

# HPV Vaccines, Challenges and Complications of Vaccination in Patients with Pre-Existing Diseases

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**Abstract:** HPV vaccination had been practiced for decades to prevent the development of cervical cancer and is recommended to be routinely vaccinated at 11 or 12 years old. Vaccination against HPV infection has been proven to prevent the transmission of viruses causing diseases effectively. Hence, consequently, it reduces the incidence of cervical cancer. Despite the benefits of vaccination, there are some cases that vaccination against HPV needs intensive concern, especially with the patients who have immunocompromised conditions such as HIV infected patients, rheumatoid (RA) patients, Systemic lupus erythematosus (SLE) patients, and organ transplanted patients. In most cases, HPV vaccination can be administrated routinely as usual while in organ transplanted patients, HPV vaccination had shown to be associated with acute organ rejection.

**Keywords:** HPV, vaccination, Vaccination in immunocompromised patients, HIV infected patients, Rheumatoid patients, SLE patients, Organ transplanted patients

## 1. Introduction

Cervical cancer starts in the cervix, where the lower part of the uterus is located. The cervix then connects to the vagina through the endocervical canal. With an estimated 570,000 cases and 311,000 deaths recorded in 2018 alone, cervical cancer is the fourth most prevalent cancer among women worldwide. It is estimated that 85 percent of the global deaths caused by cervical cancer are likely to occur in low and middle-income countries, wherein in advanced countries, the rate of death is 18 times consistently lower [1]. Human papillomavirus (HPV) infection and the integration of the HPV-causing cancer serotypes 16 and 18 into the cervical epithelial cell host chromosome are critical early events in the development of cervical lesions. Moreover, other HPV-related cancers are anal, vaginal, vulvar, penile, oral cavity, and oropharyngeal, symbolizing that males have the possibility of having genital warts caused by HPV [2]. There are four significant steps in the development of cervical cancer: metaplastic epithelium infection in the cervical transformation area, viral persistence, progression of the persistently infected epithelium to cervical precancer, and invasion through the epithelium's basement membrane [3]. In the stage of HPV infection, it can be classified as transient or latent. Transient is the process of the host immune system trying to eliminate a virus-infected cell by killing that particular cell, resulting in the death of the host cell. This event causes inflammatory responses in the cervical area. However, latency is the low level of viral activity in the epithelial cells in the cervical area, where it can be reactivated when the host immune system is suppressed. Numerous research has suggested that several risk factors for cervical cancer development involve low economic status, insufficient personal and sexual hygiene, early sexual activity, smoking, and multiple sexual partners [4].

Immunization of HPV vaccines helps to imitate an infection from the actual viruses. It causes the immune system to produce HPV-16 and -18 specific memory B-cells, producing antibodies specific to HPV-16 and -18 serotypes. HPV-specific CD8+ and CD4+ are generated along with the HPV-

specific memory B-cells. Once these lymphocytes are circulated in the body, it allows the immediate response during the pathogenic viruses invading the host body. This stops viruses from entering the epithelial cells and breaks the replication cycle of viruses [5].

The HPV vaccine is recommended to be routinely vaccinated at 11 or 12 years old. This is a recommended age to get the HPV vaccine due to the prior initial sexual activities. It is not preferable to be vaccinated if older than 26 years. [6, 7]

Vaccination against HPV infection has been proven to prevent the transmission of viruses causing diseases effectively. Hence, consequently, it reduces the incidence of cervical cancer. Despite the benefits of vaccination, there are some cases that vaccination against HPV needs intensive concern, especially with the patients who have pre-existing diseases.

### Virus-Host interaction

Human papillomaviruses (HPVs) are non-enveloped, icosahedral viruses with a minor diameter of 55 nanometers. A double-stranded, circular DNA genome is found in the HPV, about 8000 base pairs long. More than 100 different genotypes infect the stratified squamous epithelia and develop neoplastic lesions are found in human papillomaviruses (HPVs). Most of the HPVs are responsible for cutaneous warts. Infections that can induce benign, premalignant, and malignant lesions of the genitourinary organs, the anus, and the oropharynx are correlated with a third subset of HPVs. Additionally, one subset of HPV is found in the skin lesions of epidermodysplasia verruciformis, a condition that contributes to the emergence of cutaneous squamous cell carcinomas [8].

