.Joint pain 4.Chest pain 5.Abdominal pain
2015	1.Inappropriate schedule 2.Joint pain 3.Abdominal pain 4.Chest pain 5.Body ache
2016	1.Abdominal pain 2.Body ache 3.Sore throat 4.Severe headache 5.Chest pain
2017	1.Sore throat 2.Syncopal episode 3.Inappropriate schedule 4.Body ache 5.Neck pain

Table 10: Most identified terms in Text Filter field of SAS Text Miner

As seen in Table 10, throughout 2010 – 2017; similar pattern was observed with commonly identified terms in Text Filter. Several adverse events were commonly identified such as abdominal pain, joint pain, syncopal episode, chest pain and body ache. These adverse events detected falls in group of Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders and General disorders and administration site conditions.

5.2 Cluster Text Analysis by Respective Years

2010

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
5	patient experienced pain 'whole body' 'felt faint 'dry mouth' 'felt light' patient experienced fever' 'patient experienced numbness' 'pelvic pain' '+syncopal event' 'dry eyes' experienced amenorrhea' 'experienced fever'	1041	69%	0.029359
13	patient experienced chest pain' +'ovarian cyst' 'general malaise' 'lower abdominal pain' 'ovarian cysts' 'severe stomach pain' 'body heat' +'headache' +'headache prior' +'tonic-clonic seizure' +'stomach ache'	45	3%	0.133573
14	difficulty breathing' 'patient experienced rash' 'positive urine pregnancy test' 'post vaccination' 'small bumps' 'itchy rasg' 'baseline fetal tachycardia' 'breathing problems' 'experienced intrauterine growth restriction' 'fetal gastroschisis' 'fetal heart rate variability' 'abdominal pain x2'	47	3%	0.131366
16	swollen glands' 'patient experienced headache' 'abdominal pain' 'experienced urinary tract infection' 'premature rupture' 'experienced headache' 'experienced headaches' 'low grade fever' 'muscle aches' 'patient experienced headaches' 'patient experienced muscle pain' 'patient's headache'	37	2%	0.135161
19	congenital anomalies' 'arm pain' 'breast feeding' 'fetal deaths' 'preterm delivery' +'congenital anomaly' +'seasonal allergy' +'upper extremity' 'achy joints' 'experienced cysts' 'experienced irregular heart rate' 'low birth weight'	48	3%	0.130422
22	body aches' 'hair loss' 'patient experienced dizziness' 'severe pain' 'patient experienced seizures' +'severe headache' +'syncopal episode' 'seizure disorder' 'joint paint' 'patient experienced seizure' 'extreme fatigue' 'migraine headaches'	124	8%	0.139022
23	injection site reaction' +'abnormal pap smear' +'sore arm' 'abnormal pap test' 'experienced pain' 'mild dysplasia' 'atypical cells' 'cervical intraepithelial' 'cold sweats' 'fetal macrosomia' 'shoulder strain' 'squamous intraepithelial'	45	3%	0.131906
25	mother's experience' 'patient experienced syncope' 'lost consciousness' 'experienced fetal tachycardia' 'experienced syncope' 'fetal distress' 'prenatal compliacations' 'tonic clonic movements' '+syncopal event' 'bilateral arm pain' 'bipolar disorder' 'brain swelling'	46	3%	0.120776
26	allergic reaction' 'patient experienced swelling' 'rash spread' 'papilloma viral infection' 'patient experienced migraines' 'petechial rash' 'abdominal cramping' 'abdominal cramps' 'abdominal pain unknown site' 'acute peripheral neuropathy' 'acute pharyngitis' 'acute tonsillitis'	37	2%	0.106361
30	sore throat' 'high fever' burning sensation' 'fainting spell' 'running nose' 'abnormal eeg' 'deep breaths' 'nasal congestion' 'pruritic rash' 'stuffy nose' +'deep breath' +'chronic seizure'	42	3%	0.127451

2011

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
2	allergic reaction' 'experienced dizziness' 'patient experienced dizziness' 'patient experienced rash' 'patient's pain' 'swollen lump' 'allover rash' 'assessment noted rash' 'athletic pain' 'autoimmune disorders' 'bad reactions' 'breathing difficulty indicative'	33	3%	0.0131875
11	abnormal cramping' +'spontaneous abortion' 'papilloma viral infection' 'experienced headaches' 'experienced nausea' 'menstrual bleeding' 'evan's syndrome' 'experienced spontaneous abortion' 'fainting spell' 'fainting spells' 'idiopathic thrombocytopenic' 'intermittent reactive airway disease'	26	2%	0.145007
13	lost consciousness' 'bell's palsy' 'irregular periods' 'leg pain' 'chronic fatigue syndrome' 'chronic pain regimen' 'client pale face' 'constant tiredness' 'constant yeast infections' 'experienced low back pain' 'juvenile chronic epilepsy' 'muscle weakness'	17	1%	0.135964
16	cervical cancer' +'syncopal episode' 'high fever' +'stomach pain' 'abnormal pap' 'arm pain' 'atypical squamous cells' 'human papilloma virus' 'injection site reaction' 'itchy rash' +'syncopal episode' 'experienced syncope'	1046	81%	0.044207
17	joint paint' 'genital warts' 'attention deficit disorder' 'fine red rash' 'severe joint pain' 'suidical thoughts' 'axillary pain' 'chest tightness' 'chronic illness' 'cold sweats' 'double vision' 'elbow joint pain'	33	3%	0.14062
20	abdominal pain' 'experienced abdominal pain' 'throat tightness' 'acute pancreatitis' 'allergic reaction' 'anaphylactic shock' 'cervical lymphadenopathy' 'dizziness closed eyes' 'erythematous posterior pharynx' 'hair loss' 'joint pain' 'loose stools'	25	2%	0.093407
22	sore throat' +'severe headache' 'severe pain' 'swollen lymph nodes' 'abnormal pap test' 'cervical intraepithelial' 'clonic movements' 'mild sore throat' 'papanicolaou smear' 'papular rash' 'severe fatigue' 'slight headache'	50	4%	0.144546
24	chest pains' +'chest pain' 'painful joints' 'patient experienced numbness' 'achy joints' 'extreme pain' 'lost control' neck stiffness' 'sore throat' 'swollen glands' 'swollen hands' 'trouble breathing'	37	3%	0.12949
33	body aches' 'squamous intraepithelial' +'abnormal pap smear' mild tenderness' 'vaginal bleeding; 'abnormal pap smears' 'complete miscarriage' 'epithelial cell abnormality' 'experienced vulvar discomfort' 'extreme fatigue' 'four-quadrant dysplasia' 'full body rash'	22	2%	0.136121

2012

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
7	abdominal pain' 'abnormal cells' 'cervical dysplasia' 'high fever' 'addison's disease' 'chronic stomach pain' 'constipation lasting weeks' 'experienced spontaneous abortion' 'extreme back pain' 'extreme body heat' 'extreme dizziness' 'extreme nausea'	17	1%	0.205278
11	additional information' 'blurry vision' 'significant disability' 'abnormal pap smear' 'allergic reaction 'fainting spell' 'lateral sclerosis' 'patient experienced pain' 'pelvic pain' 'short term memory' 'tonic clonic movements' 'acute transverse myelitis'	208	15%	0.047283
18	additional identifying information' 'unknown number' 'patient experienced convulsions' 'additional information'	12	1%	0.083128
19	body aches' +'syncopal episode' 'lower extremities' 'neck pain' 'injection site reaction' 'patient experienced nausea' 'feeling faint' 'itchy throat' 'mild swelling' 'red area' 'syncope episode' 'abd pain'	1059	77%	0.042406
23	ovarian cysts' 'addition muscular soreness' 'injection site pain' 'injection site swelling' 'internal review seizures' 'menstrual irregularities' 'neurological issues' 'surgery ovarian cysts' 'chronic fatigue' 'stomach pains' 'patient experienced nausea' 'unknown number'	3	0%	0.235126
24	arm pain' +'joint pain' 'b streptococcus positive' 'low grade fever' 'sore throat' 'urinary tract infection' 'arm stiff' 'baby experienced hepatitis b' 'bowel obstruction' 'calf pain' 'dry mouth' 'experienced maternal toxemia'	22	2%	0.182649
26	difficulty breathing' +'elective termination' 'elective abortion due' 'elective abortions' 'included vagal response' 'infant congenital anomalies' 'patient experienced neck pain' 'previous pregnancies' 'psychiatric symptoms' 'seizure event' 'tonic motions' 'whole syncope'	13	1%	0.204939
27	patient felt faint' 'acute mastoiditis' 'extreme headache' 'extreme sore throat' 'facial pain' 'general malaise' 'poor vision' 'red raised circular' 'severe headaches' 'stomach aches' 'tonic-clonic movements' 'vision problems'	14	1%	0.19916
30	abdominal cramping' 'muscle weakness' 'body stiffness' 'left arm pain' 'body stomachache' 'extreme fatigue' 'extreme thirst' 'muscle spasms' 'muscle tension' 'persistent left arm paresthesia' 'temporary blurry vision' 'unusual weakness'	9	1%	0.202414
33	lost consciousness' 'cervical cancer' 'heart palpitations' 'hair loss' 'interview review cervical cancer' 'seizure activity' 'severe dysplasia' 'severe fatigue' 'upper body seizure' 'urinary incontinence' 'weight loss' additional information'	14	1%	0.199779

2013

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
11	positive pap smear' +'event seizure' 'experienced memory loss' 'patient experienced seizure' 'black bruise' 'celiac disease' 'cerebral hemorrhage' 'constant pain' 'determined seizures' 'experienced involuntary hand' 'experienced psychiatric events' 'experienced seizures'	20	1%	0.147093
14	felt faint' +'severe headache' 'patient experienced headache' 'general malaise' 'hot flashes' 'irregular heartbeat' 'multiple sclerosis' 'patient experienced headaches' 'chronic syncope' 'constant nausea' experienced severe backache' 'experienced severe headache'	34	2%	0.143496
21	extreme fatigue' 'patient experienced nausea' human papillomavirus' 'fainting spells' 'mild fever' muscle spasms' 'significant swelling' 'sore arm' 'acid reflux' 'aggravation next day' 'also developed swelling' 'chronic pain syndrome'	38	2%	0.140651
22	abdominal pain' 'vocation nurse' 'experienced abdominal pain' 'double vision' hyperactivity disorder' +'burning sensation' 'acute appendicitis' 'acute pancreatitis' 'attention deficit' 'burning sensations' 'constant headache' 'event seizures'	24	1%	0.114907
23	arm pain' +'chest pain' 'muscle pain' 'brain fog' 'low grade fever' 'chest pains' 'sleep problems' 'sound sensitivity' +'mal seizures' 'abdomen pain' 'achy muscles ' 'acute transverse myelitis'	50	3%	0.140885
24	difficulty breathing' 'hair loss' 'lost consciousness' 'year-old female patient' +'stomach pain' 'experienced syncope' 'red rash' 'human papilloma virus' 'patient experienced fever' 'patient experienced pain' 'patient's fever' 'seizure activity'	1643	89%	0.032278
27	patient experienced syncope' 'trouble breathing' +'bad headache' 'tonic-clonic movements' 'allergic reaction' 'bad stomachache' 'extreme nausea' 'ill feeling' 'joint swelling' 'overall bad feeling' 'patient experienced trouble breathing' 'patient experienced urticaria'	21	1%	0.127441
29	irregular periods' 'patient experienced hives' 'positive urine pregnancy test' 'severe rash' 'breast tenderness' 'lips swollen sores'	6	0%	0.12435
38	injection site reaction' 'leg pain' 'weight loss' 'extreme tiredness' 'eye pain' 'irritable bowel syndrome' 'muscle weakness' 'neurocardiogenic syncope' 'orthostatic tachycardia syndrome' 'patient experienced injection site' 'patient experienced redness' 'slight fever'	19	1%	0.13288

2014

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
16	significant disability urine pregnancy test chronic sinusitis experienced rheumatoid arthritis feeling bad gastrointestinal distress heart palpitations initially experienced swelling large hair loss low monocyte count mild myositis non-tender lump	24	1%	0.140474
17	causality assessments +causality assessment uveitis development unknown date medication error eye pain chest pains drug administration uveitis development patient experienced seizures +sore arm hurts atypical seizures	47	2%	0.148662
19	neck pain seizure activity +severe headache severe headaches bad headache experienced severe headache losing consciousness slight dizziness sore joints bad cramps blurry vision busted lip	26	1%	0.141706
25	eating disorder +blood pressure vasovagal response vasovagal syncope blood pressures dizzy put patient experienced arm pain patient experienced being diaphoretic patient experienced syncope persistent fever posterior parietal scalp hematoma strong headache	16	1%	0.125995
26	abdominal pain inappropriate schedule abdominal discomfort bilateral hip pain experienced inappropriate schedule experienced joint pain extreme abdominal pain irregular heart rate medication error mild abdominal pain mild asthma ovarian cysts	18	1%	0.123159
27	weight loss +stomach pain stomach pains subject experienced fever experienced syncope migraine headache otitis media severe stomach pain sinus infection strep throat white spots abnormal heart rate	35	2%	0.148407
31	body aches +joint pain extreme pain high fever +chest pain behaviour problems high blood pressure hot flashes irregular heartbeat joint pains mood swings positive urine pregnancy test	34	2%	0.141017
32	tourette's syndrome +syncopal episode waiting room felt faint stomachache anal condyloma development anal condyloma chart review genital warts patient experienced headache vaccine failure +injection site reaction	1680	82%	0.037632
36	local reaction difficulty breathing body pain memory problems asthma attack auto-immune symptoms bad migraine bad reaction costal chondritis experienced celiac disease fever blisters intense chest pain	17	1%	0.129233
38	experienced pain +third dose patient experienced warts experienced soreness patient experienced diarrhoea patient experienced numbness patient experienced pain patient experienced soreness red bumps abnormal papanicolaou bilateral arm numbness diffuse rash	156	8%	0.043998