The first cellular receptor agent was identified as  $\alpha 6$  integrin. The integrins are the heterodimeric glycoproteins which consist of  $\alpha$  and  $\beta$  subunits. In a range of cell types, integrins are expressed, mainly involved in cell-matrix and cell-cell interactions. Out of 17 known  $\alpha$ -subunit and eight known  $\beta$ ,

three are reported to be involved in HPV binding which is  $\alpha 6$ ,  $\beta 4$ , and  $\beta 1$ . It was established that  $\alpha 6$  integrin played a prominent role in this process, with indications that the binding degree of Viral-like particles (VLPs) was decreased by a monoclonal antibody against the  $\alpha 6$  integrin subunit, while anti- $\beta 1$  or anti- $\beta 4$  antibodies were not. The heterodimeric  $\alpha 6\beta 1$  and  $\alpha 6\beta 4$  were identified to be both capable of binding VLPs; however, the  $\alpha 6\beta 4$  complex was expressed solely in the basal cell layer of the stratified squamous epithelium, potentially the only site of productive events HPV infection, while  $\alpha 6\beta 1$  was located in comparatively more type of cells and sites not associated with HPV infection. Furthermore, the studies of Evander et al. revealed that the natural ligand for the  $\alpha 6\beta 4$  complex, human laminin, was capable of dose-dependently blocking the binding of VLPs to transform aneuploid immortal keratinocyte cells (HaCaT) [9].

### Heparan sulfate peptidoglycan

Heparan sulfate peptidoglycans (HSPGs) are glycoproteins that typically contain one or more covalently bonded chains of heparan sulfate (HS), a form of glycosaminoglycan. Heparan sulfate proteoglycans are located at the cell surface and in the extracellular matrix, which binds with many ligands [10]. HSPGs are usually present in cells for normal body function, for instance, organogenesis, angiogenesis, growth factors/cytokine behavior, wound healing, and cell adhesion. [11] The two significant subfamilies of HSPGs are syndecans and glypicans, where each of them has a specific type. For example, syndecan-4, syndecan-1, and glypican-1. HSPGs are shown to be significant for viral binding because when digested, the receptor with heparinase or heparinase resulted in an 80%-90% reduction of HPV-11 VLPs binding as well as other HPV serotypes [12]. Out of the several HSPGs, it was reported that syndecan-1 was the only type that functioned as an HPV receptor. In addition, HPV may require primary host cell receptors and secondary receptor proteins for effective internalization. Among the two candidates of the HPV receptors, it is still unclear to correctly identify whether either one will act as primary or secondary receptors. There are the possibilities of having one and the other candidates acting as both primary and secondary receptors. Letian T., Tianyu Z. assume that it is possible to mark both  $\alpha 6$  integrin and HSPGs as HPV receptors and that different receptors will be found in the future.

The viral capsid is composed of a major and minor capsid protein, L1 and L2, respectively.

L1 and L2 both are the products of late gene production. [12]

#### L1 main

L1, the main capsid protein of HPV, is a 55 kDa polypeptide that can self-assemble into virus-like particles. L1 associations with heparan sulfate (HS) carbohydrates shown on proteoglycans are primarily due to the initial interactions of the HPV capsid with the host. The binding of L1 with HSPG contributes to a change in conformation that triggers an amino-terminal portion of the minor capsid protein L2 to be exposed [13].

#### L2

Although L1 is considered the primary particle for this process, L2 is also suggested to be vital for completing viral entry to develop HPV infection. L2 is the minor capsid protein which is at about 1/30 abundance compared to L1 [14]. The association of L2 with HSPGs receptors is continued after conformational changes caused by the L1 protein. This resulted in the exposure of L2 capsid protein. Once the exposure of the portion was completed, it got cleaved by a specific enzyme called furin protease. After the cleaving of L2 appears, there is an additional conformational change in which it is believed that this change contributes to the bounding with a secondary receptor [9, 13]. Furthermore, after binding to the receptor, the ligand protein on the viral capsid changes its structure.

Once both L1 and L2 succeed in binding with associated receptors, the production of endosomes follows. This particular endosome is associated with clathrin, producing a process called "clathrin-mediated endocytosis." Clathrin-mediated endocytosis is a vesicular transport mechanism implicated in internalizing and recycling receptors involved in signal transduction, nutritional intake, and synaptic vesicle reformation activities. HPV establishes infection after interacting with host cells by passing through an endocytic pathway dependent on the annexin A2/S100A10 heterotetramer (A2t). A2t was found to have a cell surface that is not necessary for attachment with HPV. The absence of A2t could positively contribute to the difficulties in viral development from early endosomes to multivesicular endosomes, virus capsid uncoating is reduced significantly, and HPV lysosomal degradation is accelerated. [15] The endosomal vesicles were unpacked when they were moving into the cell, causing the pH of the endosome to decrease [16]. The unpacking of the endosome resulted in releasing a viral genome into the host cell [17]. After the genetic material had successfully molecularly hijacked the host cell, it started replicating its genomes, either DNA or RNA. Then, transcription and translation of its protein occur in order for the necessity of viral exits.