2015

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
13	abdominal pain body aches chest discomfort unspecified rash arm soreness patient experienced urticaria respiratory distress +low grade fever abnormal ck brain fog chronic migraines experienced severe pain	32	1%	0.138299
20	neck pain extreme fatigue back pain arm pain memory loss night sweats and ache abnormal sensations appetite loss bilateral arm pain breathing difficulties daughter experienced nausea	31	1%	0.145216
22	inappropriate schedule +syncopal episode difficulty breathing +syncope episode patient experienced syncope +allergic reaction blurry vision cervical cancer heart palpitations injection site pain lost consciousness seizure activity	2379	91%	0.042032
23	severe swelling +high fever bad headache left arm swelling dizzy while standing experienced chest pain Fahrenheit pain general fatigue hot red improvement suspect cellulitis severe muscle pain slow speech	14	1%	0.109071
27	mal seizure difficult breathing hay fever muscle weakness eye pain eyes hurt leg numbness neurological disorder nos(non?) partial seizures patient experienced muscle weakness sinus infections skin infection	10	0%	0.117916
29	experienced syncope +chest pain upset stomach abdominal cramping panic attacks +panic attack abnormal pulmonary function test blood pressure elevated chest pains clonic activity epileptic seizures felt general malaise	28	1%	0.108143
31	patient experienced headache facial swelling red area throat swelling throat tightness anaphylactic reaction difficulty hearing felt faint patient experienced headaches severe dizziness severe fatigue severe nausea	49	2%	0.149021
33	patient experienced pain +stomach pain event seizure low blood pressure personality change stomach hurt stomach pains arm stiffness convulsion disorder daily frontal headaches evening stomach pain event pain	32	1%	0.129155
35	chronic fatigue +chronic pain injection site reaction injection site swelling itchy skin major birth defects muscle pain patient experienced redness pregnancy exposures +severe headache bacterial infection bad dystonia	19	1%	0.143154
38	arm swelling postpartum hemorrhage +preterm birth chorioamnionitis onset chorioamnionitis reports clinical chorioamnionitis experienced low grade fever face swelling fetal tachycardia infant deaths maternal leukocytosis maternal tachycardia	19	1%	0.140765

2016

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
10	joint swelling ovarian swelling systemic rash weight loss black spots difficulty walking fast heart rate hair growth muscle pain neurological symptoms premature menopause stuffy nose	47	2%	0.140458
11	office manager neck pain upset stomach allergic reactions grade fever low blood pressure vasovagal reaction headpain heart palpitations memory loss mild headache muscle spasms	84	3%	0.142245
13	spontaneous prospective pregnancy report experienced maternal exposure experienced spontaneous abortion heart murmur maternal exposure miscarriage date preterm deliveries seizure disorder spontaneous abortion whooping cough office manager	20	1%	0.084326
17	body aches high fever lost consciousness human papilloma virus injection site reaction patient experienced chills patient experienced rash muscle stiffness +body ache +cause of death arm pain injection site back pains	41	1%	0.13725
18	cervical cancer +severe headache severe headaches facial swelling experienced injection site pain body aches cerebral palsy experienced weight loss metallic taste multiple sclerosis aplastic anemia autoimmune problems	37	1%	0.129165
20	injection site pain +sharp pain lower back pain brain fog hot flashes poor appetite sharp pains aggression beginning bad head ache body discomfort continual migraine costochondral chest pain	28	1%	0.129358
24	severe pain patient experienced pain unspecified age +bad headache hair loss severe fatigue blood clots inappropriate age mild rash oral mucosal eruption stomach discomfort baby's rash	32	1%	0.129479
26	patient experienced syncope +syncopal episode arm pain experienced syncope muscle weakness patient experienced dizziness premature ovarian failure +syncope episode bell's palsy local reaction unspecified adverse event's anaphylactic reaction	2746	89%	0.029924
29	difficulty breathing +chest pain +joint pain +sore throat light sensitivity shoulder pain throat tightness trouble walking abnormal involuntary movements abnormal paps back pain itchiness bowel movements	35	1%	0.133418
30	blurry vision sore arm difficulty moving arm back aches burning sensation right breast burning sensations experienced severe stomach pain feeling light felt pressure groin pain heterozygous thalassemia nausea medications	23	1%	0.129627

2017

Cluster ID	Descriptive Terms	Frequency	Percentage	RMS Std
7	back pain safety report severe headaches stiff neck bad reactions helicobacter infection high pulse lost consciousness lower back pain viral infection +autoimmune disease aforementioned events	45	2%	0.143834
16	syncope episode experienced inappropriate schedule considered inappropriate schedule patient experienced injection site follow-up information f previous temperature +allergic reaction +male patient injection site pain vaccination site mass bell's palsy cause of death	1780	84%	0.036445
22	patient experienced pain +male patient tunnel vision abdominal tightness achy throat aforementioned adverse events aforementioned event apparently lost consciousness ear disorder experienced difficulty breathing experienced runny nose experienced swelling	86	4%	0.057498
24	syncope episode +chest pain gi symptoms left arm pain benign heart murmur brain fog cloudy vision continuous nausea feeling normal soreness feeling soreness firm area itchy areas	19	1%	0.134592
31	body aches +ice pack difficulty breathing front desk lip swelling migraine headaches muscle cramps poor appetite severe fatigue visible swelling +bad headache allergic reaction symptoms	59	3%	0.138818
32	waiting room patient experienced syncope felt faint vasovagal syncope abnormal pain classic convulsion continual headaches large raised circular reaction mild extension palpable pulse patient felt back stiff body	34	2%	0.13115
33	vaccine administration patient experienced headache experienced persistent headache vasovagal response +ice pack allergic reaction secondary experienced fecal incontinence eye sensitivity feeling faint included extreme fatigue initially had redness loss brain fog	24	1%	0.0941
34	joint pain blurry vision stomach pain swollen lips extreme dizziness rash spread throat tightness abnormal menstrual periods chronic fatigue syndrome chronic headache complex regional pain syndrome dizzy spells	26	1%	0.14134
35	genital warts anogenital warts nervous system disorder postural orthostatic tachycardia syndrome small fiber neuropathy autoimmune disorder autoimmune issue considered small fiber neuropathy event autoimmune filiform wart frequent awakenings lymphocytic leukemia	11	1%	0.144782
36	cervical cancer +sore throat arm pain hair loss +sore arm panic attacks muscle aches patient experienced hair loss weight loss +panic attack breath extreme lethargy brittle nails	32	2%	0.141814

The root mean square (RMS Std) shows clusters derived in Text Cluster, SAS Text Miner. The terms are derived based on the frequency of occurrence. Closer the value to 0 depicts that the cluster text analysis is dependable on identifying the adverse events and grouping them by clusters and frequency of occurrence. For the year 2010, the lowest value is 0.029359 and the highest is 0.135161. For the year 2011, the lowest RMS Std value is 0.013187 meanwhile the highest is 0.145007. In 2012, the lowest RMS Std value is 0.042406 and the highest is 0.205278. In 2013, the lowest RMS Std value is 0.032278 and the highest is 0.147093. In 2014, the lowest RMS Std value is 0.037632 and the highest is 0.148662. In 2015, the lowest RMS Std value is 0.042032 and the highest is 0.149021. In 2016, the lowest RMS Std value is 0.029924, and the highest is 0.142245. In 2017, the lowest RMS Std value is 0.036445 and the highest is 0.144782. The Cluster Text Analysis could derive topics such as system organ class or classify the symptoms in the respective cluster into a definite condition. For example, depending on the terms (symptoms) in the cluster, condition such as guillain-barre syndrome could be concluded. To do so, we need expertise such as a physician with clinical experience to evaluate in each cluster to derive a topic into system organ class and condition. This couldn't be done in this study.

5.2 Age Groups

Year	<6 months	6-11 months	1-2 years	3-5 years	6-17 years	18-29 years	30-39 years	40-49 years	50-59 years	60-64 years	>65 years	Age Unknown
2010	14	2	4	2	1451	859	20	4	2	-	1	413
2011	2	-	2	2	1443	628	16	5	-	-	1	1
2012	3	1	2	4	928	296	9	3	2	-	2	207
2013	8	5	10	13	1552	585	29	14	4	2	2	1177
2014	11	3	13	8	1728	529	28	9	3	1	2	1429
2015	12	6	16	5	1858	464	27	8	5	1	4	2366
2016	9	6	9	10	2118	512	19	12	2	3	3	2967
2017	9	5	24	5	1719	391	13	7	3	-	1	1702

Table 11: Age distribution of AEFI from 2010-2017

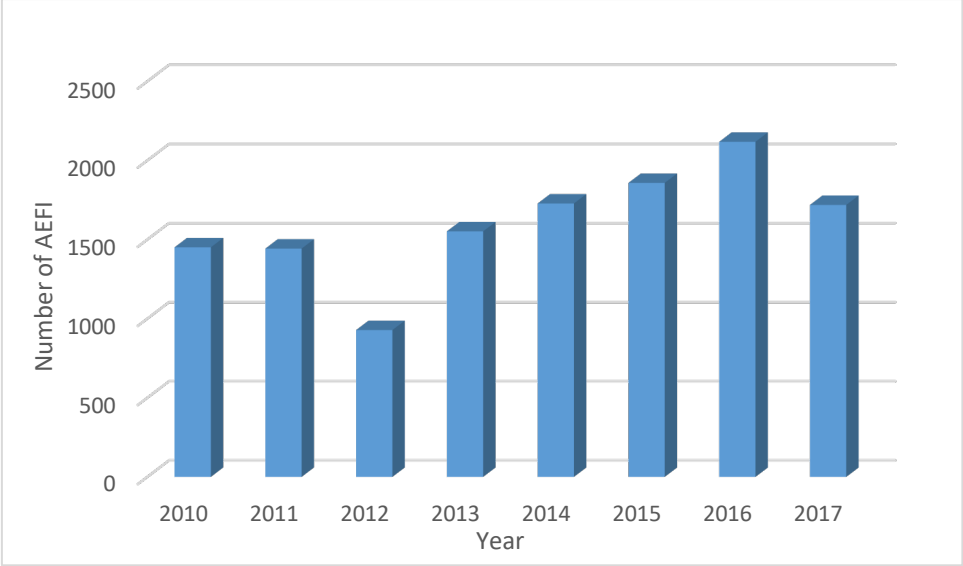


Figure 42: Number of AEFI for age group 6-17 years from 2010-2013

Most AEFI had occurred in patients age between 6-17 years, followed by patients 18-29 years, 30-39 years, 1-2 years, < 6 months, 40 – 49 years, 6 – 11 months, 50 – 59 years, 60 – 64 years and >65 years. In the remaining reports (N = 10 262) age of patients was unknown. AEFI report in patient group aged 6 – 17 years found to be highest throughout 2010 – 2017, the reason is that recommended age of available HPV vaccines in the market are between age 9 – 26 years of age. Hence, a high trend of AEFI is also observed in patients aged 18 – 29 years. The number of AEFI in patients aged 6 – 29 years appears to be constant every year with exception of the year 2012. For adverse events detected in patient age groups between < 6 months to 5, these are likely to be exposed during pregnancy or exposure through paternal cases. A total of 225 reports were identified in patients 5 years old and below. Most reports were pregnancy registry reports (exposure through maternal and paternal) meanwhile few other reports found to be wrong vaccination; where patients were inadvertently given HPV vaccines instead of Measles vaccine, Hepatitis B vaccine, and Hepatitis A vaccine.

It is unknown how did AEFI occur in patients aged between 30 through over 65 years although it past recommended the nonvalent vaccine was approved for use in adults aged 27 – 45 years old in 2018. It could have past vaccination history record. However, in the year 2010, out of 27 reports found for patients between 30 through 65 years, one report was found to be associated with male aged between 40 – 49 years with serious AEFI. The male patient in age group of 40-49 years experienced tingling, pain, and numbness of right arm which the physician reported being disabling.

5.3 Seriousness

Year	Yes	No
2010	229	2543
2011	161	2203
2012	119	1338
2013	161	3240
2014	189	3575
2015	185	4587
2016	235	5435
2017	215	3664

Table 12: Seriousness Assessment by Year from 2010 - 2017

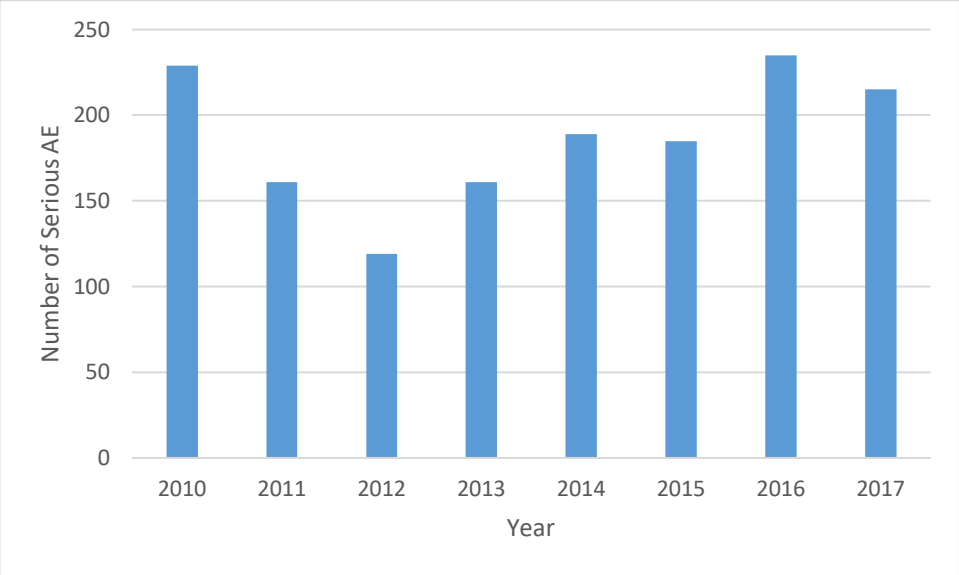


Figure 43: Comparison of Serious AEFI between year 2010-2017

Most of the AEFI reported in VAERS are found to be non-serious. Serious AEFI between year 2010 – 2017 is relatively lower compared with non – serious. Highest number of serious AEFI was found in year 2016, 2010 and 2017. A total of 1494 serious AEFI reports available between 2010 – 2017. Of these serious reports, it was further classified into 81 (5.4%) deaths, 40 (2.6%) life-threatening, 53 (3.5%) significant disabilities and 419 (28%) hospitalizations. Of the 81 death AEFI reports, most were unknown cause of death, meanwhile some report includes severe headache and passed away in sleep, seizure leading to death, sudden cardiac death, cardiac insufficiency, intracranial hemorrhage, suicide, myocarditis, infant death, cardiac respiratory arrest, and grand mal tonic-clonic seizure.

AEFI reports such as Guillain-Barre syndrome, seizure with tonic-clonic movements, Steven-Johnson syndrome, anaphylactic shock, sickle cell disease, cardiac death, coma, urticaria and angioedema, compartment syndrome, brachial deep vein thrombosis was considered as life-threatening by reporters. Causal relationship assessment for these serious reports were not assessed.