### Pathogenesis of Cervical cancer caused by Human Papillomavirus (HPV)

#### Sexually acquired

HPV, due to its asymptomatic nature and long incubation period, is a frequently prevalent infection that is rapidly and unconsciously transmitted. This infection commonly requires skin-to-skin contact and is mainly sexually transmitted. [18] Therefore, sexual intercourse is the main route of the transmission of HPV. Unfortunately, HPV infection can present in both heterosexual and homosexual intercourses, where many types of HPV have been closely associated with causing cancer in several body parts and genital warts. For example, the infection can contribute to colon cancer, cervical cancer, and oropharyngeal cancer. Infections associated with an oncogenesis form of HPV are precursors to developing cervical cancer and can assess cancer in other anatomical areas, such as the prostate, vagina, vulva, oral cavity, and oropharynx.

#### Nonsexually acquired

Other than the transmission of HPV through sexual intercourse, there are several other pathways that HPV can

get transmitted. This often refers to the non-sexually transmission. One of the ways could be through horizontal transfer such as fomites, fingers, mouth, and external skin contact. Another possible nonsexual HPV transfer course could be through vertical transfer, which occurs from the mother to the child. It mostly comes through the amniotic fluid, genetic, or even when directly contacting the maternal genital mucosa. Additionally, the transmission through the environment could happen since the DNA of HPV has been detected in the water and contaminated medical equipment. Although environmental transmission has not been reported as a case yet, the risks still exist.

Most HPV integration occurrences are found to be related to HPV oncogenesis. The causes of oncogenesis are classified into two leading causes: viral integration, where the insertion of the viral genome into the host genome, and acceleration of cell cycle by viral proteins. This provides a selective growth benefit to cells and fosters oncogenic progression. [19]

### HPV vaccine

Vaccination is an easy, secure, and efficient method to prevent infectious diseases before contacting them. To develop resistance to viral infections, it uses your body's natural defenses and makes your immune system stronger. Vaccines guide the immune system, just as it does when exposed to a disease, to produce antibodies. Since vaccines contain only killed or damaged pathogens such as viruses or bacteria, they do not cause the disease or lead to an increased risk of its complications.

HPV vaccines are found to be based on VLPs, which came from the capsid protein L1. However, of many HPV types, the L1 protein is not conserved among all HPV. Fortunately, early studies have shown L2 minor capsid protein to be strongly conserved in many HPV types. Since then, the L2 protein became a targeted antigen for developing effective vaccines for HPV. In contrast to L1 protein, the L2 protein does not develop VLPs, which causes L2 to have inadequate immunogenic responses. [20]

Since L2 proteins are ineffective in using vaccination, L1 proteins are used for protection instead. In order to develop a helpful HPV vaccine, specific L1 VLP types should be combined for HPV vaccines. As a result, three types of HPV vaccines are currently available for injection: 2-valent, 4-valent, and 9-valent. The Cervarix, a 2-valent HPV vaccine, was produced under GlaxoSmithKline, where they use the L1 protein of HPV-16/18. Merck developed two types of vaccines, which are 4-valent and 9-valent, with the brand name Gardasil and Gardasil 9, respectively. The L1 types used in 4-valent vaccines are HPV-6/11/16/18, while the 9-valent vaccine used nine serotypes consisting of HPV-6/11/16/18 /31/33/45/52/58. Furthermore, each type of vaccine has its seroconversion. HPV-31/33/45 and HPV-31 are the seroconversion for 2-valent and 4-valent HPV vaccines. However, the seroconversion of the 9-valent vaccine is still unknown. [21]

ACIP recommend practitioner to perform the following:

The Advisory Committee on Immunization Practices (ACIP) recommended that one of the three HPV vaccines, 9-valent, be used for vaccination programs. ACIP suggests both women and men who have not already been vaccinated take this vaccine, where the proper age recommendations are between 13 and 26 years for women and from 13 to 21 years for men. Furthermore, the 9-valent and 4-valent HPV vaccines were licensed to be legally used after the ACIP has reviewed additional data that proved 9-valent HPV vaccines to create immunity in both males and females after vaccination. [22]

### Three doses schedule vaccination

Two vaccine schedules of HPV vaccines are advised: 3 doses and two doses. In a 3-dose program, 2vHPV, 4vHPV, and 9vHPV are each issued. The second dose should be given at least 1 to 2 months after the first dosage, and approximately six months after the first dose, the third dose should be given. Fortunately, the vaccination sequence does not need to be restarted if the vaccine schedule is disrupted.

According to Addario M. et al., some people could not complete the 3-dose schedule; instead, they practiced the vaccination program with two doses only. Surprisingly, the results show that patients injected with two doses have the same incidence rates of getting cancer as those who could complete three doses schedule. This finding supports the vaccine that is bivalent and 4-valent HPV vaccines. However, no study can test the effectiveness of 2 doses schedules on the 9-valent HPV vaccine. [22]

### Complication of HPV vaccination with other diseases

#### HPV vaccination in HIV infected

Human immunodeficiency virus (HIV) is a viral infection that damages cells in charge of making the body's immune system resistant to other illnesses and diseases by enabling the body to combat infection. It is often transmitted through direct contact, most typically during unprotected sexual intercourse, with the body fluids with HIV.

HIV frequently decreases the vaccine's response to and efficacy, where HIV invades the helper T-cell and causes infection in the functions. Later, it leads to the reduction of B cell responses of vaccines and immunogenicity. Individuals with HIV have a higher risk and incidence of HPV development, the more persistent transmission of numerous HPV forms, and an increase in the rate of HPV-related illness, including a more rapid change to malignancies, even when successfully treated with antiretroviral treatment (ART). Furthermore, a variety of studies have tested the immunogenicity of HPV vaccines in individuals with HIV and, in particular, there has been some decrease in the levels of HPV VLP antibodies relative to HIV-negative specimens. [23]

In some cases, the number of doses required to boost the immunogenicity rises to 4 doses. A range of studies have tested the immune responses of HPV vaccines in patients with HIV, and there has been some decline in the levels of HPV VLP antibodies relative to HIV-negative subjects. Also, improved immunogenicity was highly shown when HIV

viral reproduction was regulated, and there was no apparent immunodeficiency. While significant memory B cell responses after G4 out to 4-5 years have been recorded, observational results revealed considerably decreased antibody resistance, and therefore need to inject HIV +ve subjects respond with a 4th dose too late boosting. Additionally, according to Kojic E. et al. research, it is found that the quadrivalent HPV vaccine was safe and immunogenic in women who are infected with HIV. Based on the study, the researchers analyzed that women infected with HIV are prone to have a lower rate of seroconversion after the vaccinations. [24] [25]

#### **HPV vaccination in rheumatoid (RA)**

Rheumatoid arthritis, or RA, is an autoimmune and inflammatory infection, which implies that, by accident, the immune system attacks healthy cells within the body, leading to inflammation in the areas damaged. The most prevalent presentation of RA is symmetrical inflammatory polyarthritis in any synovial joints, but the hands and feet are infected more often. Moreover, RA is a systemic disease, with frequent additional symptoms, such as subcutaneous nodules, pulmonary diseases, vasculitis, and neuropathy. Surprisingly, women are known to be at higher risk for RA development than men. Also, there is a dynamic relationship between rheumatoid arthritis, female sex hormones, and reproductive potential in modulating both the risk of disease and its clinical course in women, in addition to gender disparities in infection rate. [26]

In the field of medications for RA, most of the patients are treated with Disease-modifying antirheumatic drugs (DMARDs). DMARDs are often referred to as remitting, slow-acting drugs, or second-line drugs. Before it is effective, it will take a significant period and range from a couple of weeks to several months. DMARD treatments regulate the fundamental immunological mechanism, promote healing, and prevent joint damage and deformity in more active diseases. An example of a type of medical drug used in this treatment is Methotrexate (MTX). MTX is a metabolite antifolate that blocks the production, recovery, and cell replication of DNA. This has anti-inflammatory and immunomodulatory effects, and it was first used in 1951 to treat RA and psoriatic arthritis. Based on the European League Against Rheumatism (EULAR), DMARD, preferably MTX plus low-dose glucocorticoids, was recommended to be a primary treatment when dealing with RA. [27]

In addition, there are several other acceptable approaches to RA treatments which can be divided into two categories: before initiating therapy and while already taking therapy. Some additional suggested treatments would have DMARD monotherapy, Combination DMARDs, Anti-TNF biologics, and Non-TNF biologics. Fortunately, all of these approaches are safe to practice before starting the therapy or working on the therapy. [28]