Similarly, serious AEFI reported occurred in patients aged between 6 – 17 years old with reported 909 (61%) of 1494 reports. The breakdown according to the age group is 6 (0.40%) in infants < 6 months, 1 (0.06%) in children age between 3 – 5 years, 314 (21%) in patients age between 18 – 29 years, 5 (0.33%) in patients aged 30 – 39 years, 7 (0.47%) in patients 40-49 years, 1 (0.06) in patient aged 50 – 59 years and 253 (17%) reports with unknown patient age groups (See Figure 43)

5.5 Gender

Year	Male	Female	Unknown
2010	190	2537	45
2011	430	1890	44
2012	639	1544	330
2013	844	1743	814
2014	808	1659	1297
2015	891	1481	2400
2016	1067	1861	2742
2017	855	1499	1525

Table 13: AEFI Distribution by Gender

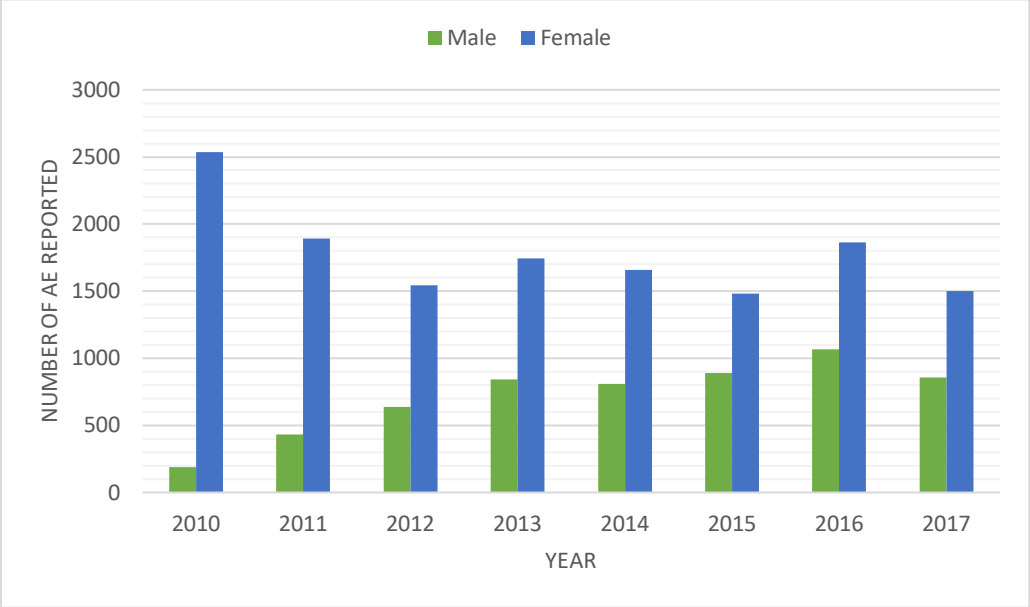


Figure 44: Comparison of AEFI Seriousness by Gender between the years 2010-2017

The trend for AEFI reported in females is higher as compared with males. AEFI in females fluctuated throughout the year 2010 – 2017 with the year 2010 being the highest. The trend of AEFI in males started off low at 190 as compared with a female with 2537, however, the trend for males increased gradually from 2011 – 2017. Both Cervarix and Gardasil were first approved for use in females in 2009 and 2006 respectively, hence the AEFI for females from the year 2010 – 2017 is relatively higher as compared with females. The trend of AEFI in boys increased gradually from the year 2011 after Gardasil was approved for use in males between the year 2009 – 2010 and subsequently Gardasil 9 was approved for use in males in 2016 which then showed a rise in AEFI. However, it is unknown if the reason for the drop in AEFI among females in years 2012 and 2015, also 2017 for males. Also, the gender of patients for several reports wasn't available in AEFI reports, therefore, the trend shown in Figure 3 is based on gender information's given only.

Chapter 6: DISCUSSION

6.1 Adverse Event and System Organ Class

The number of subjects recruited into each trial is limited and may not detect rare and severe adverse events during clinical trials. On that account, post-licensure surveillance of AEFI is fundamental to continuously monitor the safety of vaccines during routine use in the general population. Although the passive surveillance systems have been useful, it has several disadvantages including underreporting, insufficient information of the adverse event reports, missing diagnosis information such as laboratory data or patient outcome which is crucial for causality assessment. Despite that, passive surveillance systems provide valuable information as trends and signals that can be detected even if it is an incomplete report.

In this study, AEFI reports collected through VAERS may overcome these insufficiencies as text mining was able to detect adverse event terms. To our knowledge, no previous efforts have been reported of text mining used for HPV adverse event term identification in VAERS. In this study comparing AEFI from 2010 – 2017, it is important to consider that HPV vaccines and indications in genders were approved in schedules in a different timeline and the way of reporting of adverse events. A total of over 14 000 terms were reviewed during text filtering. The strength of this method on text filtering was to eliminate irrelevant terms and break text into individual words, which helped improve the accuracy to detect adverse event terms. SAS Text Miner software is useful in displaying and understanding large text data (Teng and Khong., 2021). SAS Text Miner provides the ability to gather relevant topics by filtering and extracting information from large data (Teng and Khong., 2021). The method of this study was compared to a study done by Botsis et al., 2013 where it involves the extraction of Guillain-Barre Syndrome (GBS) was classified by using text mining (Botsis et al., 2013). In a study conducted by Botsis et al., 2013, key medical terms were extracted from VAERS reports by using the Vaccine Adverse Event Text Mining (VaeTM) system (Botsis et al., 2013). VaeTM tool works by organizing and tagging important medical terms following extraction of the terms from the original free text (Botsis et al., 2013). Data mining by using VaeTM was found to be useful in extracting the information needed in an automated manner and VaeTM was able to organize it, therefore found to be useful in post-marketing safety surveillance (Botsis et al., 2013). Using both text mining tools and medical terminologies (MedDRA) along with the application of algorithms could potentially offer significant benefits in post-marketing safety surveillance (Botsis et al., 2013). This method not only could benefit medical experts in workload reduction but also provide efficient, accurate, thorough, and consistent safety surveillance data (Botsis et al., 2013).

The adverse events identified throughout 2010 – 2017 are inconsistent. The year 2012 was found to have comparably lowered adverse events identified, while 2010 had the highest adverse events identified. Due to the introduction of HPV in 2008 for girls aged 14, 2010 saw the peak of adverse events identified. However, the trend saw a rapid decrease after 2010. A similar trend was observed in the AEFI study conducted By Ramos et al., where the peak was observed in 2009 due to the introduction of the HPV vaccine in late 2008 in Spain (Ramos et al., 2016). The adverse events detected between 2015 - 2017 were higher, probably due to the introduction of the nonvalent HPV vaccine in boys in the year 2014. Our data do not allow us to compare reporting rates of adverse events associated with the HPV vaccine from 2010 – 2017. The reporting rate is estimated through the number of vaccine doses administered and the number of AEFI reported. Information on doses of vaccines administered versus reporting rate could have provided us an estimation of adverse event reporting awareness.

Other strengths of this study were that most mentioned terms were able to be identified through Text Filter. Text Filter reduces the number of parsed terms (Teng and Khong., 2021). Most identified terms were grouped into system organ class. As shown in Section 6.1, tables include General disorders and administration site conditions (pain at the injection site, swelling at the injection site, induration at the injection site, erythema/redness at the injection site, fever), nervous system disorder (headache, migraine, syncope), musculoskeletal and connective tissue disorders (myalgia, back pain), gastrointestinal disorders (nausea, vomiting), skin and subcutaneous tissue disorders (pruritus, urticaria, itching). Many of the terms or symptoms identified in our findings are like those described in product reports or product information leaflets and may seem very common. We did not detect any unusual or warning signal in this study. In this study, the text cluster also grouped terms into groups to form themes based on the frequency of the terms. Text cluster intends to help in investigating the focus of each cluster and derive specific topics or common properties. Unfortunately, it was not possible to interpret each cluster's theme into a meaningful finding. Clusters in Section 6.2 could potentially assist in categorizing symptoms into diagnoses based on the terms. Text Clusters in Section 6.2 can also be used to link respective clusters into system organ classes; however, it was observed that these terms could not be grouped into meaningful categories. Therefore, cluster analysis was not further examined for this part of the study. The text cluster needs further investigation and deep analysis to extract meaningful insights in the future. There is no report that correlates the relationship between adverse events reported under Nervous System Disorder SOC and refusal of the HPV vaccine. In my opinion, the public rather looks into the individual adverse event (for examples such as death or Guillain barre syndrome) and its seriousness of it rather than the SOC.

In a pre-marketing safety and efficacy studies on HPV vaccine conducted previously, results showed the AEFI associated with HPV vaccines are rather mild either at the side of injection or systemically (Garland et al., 2015; Future II Study Group., 2007; Pederson et al., 2007; Petaja et al., 2009; Skinner et al., 2014; Wheeler et al., 2016; Leung et al., 2018; Giancomet et al., 2014; Guiliano et al., 2015; Castellasague et al., 2015; Van Damme et al., 2016, Garland et al., 2007). Similar symptoms were observed for seven days post bivalent HPV vaccine administration, including arthralgia, fatigue, fever, gastrointestinal, headache, myalgia, rash, and urticaria. These adverse events were transient lasting no longer than 2 – 3 days, and the occurrence of adverse events did not increase with subsequent doses (Petaja et al., 2009). Findings from these safety and efficacy studies are similar to AEFI reports found between the years 2010 – 2017.

Besides, syncopal attack and tonic-clonic seizures were two common terms observed between 2010 throughout 2017. A syncopal episode (vasovagal, faint) happens due to vagal nerve stimulation with bradycardia and transient hypotension (Crawford et al., 2011). Vaccination is a triggering example of a syncopal attack (Crawford et al., 2011). The patient usually appears pale and brief loss of or alteration in consciousness and it usually occur*s in males* and female*s* aged 15 years old (Crawford et al., 2011). Meanwhile, the seizure is a sudden loss of consciousness and generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations. Seizures can be febrile, afebrile, or syncopal. The occurrence of syncope after the administration is expected as vaccination causes painful stimulation (Crawford et al., 2011). Syncope has been reported in VAERS following the introduction of many vaccines targeted at adolescents, including the quadrivalent meningococcal conjugate vaccine (Crawford et al., 2011). The occurrence of syncopal seizures has led product information to be updated including "syncope, sometimes accompanied by tonic-clonic movements" in the quadrivalent HPV vaccine (Crawford et al., 2011).

It is expected that syncope following vaccination in adolescents and young adults occurs in about 1 in 1000 doses (Kuntz et al., 2019). Vaccine providers must follow guidelines to strongly consider observing patients for 15 minutes after vaccination to prevent syncope-related injuries (Neha et al., 2020).

AEFI findings from this study were compared with Hepatitis B (HepB) vaccines AEFI. HepB is a virus infection that attacks the liver and may cause acute and chronic diseases (WHO, 2019). It is considered a life-threatening liver infection that can lead to the risk of death from cirrhosis and liver cancer (WHO, 2019). Like HPV infections, the transmission of HepB occurs through sexual contact. Often in adult's transmission of hepatitis B also occurs in unvaccinated individuals, particularly those with multiple sex partners and sex partners of people with chronic hepatitis B infection (Centers for Disease Control and Prevention, 2019). Hepatitis B is easily transmittable through sexual activity (Centers for Disease Control and Prevention, 27th August 2019). In infants, the virus is often transmitted from mother to child during birth and delivery through contact with body fluids and blood (WHO, 2019). HepB can be prevented with the HepB vaccine (WHO, 2019). HepB vaccine is indicated in infants, children, and adults. WHO recommends that all infants receive the hepatitis B vaccine preferably within 24 hours (WHO, 2019).

The AEFI findings of this study were compared with HepB because both HepB and HPV can be transmitted through sexual activities. The AEFI findings of this study were compared to previously conducted studies on AEFI of HepB vaccines data from VAERS. A study conducted between January 2005 – December 2015 through the Bayesian data mining method showed VAERS findings in both single and combination vaccines were like findings in this HPV vaccines VAERS. As shown in Figure 19, the most reported adverse events were incorrect product storage, dizziness, nausea, fever, headache, rash, pruritus, urticaria, injection site reactions, and inappropriate schedule of drug administrations (Haber et al., 2017). Findings in a study by Haber et al., 2017 found to be like AEFI findings of HPV vaccines from VAERS in this study.

Single vaccine[b] N = 4444			Combination vaccines[c] N = 15,787		
	N	%		N	%
Incorrect product storage[d]	971	22	Fever	3639	23
No adverse event[e]	967	22	Injection site erythema	1651	11
Dizziness	373	8	Vomiting	1643	10
Nausea	372	8	Irritability	1617	10
Fever	318	7	Crying	1486	9
Headache	290	7	Rash	1217	8
Rash	259	6	Diarrhea	1152	7
Pruritus	238	5	Injection site swelling	1143	7
Urticaria	234	5	Erythema	1032	7
Inappropriate schedule of drug administration	217	5	Urticaria	849	5

Figure 45 (Haber et al., 2017): Top 10 MedDRA Preferred Terms (PTs) following HepB vaccines, all ages, VAERS 2005-2015.

Meanwhile, comparison by system organ class, most AEFI fell within the system organ class of infections and infestations, nervous system disorders, general disorders and administration, immune system disorders, blood and lymphatic system disorders, cardiac disorders, gastrointestinal disorders, and musculoskeletal and connective tissue disorders (Haber et al., 2017).

Several pregnancies-related terms were identified throughout 2010-2017, such as congenital anomaly, fetal deaths, preterm delivery, spontaneous abortion, and miscarriage. The causal relationship of these terms identified with the HPV vaccine could not be able to be concluded from Text Mining. Hence it remains difficult to discuss the significance of these terms. All pregnancies risk congenital disability, loss, or other outcomes regardless of drug or vaccine exposure. HPV vaccines are not recommended for use in pregnant women. Generally, the administration of live attenuated virus vaccines is contraindicated during pregnancy (Garland et al., 2009). Due to ethical restrictions of testing drugs or vaccines in pregnant women, available data to inform on human pregnancy is limited (Goss et al., 2015). However, the HPV vaccine is recommended to women of child-bearing ages. The incidences of exposure during pregnancy could occur unintentionally in the global population (Goss et al., 2015). The Quadrivalent HPV vaccine is produced by expressing the major HPV capsid protein (L1) for each of the four types in *S.cerevisiae* (Garland et al., 2009). It does not contain viral DNA and therefore is considered noninfectious. Besides, the L1 major coat proteins of HPV or the antibodies against proteins are chemically or pharmacologically related to teratogens (Garland et al., 2009). However, vaccines have excipients that should be considered when determining safety for both the mother and child (Forinash et al., 2011). HPV vaccines do not appear to affect breastfeeding by mothers; however, it is not known if vaccine antigens or antibodies induced by HPV vaccine are excreted in human milk. In a randomized clinical trial study, no significant differences were noted in pregnancies resulting in a live birth, fetal loss, or spontaneous abortion (Garland et al., 2009). Besides, the incidence of congenital anomalies was similar compared with an incidence that occurs in the general population (Garland et al., 2009). Quadrivalent HPV vaccine was found to have no negative effect on pregnancy outcomes (Garland et al., 2009). Similarly, the bivalent vaccine has also been considered to not risk miscarriage (Wacholder et al., 2010).