The research study of Heijstek W. et al. reported the immunogenicity level in RA patients who had received HPV vaccination. The method of this study involves three doses of bivalent HPV vaccine on the participants where they are scheduled to be vaccinated at an interval of 0, 1, and 6

months. However, based on the follow-up, it is observed that there is no statistically significant difference between vaccination of HPV in healthy individuals and individuals who have RA. Therefore, this finalizes that there is a possibility that patients with RA who are ongoing with the treatment of MTX alone did not have their immunogenicity reduced even after they got vaccinated with bivalent HPV. [29]

Based on Perry L. et al., recommendations on the acceptable use of vaccines for RA patients have both been approved by the American College of Rheumatology (ACR). The ACR vaccine guidelines state that the optimal time for injecting the RA vaccine is available before taking DMARD or while the patient is being treated with DMARD. [28]

#### **HPV in Systemic lupus erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which the immune system attacks its tissues, causing the affected organs to undergo extensive inflammation and tissue damage. Several common areas that can be affected by SLE are the joints, skin, brain, lungs, kidneys, and blood vessels. The danger level of the SLE can range in a variety of stages where it can start from mild mucosal indications to the involvement of several organs in the body as well as a severe central nervous system. Unfortunately, the pathology of SLE is still unknown; however, the influences of genetics, immune systems, endocrine system, and environment are believed to be the factors that cause SLE. Moreover, the identification of SLE can be very complicated. The principal method in SLE treatment was to prevent the damaging of organs and achieve remission. Treatments can range from many different levels in which the severity of the damages will significantly determine the level of treatments. For instance, NSAIDs and antimalarials are some examples of minimal treatment, while intaking cytotoxic drugs and treating corticosteroids are the treatments for SLE infection that are more intensive. [30]

Several studies have found that patients infected with SLE are more prevalent in developing HPV infection since HPV is seen to correlate with SLE. According to the research of Segal Y. et al., the protein antigen that stimulates the occurrence of SLE is observed to contain similar peptide sequences with the L1 protein found in HPV. Consequently, the vaccination of HPV vaccine produces antibodies in which these antibodies might attack human antigens causing the condition of SLE to worsen. As a result, a more proper method in vaccinating HPV vaccine in patients who had SLE should be introduced. [31]

A research experiment was observed by Soybilgic A. et al. about the particular practices of HPV vaccination that could be done on SLE patients to promote more safety and prevent more significant risks. However, this study was based on the effect in females only since the chosen participants are all women. In terms of patient selections, Soybilgic and the research teams select the patients in the age range of 9 to 26 years old with the gender of females. In the study protocol, the recipients were scheduled to receive three doses of 0.5 ml of recombinant, quadrivalent HPV vaccine. The first dose was injected during the study entry, followed by the second

dose scheduled to be given two months after the initial dose. Then, the third dose is set to be given six months after the initial dose. Moreover, acute allergic reactions were monitored in the clinic for 30 minutes after each vaccination dosage. Patients were clinically examined at the start of the study and months 2, 4, 6, and 7. At each clinic appointment, clinical signs of SLE were thoroughly examined, and an SLE Disease Activity Index (SLEDAI) score was established. The study's result displayed a decrease in the mean number of SLEDAI scores at month 7 in the 20 participants who had completed the process. Hence, at month 7, 16 of the 20 participants who completed the study had samples available for evaluation. Seropositivity rates for HPV 6, 11, 16, and 18 following three vaccine doses were 94.4 percent, 100 percent, 100 percent, and 94.4 percent, respectively. During the seventh month, one patient exhibited no antibody response to HPV types 6 and 18 and positive but low antibody responses to HPV types 11 and 16, with titers of 75 and 65 mMu/ml, respectively. However, between the second and third vaccine doses, this patient got a biological therapy called rituximab. [32]

### HPV in organ transplanted patients

In the case where a person has been through transplanting their organs, they are at a higher risk of getting HPV. After an organ transplant, the patients will need to prescribe immunosuppressant drugs. These medicines help to prevent the transplanted organ from being attacked by the body's immune system. Organ rejection is a chronic danger; therefore, it is essential for continuous diligence to prevent the immune system from attacking the patient's transplanted organ. Due to various persistent organ rejections, organ transplantation patients are at higher risk of infection from HPV.

According to D. Kumar et al. (2013), patients were scheduled to receive three doses of the 4-valent HPV vaccine at 2 and 6 months. Quadrivalent HPV vaccination is an HPV L1 protein vaccine containing viral serotypes 6, 11, 16, and 18. The vaccine was supplied in prefilled syringes and stored 20 µg of HPV type 6 and 18 antigen and 40 µg of HPV type 11 and 16 antigens, respectively. In each dosage, the vaccine contained 0.5 mL of volume and was given to the non-dominant arm of the deltoid muscle. Before each vaccination and at month 7, serum was acquired four weeks after the third vaccine dose. Serum was also gathered for 1-year postimmunization and processed for testing at -80 ° C. Also, the patients will be notified for infusion adverse reaction evaluation at 48 h and seven days after each immunization. Significantly, certain factors of organ transplants, such as patients who had lung transplantation, must need close monitoring of HPV vaccinations. [33]

According to V. Gomez-Lobo et al. (2014), nine organ transplant recipients, seven kidneys, and two liver objected to completing the HPV vaccination program. This study was conducted due to the concerns about the rise of acute rejection (AR) in transplant vaccine recipients. Moreover, the kidney transplant recipients used in this study were recruited from CNMC, and the liver transplant recipients were from both CNMC and Medstar Georgetown University Hospital. All of the observed participants in this research must have the age range between 9 to 17 years old where

they need to have stable immunosuppression, non-pregnancy, and their post-transplant should be greater than six months. The study started with the recipients scheduled to receive the vaccine doses on day 1 of months three and month 6. However, after the nine organ transplant recipients had the vaccination schedule completed, researchers suspected that there might be a possible increase in acute rejection (AR) of kidney transplant patients. Four kidney transplant recipients and one liver transplant recipient received two doses of vaccine, while three had received one dose and one liver recipient received two doses. Screen failures due to AR resulted in six kidney transplants and two liver transplant recipients aging out during the research. [34]

Based on the data about the effects of AR among the vaccinated recipients, V. Gomez Lobo et al. deeply observed six patients consisting of five males and one female, ranging from 9.5 to 15.5 years of age. Each recipient has access to different types of donors. To begin with, the first recipient, the person was a 15 years old female who had an LR type of donor. The data reveal that the body took eight months until AR occurs after the patient's recent transplant, and there was a 3.5 months period between the occurrence of AR and the patient's last dose of vaccine that she received. The number of vaccine doses that this patient received before AR was only one dose. Hence, the woman received several immunosuppression during his AR as well, which are tacrolimus (TAC), mycophenolate mofetil (MMF), and prednisone (Pred). The second recipient was a ten years old male with the LR type of donor. A significant difference was that the boy took 64 months after his transplant to have an AR, while the time between his last dose of vaccine and AR is around two months. However, the number of vaccine doses he received before AR was two doses. Still, he had the same set of immunosuppression, just like the first women. The third recipient was only a 9.5 years old male who had a deceased donor type. The table presents that the third boy has 19 months between his transplant and AR, and he took only half a month before getting AR right after his last dose of vaccine. This patient got one dose of vaccine before the occurrence of AR. Moreover, this 9.5-year-old patient took only two types of immunosuppression which are TAC and MMF. In the fourth recipient, he was the only participant who had undergone a different donor type and was the oldest among the other recipients. The fourth patient was a 15.5 years old male who had an unrelated (LUR) donor type. It was found that the time interval between his transplant and AR was only seven months, while his body took 2.5 months to get AR after the last dose of vaccine was injected. The patient got two vaccine doses before AR, and he took only two immunosuppressors (TAC and MMF). The fifth recipient was slightly different from the other patients since he only got three doses before AR. This recipient was a 13 years old male who had a deceased donor type. After his transplantation, he took 14 months before AR happened. Fortunately, his body took up to 8 months before AR occurred, recorded right after his last dose of vaccine. Last but not least, the sixth recipient was a 9.5 years old male with LR type of donor. It was observed that this patient took the most times between transplant and AR, which is 84 months. Nevertheless, his body took only two months after receiving the last dose of vaccine, and he got only one dose of vaccine before AR. The sixth patient also received the

same set of immunosuppression with recipients one, two, and five. This data table shows example cases of patients the researcher team believed correlated with the number of vaccine doses received and AR in organ transplanted patients. [34]

Unfortunately, the committee suggested that the study be ended because the intended target and result had been reached. Patients who had not obtained the whole vaccine dose schedule were offered the option of finishing their vaccination with their primary caregiver or receiving an anti-HPV level at the time of study closure because the program is completed early. [34]

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