Unlike HPV Vaccines, HepB vaccines can be given to females during pregnancy. It is recommended in unvaccinated pregnant women, including those at high risk of HepB infections (Moro et al, 2018). Pregnancy-related AEFI in HPV vaccines from VAERS has similar findings with HepB AEFI in pregnant women. In a study conducted by Moro et al., 2018, HepB administration in pregnant women has reported side effects such as spontaneous abortion, preterm delivery (<37 weeks), elective termination, birth defects (as shown in Figure 47).

Adverse events[i]	N (%)
Pregnancy-specific AEs	61 (55.4)
Spontaneous abortion (<20 weeks gestation)	23 (20.9)
Preterm delivery (<37 weeks)	7 (6.4)
Elective termination	5 (4.5)
Vaginal bleeding	4 (3.6)
Failure to progress	4 (3.6)
Hypertension	3 (2.7)
Edema, swelling	3 (2.7)
Stillbirth (≥20 weeks gestation)	2 (1.8)
Chorioamnionitis	2 (1.8)
Premature labor	2 (1.8)
Pre-eclampsia	2 (1.8)
Other[a]	4 (3.6)
Non-pregnancy specific AEs[b]	35 (31.8)
General disorders and administration site conditions	20 (18.2)
Injection site reactions	7
Systemic reactions	12
Immune system disorders	7 (6.4)
Gastrointestinal disorders	2 (1.8)
Other[c]	6 (5.4)
Infant outcomes	22 (20.0)
Birth defects[††]	
Down's syndrome, cardiac abnormality	1
Encephalocoele and orbital roof defect	1
Tetralogy of Fallot	1
Undescended testicle	1
Absence of heart	1
Death from small bowel perforation and mild hyaline disease in preterm infant (27 weeks) [c]	1
Jaundice	3
Other [d]	13

Figure 46 (Moro et al., 2018): Adverse Events following Hepatitis B vaccination during pregnancy in the VAERS, United States, 1990-2016

6.2 Age Groups

Understandably, most reported events in VAERS occurred in patients between age 6-17 years and 18-29 years since the HPV vaccine is indicated for use in adolescents between ages 11-26 for females and 11-21 for males. However, it is unclear on AEFI occurrences in adults above 30 years old since the data reviewed was between 2007-2017. Only in the year 2018, the nonvalent HPV vaccine was approved by the FDA for use in adults aged 27-45 years old. Both age groups (30-39 years old and 40-49 years old) appeared to be among the top age groups with high reported events in VAERS. Reports in children below 5 years explain that it could be monitoring the fetus or mother's pregnancy outcome upon getting exposed to HPV vaccination during pregnancy. There are chances that drugs could potentially affect fetus growth during pregnancy, and many women may not realize they are pregnant during the first trimester. This also applies to men trying to father a child. As explained above in Section 1.1.6, the HPV vaccine is indicated to women of child-bearing ages and men who could father a child. In spontaneous adverse event reporting, cases for both newborn child's health should be made or followed up to a year after birth. This is done to obtain the full event occurred and register any congenital anomaly that occurred (Morgan et al., 2011).

The findings of age groups comparison in this study were similar in comparison with the HepB vaccine. Most reported AEFI in single Hep B vaccine or combination/co-administered vaccine were in patients aged between 2-18 years and above 18 years old (as shown in Figures 48 and 49).

Characteristics	Age category			
	<1 month N = 240 N (%)	1.5–23 months N = 235 N (%)	2–18 years N = 310 N (%)	>18 years[b] N = 2365 N (%)
Male	128 (53)	95 (40)	119 (38)	670 (28)
Median age (range)[c]	1 (0–30)	6 (1–23)	12 (2–18)	38 (19–88)
Onset interval in days (median range)	1 (0–737)	0 (−7 to 2047)	0 (0–768)	0 (−30 to 1340)
Death	27 (11)	13 (5.5)	–	3 (0.1)
Non-death, serious[d]	64 (27)	26 (11)	15 (5)	139 (6)
Type of reporter				
Vaccine provider	46 (19)	89 (38)	151 (49)	1195 (52)
Other[e]	52 (22)	34 (14)	53 (17)	475 (20)
Parent	40 (17)	16 (7)	24 (8)	175 (7)
Manufacturer	102 (43)	96 (41)	80 (26)	516 (22)
Unknown reporter	0	0	2 (<1)	4 (<1)

Figure 47 (Haber et al., 2017): Characteristics of VAERS reports following single HepB vaccine, all ages VAERS 2005 – 2015.

Characteristics	Age category		
	1.5–23 month N = 9816 N (%)	2–18 years N = 2278 N (%)	>18 years[b] N = 3502 N (%)
Male	5112 (52)	1084 (48)	1275 (36)
Median age (range)[c]	4 (1–23)	6 (2–18)	37 (19–101)
Onset interval in days (median range)	1 (−10 to 1841)	0 (−90 to 2193)	1 (0–1710)
Death	388 (4)	2 (<1)	12 (<1)
Non-death, serious[d]	1925 (20)	87 (4)	228 (7)
Type of reporter			
Vaccine provider	5928 (60)	1490 (65)	2011 (57)
Other[e]	2492 (25)	593 (26)	907 (26)
Parent	628 (6)	83 (4)	228 (7)
Manufacturer	761 (8)	11 (5)	356 (10)
Unknown reporter	7 (<1)	0	0

Figure 48 (Haber et al., 2017): Characteristics of VAERS reports following combination and/or co-administered vaccines, all ages VAERS 2005 – 2015.

6.3 Seriousness

Serious adverse events described if a patient experiences an unexpected adverse event with the outcome of death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices) or other serious important medical events (www.fda.gov Assessed: 16th February 2022). Life-threatening refers to an event where the patient was at risk of dying at the time the adverse event occurred (www.fda.gov Assessed: 16th February 2022). Other serious important medical events refer to when an event may have jeopardized the patient and may need medical or surgical intervention (treatment) to prevent one of the other outcomes (www.fda.gov Assessed: 16th February 2022).

Throughout 2010-2017, most reports in VAERS were considered non-serious. Although, several serious reports as described in section 6.4. Overall, serious adverse events detected in our study were like the study by Hart et al., where the following incidences from VAERS include death, deep vein thrombosis, Guillain-Barre syndrome, and seizures (Borja-Hart et al., 2009).

The incidence of Guillain-Barre syndrome (GBS) has been investigated in previous studies. GBS is considered one of the most common neurological sequelae of various types of vaccination (Souayah et al., 2011). GBS is described as a rare, serious autoimmune disorder of the peripheral nerves involving muscle weakness and loss of

reflexes. GBS occurs predominantly in males and increases with age. Although the cause of GBS is unknown, it is believed, GBS is caused by, it is believed molecular mimicry is the mechanism for stimulation of antigenic resulting in autoimmune demyelination and damages to peripheral nerves (Souayah et al., 2011). Within a couple of weeks prior to the onset of GBS following vaccination, most patients describe it (Gee et al., 2017). Characteristics of the vaccines such as the Gardasil vaccine GBS due to its antigenicity of the vaccine's recombinant proteins especially aluminium, the antigenicity of the vaccine component, and recipient's genetic predisposition to develop vaccine-induced autoimmunity, could be the trigger reason for GBS. (Souayah et al., 2011).

In a data study conducted by VAERS between 2006-2009, there were 69 reported cases of GBS after vaccination with Gardasil in the United States. GBS occurrence was nearly 2.5 to 10 times greater within six weeks after Gardasil vaccination compared with the general population (Souayah et al., 2011). Similarly, a similar GBS investigation study done through Vaccine Safety Datalink showed the incidence rate of GBS was 2.52 cases per million quadrivalent HPV vaccine doses administered; 2.10 per million doses for females and 3.44 per million doses for males (Gee et al., 2017). Incidence of GBS was compared with HepB vaccine, in a study conducted by McMahon et al., 1992, it was concluded occurrence of GBS is unlikely associated with HepB vaccine (McMahon et al., 1992). In this study, two patients developed GBS following vaccination and patients developed reactions 12 weeks and 9 months following administration of HepB dose (McMahon et al., 1992). A patient usually develops a GBS reaction within eight weeks following vaccine administration, therefore the occurrence of GBS following HepB was concluded as not associated with HepB vaccination (McMahon et al., 1992). In another study by Chen et al., 2019, it was found that no increase in the risk of GBS following HepB vaccination (Chen et al., 2019). In this study, the HepB vaccine was the most used vaccine in the study population among other vaccines (Chen et al., 2019). Although there were incidences of GBS associated with HepB vaccine found in this study, the association of HepB and GBS was reported as difficult to be interpreted as it is not possible to determine if the observed event was causal or coincidental (Chen et al., 2019). Until now, there is no evidence that supports a causal relationship between the occurrence of GBS and vaccination (Chen et al., 2019). It is assumed that stimulation of the immune system is a factor in its pathogenesis (Chen et al., 2019). There has been evidence of vaccine-induced antibodies, anti-ganglioside (anti-GM1) observed in mice during pathophysiology of GBS following immunization (Chen et al., 2019). The causal relationship between GBS and vaccination must be carefully evaluated and established as it may influence impact vaccination coverage (Souyah et al., 2009). Vaccination policies must be amended if there is true evidence of GBS following vaccination where the policy must state specific populations who may be at risk of experiencing GBS following vaccination (Souyah et al., 2009).

We also observed postural orthostatic tachycardia syndrome (POTS). POTS is a systemic syndrome that has been known for a long time under different names and is still poorly understood (www.ema.europa.eu, Assessed:09th October 2021). About a hundred and fifty girls and young women per million experiences POTS each year (www.ema.europa.eu Assessed: 09th October 2021). POTS is characterized by tachycardia longer than ten minutes upon standing and rise in heartbeat to above 120 beats per minute (www.ema.europa.eu Assessed: 09th October 2021). However, POTS can't be diagnosed based on these symptoms, other symptoms the patients may experience include fatigue, syncope, headaches, light-headedness, tremor, diaphoresis, exercise intolerance, palpitations, near

syncope upon standing and these symptoms may vary in patients (www.ema.europa.eu Assessed: 09th October 2021). The cause of POTS is unknown, and it often occurs predominantly in females from adolescence to early adulthood. In a VAERS HPV vaccine study between 2006 through 2015, a total of 91 reports were US reports, and 146 were on females; meanwhile, 73 reports met the regulatory definition for a serious report. In this study, the incidence of POTS was observed in individuals aged between 11-26 years old, the age of HPV recommended (Arana et al., 2017). European Medicines Agency (EMA) conducted a safety review to assess the relationship between HPV vaccination and POTS (Arana et al., 2017). In a report published in November 2015, the EMA concluded based on available evidence, the causal relationship between HPV and POTS couldn't be determined. (Arana et al., 2017). In a clinical trial data review, it was found no cases were identified in the Cervarix and comparators (www.ema.europa.eu Assessed: 09th October 2021). This data review includes 60, 594 subjects for Gardasil® and Gardasil9® and 42, 047 subjects for Cervarix (www.ema.europa.eu Assessed: 09th October 2021). During clinical trials of Gardasil® and Gardasil9®, it was discovered the incidence of POTS was low with 1 case per 10,000 person-years compared to the placebo cohort (www.ema.europa.eu Assessed: 09th October 2021). Meanwhile, a study conducted by the CDC and US FDA showed POTS event was rarely reported following HPV vaccination, and no unusual or unexpected patterns of reporting for POTS were detected in safety reports (Arana et al., 2017). The occurrence of POTS following vaccination has created controversial news (Rull and Lobo., 2020). The occurrence of POTS is not only reported in the HPV vaccine, but also in other vaccines including the H1N1 Influenza vaccine, meningococcal vaccination, and varicella vaccine (Rull and Lobo., 2020). The occurrence of POTS following HPV vaccination is three times greater as compared with other vaccinations and the reason is unknown (Rull and Lobo., 2020). One possible reason POTS occurs following vaccination is due to the administration of multiple doses within short intervals (Rull and Lobo., 2020). Aluminium containing HPV vaccine, the Gardasil® type contains aluminium which can impact change in the immune system, ASIA-autoimmune/autoinflammatory syndrome induced by adjuvant (Rull and Lobo., 2020). As the HPV vaccine shares similar peptides with human proteins, evidence has shown it is associated with cases of cardiac manifestations as it influences circulation (Rull and Lobo., 2020).

6.4 Gender

The occurrence of adverse events in this study was found to be higher in females compared with males. As shown in Figures 20 and 21, similar findings were observed in VAERS of HepB vaccines AEFI where between 2005 and 2015, 51% of AEFI occurred in females compared with males (Haber et al., 2018). A true comparison of why females experienced more adverse events as compared with males could be done if a total number of vaccine administration data were available. In this study, we did not have data of vaccine distribution data. The occurrence of adverse events is 50 to 75% more likely in women than men. These could be due to differences in both drug pharmacokinetics and pharmacodynamics in both genders. Differences in lean body mass are important for some drugs. For example, females have a higher distribution volume than males for diazepam, which is the same way round for alcohol. Hepatic clearance of certain drugs such as temazepam, acetaminophen, and digoxin are higher in males than women, while hepatic clearance of verapamil, erythromycin, and cyclosporin are greater in women. Certain adverse events appear to have an immunological etiology. It is well known that the females have several skin diseases believed to have an immunological basis, such as systemic lupus erythematosus, systemic sclerosis, linchen planus, and photosensitivity (Rademaker M., 2001). Higher occurrence of an adverse event in females

could relate to the acceptance of HPV vaccine uptake in both males and females. In general, acceptance of HPV vaccination in parents of females is higher than with parents of males (Oldach et al., 2012). With the higher intake of HPV vaccines in females, the rate of adverse events in females can be higher than the males.

6.5 Risk Assessment of HPV Vaccine

The progression of HPV infection to cancer is slow, therefore, the effectiveness of the vaccine can only be estimated after a long time (Vanska et al., 2018). The HPV prevalence provides early risk assessment evaluation of the HPV vaccines (Vanska et al., 2018). In a study conducted in Sweden, it was shown the efficacy against HPV infection by HPV vaccination was 52.2% and 49.6% in post-vaccination individuals (Vanska et al., 2018). In this study, the efficacy measurement was done through HPV prevalence data collected among women aged 15-39 years old from pre-and post-vaccination timelines who underwent public cervical cancer screening. In a similar study conducted in Japan, the result showed the prevalence of HPV-16 and HPV-18 infection reduced significantly from 1.3% in 2014 to 0% in 2017 (Sekine et al., 2020). This study showed the prevalence of HPV strain 16 and 18 infections reduced dramatically and other type-specific HPV infections changed after HPV vaccination (Sekine et al., 2017). With the increase in HPV vaccination rate from 30.7% in 2014 to 93.7% in 2017, the prevalence of high-risk HPV infection shown to increase from 10% in 2014 to 11.3% in 2015, 11.2% in 2016, and 11.6% in 2017 (Sekine et al., 2017). Herd immunity has also proven to reduce the infection rate of HPV-16 and HPV-18 among unvaccinated individuals in vaccinated generations in countries such as Australia, the United Kingdom, and the United States (Sekine et al., 2017).

A cross-sectional study conducted for data collected between 2009 to 2016 from National Health and Nutritional Examination Survey (NHANES), it showed infection rate between HPV types 6, 11, 16, or 18 was found to be reduced among vaccinated women as compared with unvaccinated women. This study was conducted by evaluating behavior data among participating women and vaginal swab specimens. The predicament showed infection among unvaccinated women and those with more than 5-lifetime male sexual partners are higher (Sanowane et al., 2019). There is little epidemiological data on HPV prevalence among men to date (Fappani et al., 2021). In a study conducted, among men, the prevalence of anogenital wart diagnosis in males aged 15-19 years has decreased significantly by 48% (Drolet et al., 2019). Similarly, the study also revealed, the anogenital wart diagnosis in men aged 20-24 years decreased significantly by 32% (Drolet et al., 2019).

6.6 Post-Marketing Surveillance Methods

Passive surveillance reports such as the VAERS have their disadvantages (Salmon et al., 2016). Often underreporting or overreporting is a common issue with passive surveillance systems (Salmon et al., 2016). In passive surveillance methods, the number of individuals taking the vaccines and rates of adverse events after vaccination can't be established (Salmon et al., 2016). In a passive surveillance system, the rates of vaccine intake by unvaccinated and vaccinated populations can be made, which makes it difficult to compare the rates (Salmon et al., 2016). Another method of post-marketing surveillance is through active surveillance (Salmon et al., 2016). In the active surveillance methods, the rate of adverse events in vaccinated individuals can be determined by comparison of the unvaccinated populations (Salmon et al., 2016). Some examples of active surveillance systems are Vaccine Safety Datalink (VSD), Post licensure Rapid Immunization Safety Monitoring (PRISM) Network, Drug Safety Research Unit (DSRU), Vaccine Adverse Event Surveillance and Communication (VAESCO), Exploring and Understanding Adverse Drug Reactions by Integrative mining of Clinical Records and Biomedical Knowledge (EU-ADR) Alliance (Salmon et al., 2016). Often, signals arise from passive surveillance are analyzed in active surveillance system (Salmon et al., 2016). Information's such as exposure to vaccine, hospitalization, laboratory data and outpatient visits are needed for further evaluation mainly in concluding the causal-relationship assessment (Salmon et al., 2016).

Chapter 7: CONCLUSION

Predictive text analytics (cluster text) was carried out on VAERS data to achieve the research objectives and answer the research questions. Answering Research Questions 1, 2, and 3, the most affected organs classified by the MedDRA system (Section 6.1) were Nervous System Disorders followed by General Disorders and Administration Site Conditions, Skin and Subcutaneous Disorders, Musculoskeletal and Connective Tissue Disorders. Meanwhile, most identified adverse events were general disorders such as injection site reactions (pain, redness, swelling, itching), headaches. This may improve concern for HPV vaccine safety by further increasing vaccination acceptance and reducing public refusal. Some serious adverse events were identified through text analytics such as death, GBS, and POTS, which correlate well with vaccination refusal due to safety concerns (Section 6.4). Answering Research Questions 4, the most adverse events occurred in the patient group between 6 – 29 years old. This is the age of HPV vaccination recommended. Hence the reason most adverse events were observed in this group of patients.

In pharmacovigilance, underreporting of adverse events has always been a concern of pharmaceutical industries (manufacturing license holders) and regulatory authorities. In this study, there were no unusual or unexpected safety signals were detected in VAERS reports following HPV vaccination. Findings from this study is consistent with previously available data from pre-licensure trials and other post-licensure research studies. Big Data Analytics by using SAS Text Miner software could be implied in the pharmacovigilance field by pharmaceutical industries and regulatory authorities to detect safety signals. In conclusion, big data analytics of AEFI reported through VAERS provides beneficial information about HPV vaccines' safety related to the system organ class. Besides, findings of HPV vaccines by patient's characteristics (such as age groups and genders) and seriousness of the adverse events found to be like other available vaccines in the market (comparisons with HepB vaccines).

7.1 Contributions of this study

This research demonstrated big data analytics through SAS Text Miner, which can be used to understand adverse events related to HPV vaccines. Pharmacovigilance is an evolving discipline, and text mining can play an important role. Text mining can be useful in supporting pharmacovigilance fields to look for key terms in either health records, spontaneous reports, clinical trials, product labeling, social media, biomedical literature, and search logs (Harpaz et al., 2014). This study complemented big data mining for adverse event detection from previous studies (Gurulingappa et al., 2013; Botsis et al., 2011). The results of the method contribute to adverse event detection and knowledge. Studies have proven that text mining is useful in extracting safety-related information from text sources (Harpaz et al., 2014). Text mining can detect unreported adverse events, which can be added to the safety signal process. Text mining software can support pharmacovigilance tasks in healthcare and industry (Gurulingappa et al., 2013). Rapid signal detection can be done through text mining compared with other pharmacovigilance practices (Martin et al., 2013).

7.2 Limitations and future research

This study uses publicly available data taken from VAERS. Although the datasets are statistically large enough to conclude the study results, they may miss data such as causal relationship assessment, seriousness, age groups, gender. The VAERS serves a purpose as early or unusual signal detection and to conclude if an AE was caused by a vaccine. Information's available in VAERS needs further evaluation to perform a benefit-risk assessment of a product. Follow-up with patients with AEFI, especially if it is a serious adverse event, should be done by reporting healthcare professionals or industry to ensure information are available for analysis. Another limitation of this study includes adverse events reported in VAERS are not only by healthcare professionals but also consumers or caregivers. Therefore, an adverse event described by a non-healthcare professional reporter may not be as accurate as those reported by healthcare professionals. This may have had limitations in text analysis through SAS Text Miner, where terms identified may not have been accurate symptoms experienced by patients. The Text Cluster analysis could be further evaluated to derive diagnosis or system organ class based on the clusters. To do so, we need expertise such as an experienced medically qualified physician to conclude the diagnosis or system organ class of each cluster. Future studies should compare the causal relationship assessment of adverse events identified through text mining, as it may be useful in future surveillance of adverse events.

REFERENCES

Ackerson, B., Hechter, R., Sidell, M., Sy, SL., Slezak, J., Chao, C., Patel, N., Tseng, HF., and Jacobsen, S. (2017) Human Papillomavirus Vaccine Series Completion in Boys Before and After Recommendation for Routine Immunization. *Vaccine*, 35(6), pp.897-902.

Agergaard, TE., Smith, ME., and Nielsen, KH. (2020) Vaccine Assemblages on Three HPV Vaccine-Critical Facebook Pages in Denmark from 2012 to 2019. *Media and Communication*, 8(2), pp.339-352.

Alguacil-Ramos, AM., Muelas-Tirado, J., Garrigues-Pelufo, TM., Portero-Alonso, A., Diez-Domingo, J., Pastor-Villalba, E. and Lluch-Rodrigo, JA. (2016) Surveillance for adverse events following immunization (AEFI) for 7 years using computerized vaccination system. *Public Health,* 135 (66), pp.66-74.

Allison, MA., Dunne, EF., Markowitz, LE., O'Leary, ST., Crane, LA., Hurley, LP., Stokley, S., Babbel, CL, Brtnikova, M., Beaty, B. and Kempe, A. (2013) HPV Vaccination of Boys in Primary Care Practices. *Academic Pediatrics*, 13(5), pp.466-474.

Arana, J., Mba-Jonas, A., Jankosky, C., Lewis, P., Moro, PL., Shimabukuro, TT. and Cano, M. (2017) Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. *Journal of Adolescent Health,* 61(5), pp.577-582.

Ashrafi, GH., Salman, NA. (2016) Pathogenesis of Human Papillomavirus – Immunological Responses to HPV Infection. *IntechOpen.* [Online]. Available at: https://doi.org/10.5772/63965 [Assessed 30th April 2021].

Barnighausen, T., Bloom, D., Cafiero-Fonseca, E. and O'Brien, C. (2014) Valuing Vaccination. *PNAS*, 111(34), pp.12313-12319.

Boda, D., Oanadocea, A., Calina, D., Adrianailie, M., Caruntu, C., Sabinazurac., Neagu, M., Contantine, C., Elenebranisteanu, E., Voiculescu, V., Mamoulakis, C., Tzanakakis, G., Spandidos, AD., Drakoulis, N and Tstatsakis, MA. (2018) Human Papilloma Virus; Apprehending the Link with Carcinogenesis and Unveiling New Research Avenues. *International Journal of Oncology.* 52(3), pp.637-655.

Bolhassani, A., and Kardani, K. (2018) HPV Proteins and Their Functions. *HPV Infections: Diagnosis, Prevention and Treatment,* pp.8-29.

Barboi, A., Gibbons, CH., Axelrod, F., Benarroch, EE., Biaggioni, I., Chapleau, MW., Chelimsky, G., Chelimsky, T., Cheshire, WP., Claydon, VE., Freeman, R., Goldstein, DS., Joyner, MJ., Kaufmann, H., Low, PA., Norcliffe-Kaufmann, L., Robertson, D., Shibao, CA., Singer, W., Snapper, H., Vernino, S., and Raj, SR. (2019) Human Papillomavirus (HPV) Vaccine and Autonomic Disorders: A Position Statement from the American Autonomic Society. *Clinical Autonomic Research,* 30(1), pp.13-18.

Brand, HM., Pierce, JY. and Crary, A. (2016) Increasing HPV vaccination through policy for public health benefit. *Human Vaccines & Immunotherapeutics*, 12(6), pp.1623-1625.

Brewer, N. and Fazekas, K. (2007) Predictors of HPV Vaccine Acceptability: A Theory-Informed, Systematic Review. *Preventive Medicine*, 45(2), pp.107-144.

Brill, David. (2013) Australia launches national scheme to vaccinate boys against HPV. *BMJ,* 346. [Online]. Available at: https://doi.org/10.1136/bmj.f924 [Accessed 15th November 2019].

Bonanni, P., Zanella, B., Santomauro, F., Lorini, C., Bechini, A. and Boccalini, A. (2017) Safety and Perception: What are the Greatest Enemies of HPV Vaccination Programmes? *Vaccine*, 36(36), pp.5424-5429.

Bordignon, V., Di Domenico, EG., Trento, A., D'Agosto, G., Cavallo, I., Pontone, M., Pimpinelli, F., Mariani, L and Ensoli, F. (2017) How Human Papillomavirus Replication and Immune Evasion Strategies Take Advantage of the Host DNA Damage Repair Machinery. *Viruses,* 9(12), pp.390

Borja-Hart, NL., Benavides, S. and Christensen, S. (2009) Human Papillomavirus Vaccine Safety in Pediatric Patients: An Evaluation of the Vaccine Adverse Event Reporting System. *The Annals of pharmacotherapy,* 43(2), pp.356-359.

Botsis, T., Nguyen, MD., Woo, EJ., Makatou., M. and Ball,R. (2011) Text mining for the Vaccine Adverse Event Reporting System: medical text classification using informative feature selection. *Journal of the American Medical Informatics Association,* 18(5), pp.631-638.

Botsis, T., Woo, EJ., Ball, R. (2013) The Contribution of the Vaccine Adverse Event Text Mining System to the Classification of Possible Guillain-Barre Syndrome Reports. *Application Clinical Information,* 4(1), pp.88-99.

Brown, B., Gabra, MI., and Pellman, H. (2016) Reasons for Acceptance or Refusal of Human Papillomavirus Vaccine in a California Pediatric Practice. *The Pediatric Infectious Disease Journal*, 35(1), pp.119-120.

Burchell, A., Winer, R., Sanjose, S. and Franco, E. (2006) Epidemiology and Transmission Dynamics of Genital HPV Infection. *Vaccine*. 24(3), pp.52-61.

Burger, EA., Portnoy, A., Campos, NG., Sy, S., Regan, C., Kim, JJ. (2021) Choosing the Optimal HPV Vaccine: The Health Impact and Economic Value of the Nonavalent and Bivalent HPV Vaccines in 48 Gavi-Eligible Countries. *International Journal of Cancer*, 148(4), pp.932-940.

Castellsague, X., Giuliano, AR., Golstone, S., Guevara, A., Mogensen, O., Palefsky, JM., Group, T., Shields, C., Liu, K., Maansson, R., Luxembourg, A. and Kaplan, SS. (2015) Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine,* 33(48), pp.6892-6901.

CDC.Gov.com, (2019) Centers for Disease Control and Prevention's Official Website. [online] Available at: http://www.cdc.gov.com [Accessed 15 Nov.2019].

Chabeda, A., Yanez, R., Lamprecht, R., Meyers, A., Rybicki, E. and Hitzeroth, I. (2018) Therapeutic Vaccines for High-Risk HPV-Associated Diseases. *Papillomavirus Research*, 5, pp.46-58.

Chakraborty, G., Pagolu, M. & Garla, S. (2014) *Text Mining and Analysis: Practical Methods, Examples, and Case Studies Using SAS* SAS Institute.

Chan, SS., Cheung, TH., Lo, W. and Chung, TK. (2007) Women's Attitudes on Human Papillomavirus Vaccination to Their Daughters. *Journal of Adolescent Health*. 41(2), pp.204-207.

Chatterjee, A. and O'Keefe, C. (2010) Current controversies in the USA regarding vaccine safety. *Expert review of vaccines*, 9(5), pp.497-502.

Chazard E., Ficheur, G., Bernoville, S., Lucykx, M. and Beuscart, R. (2011) Data Mining to Generate Adverse Drug Events Detection Rule. *IEEE Trans Inf Technol Biomed,* 15(6), pp.823-830.

Chen, Li., Ling, Qi., Cao, T., and Han, K. (2020) Mislabeled, Fragmented, and Conspiracy-Driven: A Concept Analysis of the Social Media Discourse about the HPV Vaccine in China. *Asian Journal of Communication*, 30(6), pp.450-469.

Chen, Y., Zhang, J., and Chu, X. (2020) Vaccines and the Risk of Guillain-Barre Syndrome. *European Journal of Epidemiology*, 35, pp.363-370.

Chido-Amajuoyi, OG., Talluri, R., Shete, SS. and Shete, S. (2021) Safety Concerns or Adverse Effects as the Main Reason for Human Papillomavirus Vaccine Refusal: National Immunization Survey-Teen, 2008 to 2019. *JAMA Pediatr*, 175(10), pp.1074-1076.

Choi, EPH., Wong, JYH., Lau, AYY., Fong, DYT. (2018) Gender and Sexual Orientation Differences in Human Papillomavirus (HPV) Vaccine Uptake among Chinese Young Adults. International *Journal of Environmental Health and Public Health*, 15(6), pp.1099

Chow, SN., Soon, R., Park, JS., Pancharoen, C., Qiao, YL., Basu, P. and Ngan, HY. (2010) Knowledge, Attitudes, and Communication Around Human Papillomavirus (HPV) Vaccination Amongst Urban Asian Mothers and Physicians. *Vaccine*, 28(22), pp.3809-3817.

Cipriano, J., Scoloveno, R. and Kelly, A. (2017) Increasing Parental Knowledge Related to the Human Papillomavirus (HPV) Vaccine. *Journal of Pediatric Health Care.* 31(1), pp.29-35.

Cooper, DL., Zellner-Lawrence, T., Mubasher, M., Banerjee, A., Hernandez, ND. (2018) Examining HPV Awareness, Sexual Behaviour, and Intent to Receive the HPV Vaccine Among Racial/Ethnic Male College Students 18-27 years. *American Journal of Men's Health,* 12(6), pp.1966-1975.

Crawford, NW., Clothier, HJ, Elia, S., Lazzaro, T., Royle, J. and Buttery, JP. (2011) Syncope and seizures following human papillomavirus vaccination: a retrospective case series. *The Medical Journal of Australia,* 193(1), pp.16-8.

Darden, PM., Thompson, DM., Roberts, JR., Hale, JJ., Pope, C., Naifeh, M. and Jacobson, RM. (2013) Reasons for Not Vaccinating Adolescents: National Immunization Survey of Teens, 2008-2010. *Pediatrics*, 131(4), pp.645-651.

Degarege, A., Krupp, K., Fennie, K., Srinivas, V., Li, T., Stephens, DP., Madhivanan, P. (2019) An Integrative Behaviour Theory Derived Model to Assess Factors Affecting HPV Vaccine Acceptance Using Structural Equation Modeling. *Vaccine*, 37(7), pp.945-955.

De La Fuente, J., Hernandez, Aguado, JJ., San Martin, M., Ramirez Boix, P., Cedillo Gomez, S., Lopez, N. (2019) Estimating the Epidemiological Impact and Cost-Effectiveness Profile of a Nonavalent HPV Vaccine in Spain. *Human Vaccine Immunotherapy,*15(7-8), pp.1949-1961.

De Vincenzo, R., Conte, C., Ricci, C., Scambia, G. and Capelli, G. (2014) Long-term Efficacy and safety of human papillomavirus vaccination. *International Journal of Women's Health*, 3(6), pp.999-1010.

Dempsey, A. (2008) Human Papillomavirus: The Usefulness of Risk Factors in Determining Who Should Get Vaccinated. *Obstetrics & Gynecology*, 1(3), pp.122-128.

Deng, C., Chen, X., Liu, Y. (2020) Human Papillomavirus Vaccination: Coverage Rate, Knowledge, Acceptance, and Associated Factors in College Students in Mainland China. *Human Vaccines and Immunotherapeutics*, 17(3), pp.828-835

Di Pasquale, A., Bonnani, P., Garcon, N., Stanberry, LR., El-Hodhod, M., Taveres Da Silva, F. (2016). Vaccine Safety Evaluation: Practical Aspects in Assessing Benefits and Risks. *Vaccine*, 34(52), pp.6672-6680.

Dinh Thu, H., Nguyen Thanh, H., Hua Thanh, T., Nguyen Hai, L., Tran Thi, V, Nguyen Manh, T., Buve, A. (2018) Mothers' Willingness to Pay for Daughters' HPV Vaccine in Northern Vietnam. *Health Care Women International*, 39(4), pp.450-462.

Drolet, M., Benard, E., Perez, N., and Brisson, M. (2019) HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet,* 10(394), pp.497-507.

Du, J., Shegog, R., Bian, J., Cunningham, RM., Boom, JA., Poland, GA., Chen, Y., and Tao, C. (2020) Use of Deep Learning to Analyze Social Media Discussions about the Human Papillomavirus Vaccine. *JAMA Network Open*, 3(11), doi:10.1001/jamanetworkopen.2020.22025.

Duggirala, HJ., Tonning, JM., Smith, E., Bright, RA. Baker, JD., Ball, R., Bell, C., Bright-Ponte, SJ., Botsis, T., Bouri, K., Boyer, M., Burkhart, K., Condrey, GS., Chen, JJ., Chirtel, S., Filice, RW., Francis, H., Jiang, H., Levine, J., Martin, D., Oladipo, T., O'Neill, T., Palmer, LA., Paredes, A., Rochester, G., Sholtes, D., Szarfman, A., Wong, HL., Xu, Z. and Kass-Hout, T. (2016) Use of data mining at the food and drug administration. *Journal of the American Medical Informatics Association: Jamie,* 23(2), pp.428-430.

Dunn, AG., Surian, D., Leask, J., Dey, A.,Mandl, KD., and Coiera, E. (2017). Mapping Information Exposure on Social Media to Explain Differences in HPV Vaccine Coverage in the United States. *Vaccine*, 35(23), pp.3033-3040.

Duval, F., Caffarena, E., Cruz, O. and Silva, F. (2014) Mining for Adverse Drug Events on Twitter [online]. Available at: Doi: 10.5220/0005135203540359 (Accessed: 25 November 2019).

Elbasha, EH. And Dasbach, EJ. (2010) Impact of vaccinating boys and men against HPV in the United States. *Vaccine*, 28(42), pp.6858-6857.

European Medicines Agency. Annex Scientific Conclusions. [Online]. Available at: https://www.ema.europa.eu/en/documents/referral/hpv-vaccines-article-20-procedure-scientific-conclusion-annex_en.pdf [Assessed: 09th October 2021].

Fappani, C., Bianchi, S., Panatto, D., Petrelli, F., Colzani, D., Scuri, S., Gori, M., Amendola, A., Grappasonni, I., Tanzi, E. and Amicizia D. (2021) HPV Type-Specific Prevalence a Decade after the Implementation of the Vaccination Program: Results from a Pilot Study. *Vaccines*, 9(4), pp.336

Forinash, AB., Yancey, AM., Pitlick, JM. And Myles, TD. (2011) Safety of the HPV Bivalent and Quadrivalent Vaccines During Pregnancy. *The Annals of Pharmacotherapy,* 45(2), pp.258-262.

Ferris, DG., Waller, L., Miller, J., Patel, P., Price, GA., Jackson, L and Wilson C. (2009) Variables Associated with Human Papillomavirus (HPV) Vaccine Acceptance by Men. *Journal of the American Board of Family Medicine*, 22(1), pp.34-42.

Finney Rutten, LJ., St Sauver, JL., Beebe, TJ., Wilson, PM., Jacobson, DJ., Fan, C., Breitkopf, CR., Vadaparampil, ST., MacLaughlin, KL., Jacobson, RM. (2017) Association of Both Consistency and Strength of Self-Reported Clinician Recommendation for HPV Vaccination and HPV Vaccine Uptake Among 11- to 12-year-old Children. *Vaccine*, 35(45), pp.6122-6128.

Garland, SM., Cheung, TH., McNeill, S., Petersen, LK., Romaguera, J., Vazquez-Narvaez., J., Bautista, O., Shields, C., Vuocolo, S. and Luxembourg, A. (2015) Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. *Vaccine,* 33(48), pp.6855-6864.

Gerend, MA. And Barley, J. (2009) Human Papillomavirus Vaccine Acceptability Among Young Adult Men. *Sexually Transmitted Diseases*, 36(1), pp.58-62.

Giacomet, V., Penagini, F., Trabattoni, D., Vigano, A., Rainone, V., Bernazzani, G., Bonardi, CM., Clerici, M., Bedogni, G. and Zuccotti, GV. (2014) Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIVE-infected and HIVE-negative adolescents and young adults. *Vaccine*, 32(43), pp.5657-5661.

Giuliano, AR., Isaacs-Soriano, K., Torres, BN., Abrahamsen, M., Ingles, DJ., Sirak, BA., Quiterio, M. and Lazcano-Ponce, E. (2015) Immunogenicity and safety of Gardasil among mid-adult aged men (27-45 years) – The MAM Study. *Vaccine*, 33(42), pp.5640-5646.

Garland, SM., Hernandez-Avila, M., Wheeler, CM., Perez, G., Harper, DM., Leodolter, S., Tang, GW., Ferris, GW., Steben, M., Bryan, J., Taddeo, FJ., Railkar, R., Esser, MT., Sings, HL., Nelson, M., Boslego, J., Sattler, C., Barr, E., Koutsky, LA. and Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators (2007) Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions. *The New England Journal of Medicine,* 356(19), pp.1928-1943.

Garland SM., Ault, KA., Gall, SA., Paavonen, J., Sings, HL., Ciprero, KL., Saah, A., Marino, D., Radley, D., Zhou, H., Haupt, RM., Garner, EL. And Quadrivalent Human Papillomavirus Vaccine Phase III Investigators. (2009) Pregnancy and Infant Outcomes in the Clinical Trials of a Human Papillomavirus Type 6/11/16/18 Vaccine: a combined analysis of five randomized controlled trials. *Obstetrics and gynecology,* 111(6), pp.1179-1188.

Gee, J., Sukumaran, L., Weintraub, E. and Vaccine Safety Datalink Team. (2017) Risk of Guillain-Barre Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink. *Vaccine,* 35(43), pp.5756-5758.

Gerend, AM., and Barley, J. (2009) Human Papillomavirus Vaccine Acceptability Among Young Adult men. *Sexually Transmitted Diseases,*36(1), pp.58-62.

Giuliano, AR., Joura, AE., Garland, SM., Huh, WK., Iversen, OE., Kjaer, SK., Ferenczy, A., Kurman, RJ., Ronnett, BM., Stoler, MH., Bautista, OM., Moeller, M., Ritter, M., Shields, C. and Luxembourg, A. Nine-valent

HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population. *Gynecologic Oncologic*, 154(1), pp.110-117

Gualano, MR., Bert, F., Voglino, G., Buttinelli, E., D'Errico, MM., De Waure, C., Di Giovanni, P., Fantini, MP., Giuliani, MR., Marranzano, M., Masanotti, G., Massimi, A., Nante, N., Pennino, F., Squeri, R., Stefanati, A., Signorelli, C., Siliquini, R. and Collaborating Group (2018). Attitudes Towards Compulsory Vaccination in Italy: Results from the NAVIDAD Multicentre Study. *Vaccine*, 36(23), pp.3368-3374.

Gurulingappa, H., Toldo, L., Rajput, AM., Kors, JA., Taweel, A. and Tayrouz, Y. (2013) Automatic detection of adverse events to predict drug label changes using text and data mining techniques. *Pharmacoepidemiology and Drug Safety*, 22(11), pp.1189-1194.

Goss, MA., Lievano, F., Buchanan, KM., Seminack, MM., Cunningham, ML, and Dana, A. (2015) Final Report on Exposure During Pregnancy from a Pregnancy Registry for Quadrivalent Human Papillomavirus Vaccine. *Vaccine*, 33(29), pp.3422-3428.

Grandahl, M., Chun Paek, S., Grisurapong, S., Sherer, P., Tyden, T., and Lundberg, P. (2018) Parents' knowledge, beliefs, and acceptance of the HPV vaccination in relation to their socio-demographics and religious beliefs: A Cross-Sectional Study in Thailand. *Plos One*, 13(2), https://doi.org/10.1371/journal.pone.0193054

Haber, P., Moro, PL., Ng, C., Lewis, PW., Hibbs, B., Schillie, SF., Nelson, NP., Li, R., Stewart B., Cano, MV. (2018) Safety of Currently Licensed Hepatitis B Surface Antigen Vaccines in the United States, Vaccine Adverse Event Reporting System (VAERS), 2005-2015. *Vaccine*, 36(4), pp.559-564.

Harpaz, R., Callahan, A., Tamang, S., Low, Y., Odgers, D., Finlayson, S., Jung, K., LePendu, P. and Shah,NH. (2014) Text Mining for the Adverse Drug Events: The Promise, Challenges, and State of the Art. *Drug Safety,* 37(10), pp.777-790.

Hauben, M. and Bate, A. (2009) Decision support methods for the detection of adverse events in post-marketing data. *Drug Discovery Today,* 14(7). pp.343-357.

Hebner, C. and Laimins, L. (2006) Human Papillomavirus: Basic mechanisms of pathogenesis and oncogenicity. *Reviews in Medical Virology*, 16(2), pp.83-97.

HPVInformationCentre (2019) [Online]. Available at: http://www.hpvcentre.net/datastatistics.php. [Accessed 30 June 2021].

Juntasopeepun, P., Thana, K. (2018) Parental Acceptance of HPV Vaccines in Chiang Mai, Thailand. *International Journal of Gynaecology Obstetrician,* 142(3), pp.343-348.

Joshi, J., Das, MK., Polpakara, D., Aneja, S., Agarwal, M. and Arora, NK. (2018) Vaccine Safety and Surveillance for Adverse Events Following Immunization (AEFI) in India. *Indian J Pediatr*, 85(2), pp.139-148.

Kempe, A., O'Leary, ST., Markowitz, LE., Crane, LA., Hurley, LP., Brtnikova, M., Beaty, BL., Meites, E., Stockley, S., Lindley, MC. (2019) HPV Vaccine Delivery Practices by Primary Care Physicians. *Pediatrics*, 144(4), doi: 10.1542/peds.2019-1475.

Khong, KW., Tan, SL., Teng, S. and Ong, FS. (2018). Predictive Modelling Using Unstructured Data from Online Forums: A Case Study on E-cigarette Users [Online]. Available at: https://pdfs.semanticscholar.org/56a7/af85fadc0b95d315fbbe203f16973622a02a.pdf [Accessed: 20 July 2019]

Kim, AM., Han, HG., Kim, JH. and Seo, K (2018). Current Status of Human Papillomavirus Infection and Introduction of Vaccination to the National Immunization Program in Korea; an Overview. *J Korean Med Sci*, 33(52), pp.331-348.

Kornides, ML., McRee, AL., and Gilkey, MB. (2018) Parents who Decline HPV Vaccination: Who Later Accepts and Why? *Academy of Pediatrician*, 18(2S), pp.37-43

LaMontagne, DS., Bloem, PJN., Brotherton, JML., Gallagher, KE., Badiane, O., Ndiaye, C. (2017) Progress in HPV Vaccination in Low and Lower Middle-Income Countries. *International Journal of Gynaecology Obstetrician,* 138(1), pp.7-14.

LPPKN, Lembaga Penduduk dan Pembangunan Keluarga Negara (2019). [Online]. Available at: http://www.lppkn.gov.my [Accessed: 01 July 2021].

Leung, TF., Liu, AP., Lim, FS., Thollot, F., Oh, HML., Lee, BW., Tan, NC., Rouzier, R., De Simoni, S., Suryakiran, P., Hezareh, M., Thomas, F., Folschweiller, N. and Struyf, F. (2018) Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two- or three-dose schedules in girls aged 9-14 years: Results to month 36 from a randomized trial. *Vaccine,* 36(1), pp.98-106.

Liu, M., Hu, Y. and Tang, B. (2014) Role of Text Mining in Early Identification of Potential Drug Safety Issues. *Methods in Molecular Biology,* 1159, pp.227-251.

Jit, M., (2021) Informing Global Cost-Effectiveness Thresholds Using Country Investment Decisions: Human Papillomavirus Vaccine Introductions in 2006-2018. *Value Health*, 24(1), pp.61-66.

Margolis, MA., Brewer, NT., Shah, PD., Calo, WA., Gilkey, MB. (2019) Stories about HPV Vaccine in Social Media, Traditional Media, and Conversations. *Preventive Medicine*, 118, pp.251-256.

Marti, M., De Cola, M., MacDonald, NE., Dumolard, L. and Duclos, P. Assessment of Global Drivers of Vaccine Hesitancy in 2014 – Looking Beyond Safety Concerns. *PLoS One*, 12(3), doi: 10.1371/journal.pone.0172310

Martin, D., Meschik, D., Bryant-Genevier, M. and Ball, R. (2013) Data Mining for Prospective Early Detection of Safety Signals in the Vaccine Adverse Event Reporting (VAERS): A Case Study of Febrile Seizures after a 2010-211 Seasonal Influenza Virus Vaccine. *Drug Safety*, 36(7), pp.547-556.

Massey, PM., Kearney, MD., Hauer, MK., Selvan, P., Koku, E., Leader, AE. (2020) Dimensions of Misinformation About the HPV Vaccine on Instagram: Content and Network Analysis of Social Media Characteristics. *Journal of Medical Internet Research,* 22(12), doi:10.2196/21451

McClure, C., Cataldi, J., and O'Leary, S. (2017) Vaccine Hesitancy: Where We Are and Where We Are Going. *Clinical Therapeutics*. 39(8), pp.1550-1562.

McMahon, BJ., Helminiak, C., Wainwright, RB., Bulkow, L., Trimble, BA., Wainwright, K (1992). Frequency of Adverse Reactions to Hepatitis B Vaccine in 43,618 persons. *The American Journal of Medicine,* 92(3), pp.254-256.

Mendez Lobao, W., Duarte, FG., Burns, JD., de Souza Teles Santos, CA., Chagas de Almeida, MC., and Reingold, A. (2018) Low Coverage of HPV Vaccination in the National Immunization Programme in Brazil: Parental Vaccine Refusal or Barriers in Health-Service Based Vaccine Delivery? *Plos One*, 13(11), doi: 10.1371/journal/pone.0206726

Min, J., Osborne, V., Kowalski, A., Prosperi, M. (2018) Reported Adverse Events with Painkillers: Data Mining of the US Food and Drug Administration Adverse Events Reporting System. *Drug Safety*, 41(3), pp.313-320.

Moro, PL., Zheteyeva, Y., Barash, F., Lewis, P., and Cano, M. (2018) Assessing the Safety Of Hepatitis B Vaccination During Pregnancy In The Vaccine Adverse Event Reporting System (VAERS). *Vaccine,* 36(1), pp.50-54

Morgan, M., De Jong-van den Berg, LT. and Jordan, S. (2011) Drug safety in pregnancy – monitoring congenital anomalies. *Journal of Nursing Management*, 19(3), pp.305-310.

Muhamad, N., Buang, S., Jaafar, S. (2018) Achieving High Uptake of Human Papillomavirus Vaccination in Malaysia through School-Based Vaccination Programme, *BMC Public Health,* 18, pp.1402

NCSL.Org.com, (2018) National Conference of State Legislatures. [online]. Available at: http://www.ncsl.org.com / [Accessed 20 November 2019].

NSCL.Org.com, 2019) National Conference of State Legislature. [Online]. Available at: http://www.ncsl.org.com/ [Accessed 30th March 2021]

Ndikom, CM., and Oboh, PI. (2017) Perception, Acceptance and Uptake of Human Papillomavirus Vaccine Among Female Adolescents in Selected Secondary Schools in Ibadan, Nigeria. *African Journal of Biomedical Research*, 20, pp. 237-244.

Neha, R., Subeesh, V., Beulah, E., Gauri, N. and Maheswari, W. (2020) Postlicensure Surveillance of Human Papillomavirus Vaccine Using the Vaccine Adverse Event Reporting System, 2006-2017. *Perspect Clinical Research*, 11(1), pp.24-30.

Oldach, BR. and Katz, ML. (2012) Ohio Appalachia Public Health Department Personnel: Human Papillomavirus (HPV) Vaccine Availability, and Acceptance and Concerns Among Parents of Male and Female Adolescents. *Journal of Community Health,* 37(6), pp.1157-1163.

Okita, T., Enzo, A., Kadooka, Y., Tanaka, M., and Asai, A. (2020) The Controversy on HPV Vaccination in Japan: Criticism of the Ethical Validity of the Arguments for the Suspension of the Proactive Recommendation. *Health Policy*, 124(2), pp.199-204.

Okunade, KS., Sunmonu, O., Osanyin, GE., and Oluwole, AA. (2017) Knowledge and Acceptability of Human Papillomavirus Vaccination among Women Attending the Gynaecological Outpatient Clinics of a University Teaching Hospital in Lagos, Nigeris. *Journal of Tropical Medicine.* [online]. Available at: https://doi.org/10.1155/2017/8586459 [Accessed 19th January 2021]

Pedersen, C., Petaja, T., Strauss, G., Rumke, HC., Poder, A., Richardus, JH., Spiessens, B., Descamps, D., Hardt, K., Lehtinen, M. and Dubin, G. (2007) Immunization of Early Adolescent Females with Human Papillomavirus Type 16 and 18 L1 Virus-Like Particle Vaccine Containing AS04 Adjuvant. *Journal of Adolescent Health,* 40(6), pp.564-571.

Petaja, T., Keranen, H., Karppa, T., Kawa, A., Lantela, S., Siitari-Mattila, M., Levanen, H., Tocklin, T., Godeauz, O., Lehtinen, M. and Dubin, G. (2009) Immunogenicity and Safety of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine in Healthy Boys Aged 10-18 Years. *Journal of Adolescent Health,* 44(1), pp.33-40.

Perez, S., Zimet, GD., Tatar, O., Stupiansky, NW., Fisher, WA., Rosberger, Z. (2018) Human Papillomavirus Vaccines: Successes and Future Challenges. *Drugs*, 78(14), pp.1385-1396.

Rademaker, M. (2001) Do Women Have More Adverse Drug Reactions?. *Clinical Dermatology,* 2(6), pp.349-351.

Raja, U., Day, T., Mitchel, T. and Hardin, JM. (2008) Text Mining in healthcare. Applications and Opportunities. *Journal of Healthcare Information Management*, 22(3), pp.52-56.

Rull, G. and Lobo, MD (2021). Is POTS an Autoimmune Condition? In: Gall.N., Kavi, L., Lobo MD. Postural Tachycardia Syndrome. *Springer, Cham*. Available at: https://doi.org/10.1007/978-3-030-54165-1_20 [Assessed 11th October 2021]

de Sanjose S, Brotons, M., Pavon, MA. (2017) The Natural History of Human Papillomavirus Infection. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 47(2), pp.2-13.

Salmon, DA, and Halsey, NA. (2016), How vaccine safety is monitored*,* The Vaccine Book*, Academic press* pp.153-156.

Sekine, M., Yamaguchi, M., Kudo, R., J B Hanley, S., Hara, M., Adachi, S., Ueda, Y., Miyagi, E., Ikeda, S., Yagi, A. and Enomoto, T. (2020) Epidemiologic Profile of Type-Specific Human Papillomavirus Infection after Initiation of HPV Vaccination. *Vaccines*, 29;8(3), pp.425

Sonawane, K., Nyitray, AG., Nemutlu, GS., Swartz, MD., Chhatwal, J. and Deshmukh, AA. (2019) Prevalence of Human Papillomavirus Infection by Number of Vaccine Doses Among US Women. *JAMA Netw Open*, 2(12) Available at: https://doi.org/10.1001/jamanetworkopen.2019.18571

SAS (2016) SAS(R) Visual Analytics 7.2: User's Guide. Available online: https://support.sas.com/documentation/cdl/en/vaug/68027/HTML/default/viewer.htm#n1g7jt49jx4ifln0ztc6adzdjp7x.htm [Accessed 05th March 2020]

Sato, A. (2018) What is the Importance of Vaccine Hesitancy in the Drop of Vaccination Coverage in Brazil? *Revista de saude publica*, 52(96), https://doi.org/10.11606/S15188787.2018052001199

Serrano, B., Brotons, M., Bosch, F. and Bruni, L. (2017) Epidemiology and Burden of HPV-Related Disease. *Best Practice & Research Clinical Obstetrics and Gynaecology*.47, pp.14-26.

Skinner, SR., Szarewski, A., Romanowski, B., Garland, SM., Lazcano-Ponce, E., Salmeron, J., Del Rosario-Raymundo, MR., Verheijen, RH., Quek, SC., da Silva, DP., Kitchener, H., Fong, KL., Bouchard, C., Money, DM., Ilancheran, A., Cruickshank, Me., Levin, MJ., Chatterjee, A., Stapleton, JT., Martens, M., Quint, W., David, MP., Meric, D., Hardt, K., Descamps, D., Geeraerts, B., Struyf., F., Dubin, G. and VIVIANE Study Group (2014) Efficacy, safety and immunogenicity of the human papillomavirus 16/18 AS04-adjuvant vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomized controlled VIVIANE study. *Lancet*, 384(9961), pp. 2213-2227.

Souayah, N., Nasar, Abu MS., Suri, M Fareed., Qureshi, Adnan I (2009) Guillain-Barre Syndrome After Vaccination in United States: Data from the Centers for Disease Control and Prevention/Food and Drug Administration Vaccine Adverse Event Reporting System (1990-2005). *Journal of Clinical Neuromuscular Disease,* 11(1), pp.1-6.

Souayah, N., Michas-Martin, PA., Nasar, A., Krivitskaya, N., Yacoub, HA., Khan, H. and Qureshi, Al (2011) Guillain-Barre syndrome after Gardasil vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009. *Vaccine,* 29(5), pp.886-889.

Stanley, M. (2006) Immune Responses to Human Papillomavirus. *Vaccine*, 24(1), pp.16-22.

Stanley, M. (2012) Epithelial Cell Responses to Infection with Human Papillomavirus. *Clinical Microbiology*, 25(2), pp.215-222.

Tisi, G., Salinaro, F., Apostoli, P., Raffaella, B., Bellicini, A., Groppi, L., Donarini, P. and Pecorelli, S. (2013) HPV vaccination acceptability in young boys. *Annalli dell'Istituto superior di sanita*, 49(3), pp.286-291.

Teng, S. and Khong KW. (2021) Examining Actual Consumer Usage of E-Wallet: A Case Study of Big Data Analytics. *Computers in Human Behavior*, 121, [Online]. Available at: https://doi.org/10/1016/j.chb.2021/106778. [Assessed: 09 October 2021].

Tremblay, MC., Berndt, DJ., Luther, SL., Foulis, PR. and French, DD. (2005) Utilizing Text Mining Techniques to Identify Fall Related Injury. *Inf Technol Manag,* 10, pp.253-265. [online]. Available at: 10.1007/s10799-009-0061-6. [Accessed 27 November 2019].

Van Damme, P., Meijer, CLM., Kieninger, D., Schuyleman, A., Thomas, S., Luxembourg, A. and Baudin, A. (2016) A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. *Vaccine,* 34(35), pp. 4205-4212.

Vänskä, S., Söderlund-Strand, A., Uhnoo, I., Lehtinen, M. and Dillner, J. (2018) Estimating effectiveness of HPV vaccination against HPV infection from post-vaccination data in the absence of baseline data. *Vaccine*, 36(23), pp. 3239-3246.

Ventola, CL. (2018) Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. *P&T,* 43(6), pp.340-351.

Verma, ML., Singh, U., Rai., P., Sachan, R and Sankhwar., PL. (2020) Safety and Acceptance of HPV Vaccine: A Hospital-Based Survey at Tertiary Care Centre. *Journal of Gynecological Oncology*, 3(6), pp.1907-1915.

Wacholder, S., Chen, BE., Wilcox, A., Macones, G., Gonzalez, P., Befano, B., Hildesheim, A., Rodriguez, CA., Solomon, D., Herrero, R. and Schiffman, M. (2010) Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomized controlled trials. *BMJ,* 340(712). [Online]. Available at: https://doi.org/10.1136/bmj.c712 (Accessed: 29 November 2019).

Weiss, TW., Zimet, GD., Rosenthal, SL., Brenneman, SK. and Klein, JD. (2010) Human Papillomavirus Vaccination of Males: Attitudes and Perceptions of Physicians Who Vaccinate Females. *Journal of Adolescent Health*, 47(1), pp.3-11.

Westrick, SC., Hohmann, LA., McFarland, SJ., Teeter, BS., White, KK., and Hastings, TJ. (2017) Parental Acceptance of Human Papillomavirus Vaccinations and Community Pharmacies as Vaccination Settings: A Qualitative Study in Alabama. *Papillomavirus Research*, 6(3), pp.24-29.

Wheeler, CM., Skinner, SR., Del Rosario-Raymundo, MR., Garland, SM., Chatterjee, A., Lazcano-Ponce, E., Salmeron, J., McNeil, S., Stapleton, JT., Bouchard, C., Martens, MG., Money, DM., Quek, SC., Romanowski, B., Vallejos, CS., Ter Harmsel, B., Prilepskaya, V., Fong, KL., Kitchener, H., Minkina, G., Lim, YKT., Stoney, T., Chakhtoura, N., Cruickshank, ME., Savicheva, A., da Silva, DP., Ferguson, M., Molijn, AC., Quint, WGV., Hardt, K., Descamps, D., Suryakiran, PV., Karkada, N., Geeraerts, B., Dubin, G., Struyf, F. and VIVIANE Study Group (2016) Efficacy, safety and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomized controlled VIVIANE study. *The Lancet. Infectious Disease,* 16(10), pp.1154-1168.

World Health Organization. (2019). Hepatitis B. Available online: https;//www.who.int/news-room/fact-sheets/detail/hepatitis-b [Accessed 15th March 2020]

Widjaja, VN. (2019) Awareness, Knowledge and Attitudes of Human Papillomavirus (HPV) among Private University Students-Malaysia Perspective. *Asian Pacific Journal of Cancer Prevention,* 20(7), pp. 2045-2050.

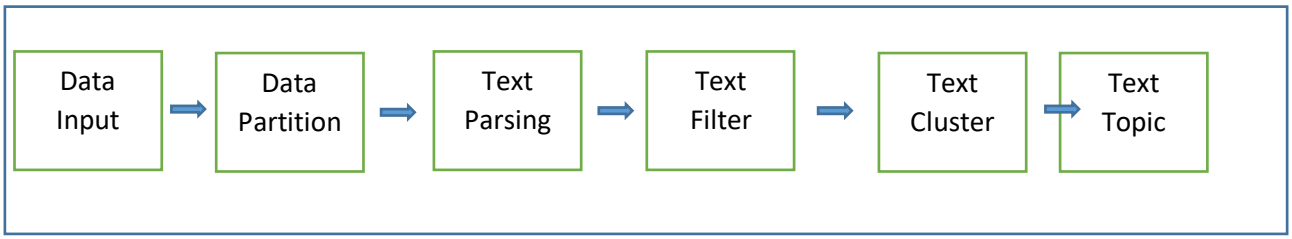
Wong, LP., Alias, HA., Sam, IC., and Zimet, GD. (2018) A Nationwide Study Comparing Knowledge and Beliefs about HPV among Female Students Before and After HPV Vaccination. *Journal of Pediatric and Adolescent Gynecology,* 32(2), pp.158-164.

APPENDICES

SAS Text Mining used to extract the key topic; adverse events associated with HPV immunization from the descriptions. Text analytics helps in extracting patterns, meanings, and hidden structures in unstructured textual data (Chakraborty et al., 2014). Text mining converts text into the numeric form and allows it to be used for analysis (Raja et al., 2008). Text mining approaches count of words in documents (Tremblay et al., 2005). The algorithm works by eliminating specified words (stop list) or keeping specified words (start list) and words with common roots are stemmed and removed since they have little power in discriminating documents (Tremblay et al., 2005). SAS Enterprise Miner has algorithms to automate word stemming and provide synonyms (Tremblay et al., 2005). A term-by-document frequency matrix is created, with the row dimension of the matrix limited to the 100 most frequent terms (Tremblay et al., 2005). Text mining by using SAS Text Miner derives a quantitative representation of documents (Chakraborty et al., 2014). When a text is changed into a set of numbers, it captures patterns in the textual data, statistical model, or data mining algorithm that can be used on the numbers for predictive modeling (Chakraborty et al.,2014).

Underlying key topics were extracted and grouped in a similar document called clusters. Cluster refers to terms and the frequency of occurrence in the corpus of documents and within each document. Text clustering is a process of data grouping into classes or clusters so that the objects within a cluster have similarities in comparison with one another but are unsimilar to objects in other clusters (Tremblay et al., 2005). Clustering is done based on measures of distance or similarity (Tremblay et al., 2005). Through clusters, the relationship between terms and their strength is explored through a feature called “concept linking” (Tremblay et al., 2005).

Several processes were performed using SAS Text Miner which are text parsing, filter, topic, and cluster before classifying by system organ class as shown in Figure 13.



Text Mining Process Flow

Text Mining Process

Text parsing is a process to clean, extract and create a dictionary of words from the documents using NLP algorithms. Text parsing includes the identification of sentences, determining parts of speech, and stemming words. It involves parsing the extracted words to identify entities, removing stop words, and spell-checking (Chakraborty et al.,2014). With that, the text parsing process keeps relevant and meaningful terms (including commonly found and rare adverse events terms) that were shown by the frequency of occurrence in the dataset (Khong et al., 2018). Table 5 below has a list of options available in SAS Text Parsing Node with its explanation and input:

SAS Text Parsing Node	Description	Setting
Include parts of speech	Determines whether the terms are classified by the parts of speech usage role	This was selected so that the different parts of speech were treated as different terms
Extract Noun Groups	Controls if nouns should be grouped or not	This was selected so that the nouns were grouped
Use Entity Extraction	Determines whether the entity extractor should use the standard list of entities	This was selected so that the entity extractor used the standard list
Stem Words	Stemming identifies the possible root from of an inflected word	This was selected so that stem words were identified
Stop List	A stop list is a simple collection of low-information or extraneous words that you want to remove from the text	Stop List was not incorporated as the results of the analysis will not be affected when the stop words are disregarded

Source: SAS Visual Analytics 7.2 (2016)

SAS Text Parsing Node - Description and Input

In a document, it will likely have many terms that are irrelevant it is time-consuming to eliminate those irrelevant terms through manual browsing. Text filtering alters the term by document matrix. Adverse events were identified manually to through document summary to eliminate terms such as patient medical histories, and irrelevant symptoms. It helps to improve the accuracy and speed of text analysis (Chakraborty et al.,2014). Table 6 list the options available in the SAS Text Filtering node, its explanation, and input:

SAS Text Filtering node	Description	Setting
Cell Weight	Determines how cells are weighted in the term by document matrix (the cell weight is a function by that is applied to every entry in the term by document matrix to moderate the effect of a term that is repeated with a document)	This was selected to track the cell weight because of a repeated term in a document (Logarithmic setting was chosen to deemphasize terms that appear many times in relatively few documents)
Term Weight	Controls how terms are weighted. The term weight is a positive number that is assigned to each term based on the distribution of that term in the document collection (this weight can be interpreted as an indication of the importance of that term to the document location)	This was selected so that terms were weighted based on the distribution of that term in the document collection (entropy setting was chosen to emphasize terms that has a low frequency across the document collection)
Document Threshold	The minimum number of documents in which a term must appear to be included in the analysis	The value was set to 2 to include more documents to be analyzed

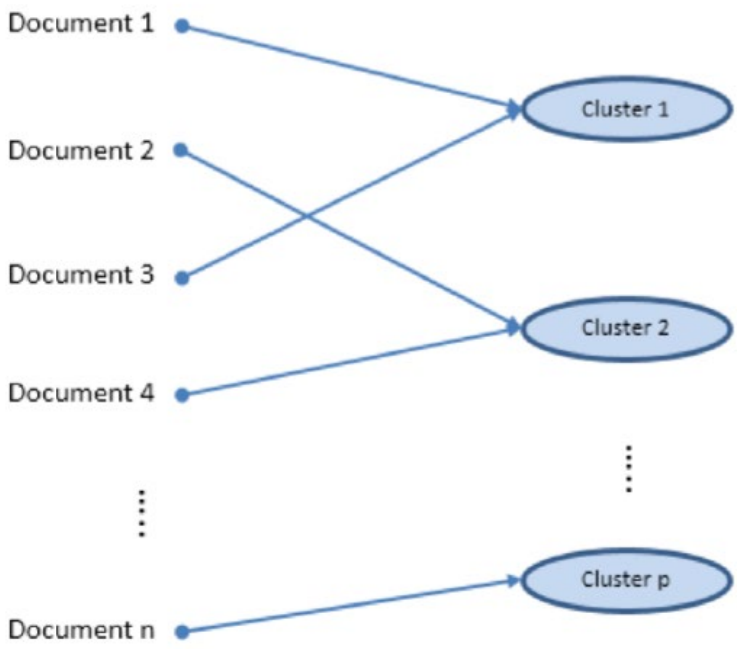
Source: SAS Visual Analytics 7.2 (2016).

SAS Text Filtering Node – Description and Input

Text cluster separate data set into groups so that the subject within a group is similar and the subjects between the groups are dissimilar. The process displays documents into nonoverlapping groups. Each document may fall into more than one topic area after classification. The key difference between clustering and the general text classification process is it provides a solution to text classification when groups must be mutually exclusive.

In the text cluster, document collection is divided into mutual groups based on themes (as shown in Figure 14). These themes help to better understand customers, concepts, or events. These clusters are identified using a set of descriptive terms that each cluster contains. Clusters are generated based on the relative positioning of documents in the vector space using an algorithm (Chakraborty et al., 2014).

There are two types of clustering algorithms used by SAS Text Miner, which are expectation-maximization and hierarchical clustering. The Latent Semantic Indexing (LSI) is used to improve dimensionality in the clustering process. Singular Value Decomposition (SVD) is used in LSI to break down unstructured data into linearly independent components. High SVD values indicate result has a loss of information and dimensionality (Chakraborty et al., 2014).



Text Clustering Process

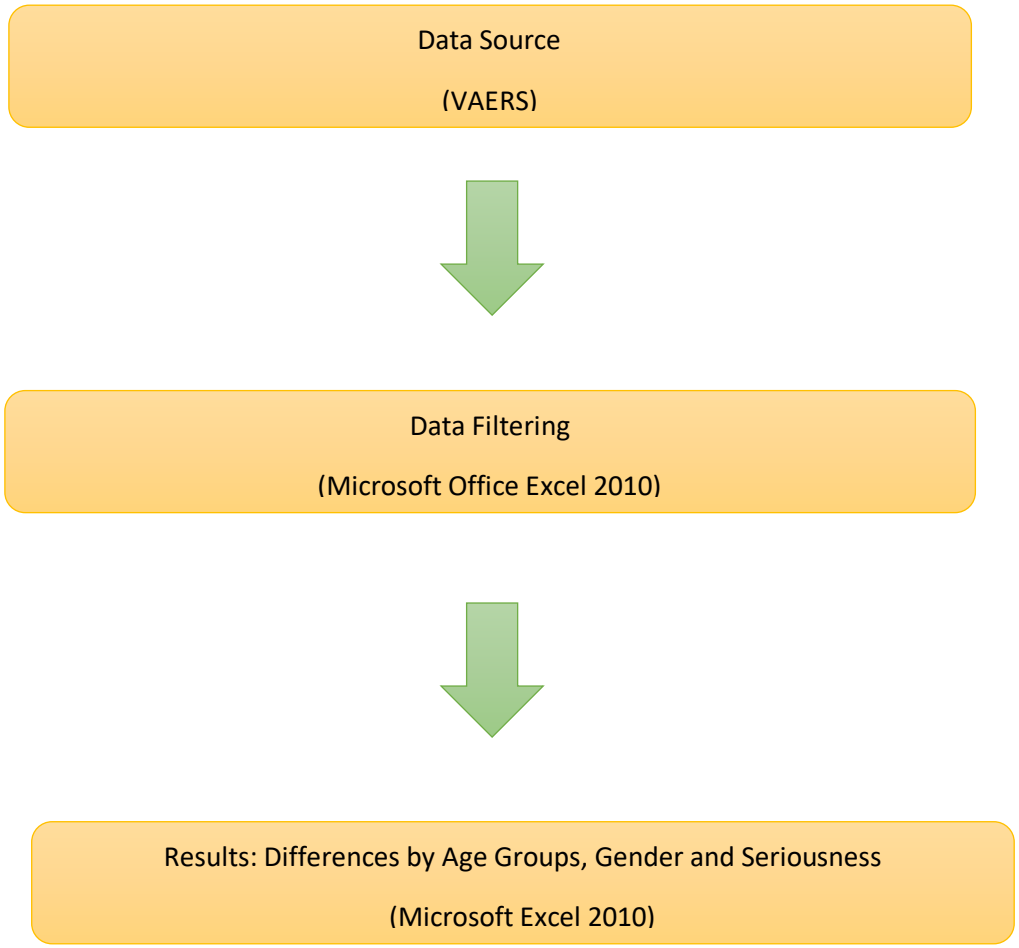
Table 7 list the options available in the SAS Text Cluster Node, its explanation, and the Input

SAS Text Cluster Node	Description	Setting
SVD Resolution	Used with the Max SVD Dimensions parameter to find the recommended number of topics	This value was set to 'High' to generate the SVD dimensions, to gather more topics
Max SVD Dimensions	Specifies the maximum number of SVD Dimensions to generate	This value was set to 50 as recommended
Exact or Maximum Number	Specifies whether to find an exact number of clusters or any number less than or equal to a maximum number of clusters	This value was too 'Exact' as recommended
Number of Clusters	Specifies the number of clusters to be created	This value was set to 20 to match the Maximum Topics from the SAS Text Topic Node
Cluster Algorithm	Specifies the clustering algorithm to use	This value was set to 'Hierarchical' where it is more efficient if the hierarchical generation is not complete along the way down to individual document leaves
Descriptive Term	Specifies the number of descriptive terms to display for each cluster	This value was set to 4 to match the Topic Label Length from the SAS Text Topic Node

Source: SAS Visual Analytics 7.2 (2016)

SAS Text Cluster Node – Description and Selection / Input

The second part of the research was to classify adverse events reported by age, gender, and seriousness criteria. Data downloaded from VAERS was filtered in Microsoft Excel and classified as shown in results, Section 6.4, 6.4, and 6.5.



Research Design: Classifying Adverse Events into Groups; Age, Gender, and Seriousness