Chapter

HPV Vaccines: Myths and Facts

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Abstract

Many types of HPV virus found in nature are known to cause anogenital diseases and cancers in both of men and women. Genital condylomas caused by some types of HPV can cause important dermocosmetic, social, and psychological problems. On the other hand, cervical cancers caused by high-risk HPV types can be detected and treated in early stage or preinvasive period by using effective screening programs. But the main goal is to fight with the viruses causing the disease. Therefore, protective and preventive HPV virus vaccines are important. However, for effective administration of vaccines, it is necessary to know the effects of the vaccines, to whom it is applicable, any adverse effects, and to overcome prejudices against the vaccines and to clarify misinformation. In this chapter, in the light of current information about HPV vaccines, known facts and myths about vaccines are shared.

Keywords: HPV vaccines, cervical cancer, anogenital cancer, anogenital warts, efficacy, side effects

1. Introduction

The discovery of HPV (human papillomavirus) was awarded by Nobel Prize. Since 2008, when Prof. Dr. Harald zur Hausen (German Cancer Research Centre, Heidelberg, Germany) found the relationship between HPV and cervical cancer, the debate on HPV and its vaccine never ended (**Figure 1**).

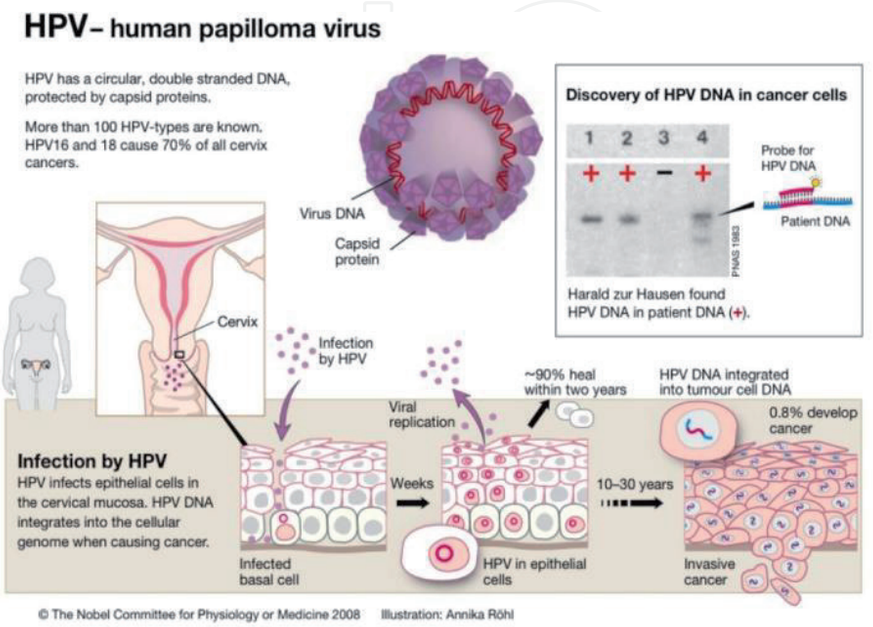

Figure 1.
HPV and cervical cancer (the Nobel Prize in Physiology or Medicine 2008).

There are more than 200 known types of HPV and 35–40 types are responsible for anogenital diseases. Fifteen high-risk types were also related to cancer. In order of their level of connection to cancer, the HPV types are: 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 51, 39, 68, 73, and 82. Out of those, 16 and 18 are responsible for 71–80% of the cancers and are five times more oncogenic than the other 13 types. From the low-risk types, 6 and 11 are responsible for 90% of the anogenital wart [1].

Looking geographically, 16, 18, 45, 31, 33, 52, and 58 are the seven most prevalent types, with little variation between locations [1]. In Turkey, Usubütün et al. found that types 16 and 18 had 76% prevalence in cervical cancers. The first six types (16, 18, 45, 31, 33, and 52) are responsible for 90.6% of the cancers [2].

In **Figure 2**, the full structure of both early (E) and late (L) proteins of HPV are shown, as well as their functions.

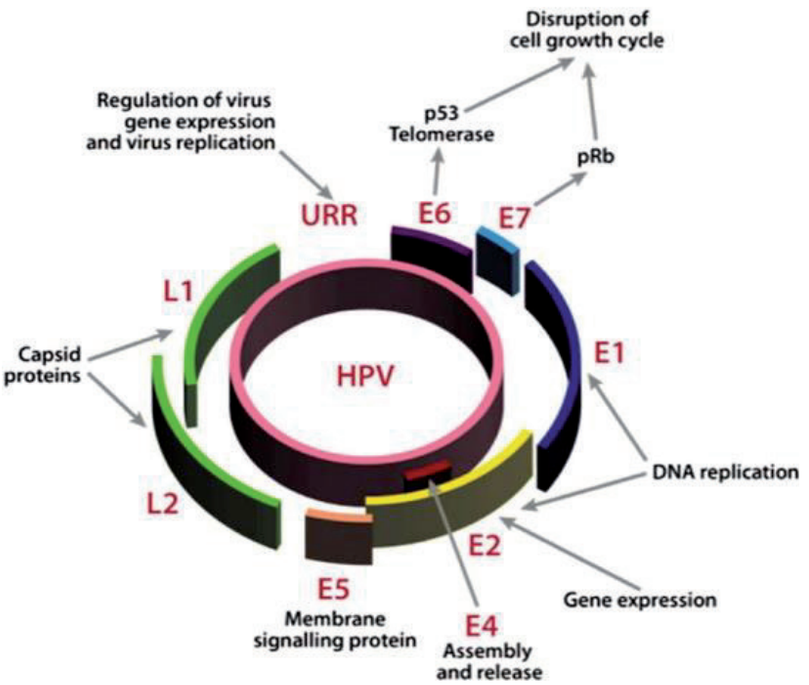

Figure 2.
L and E proteins of HPV and their functions.

In their lifetime, women have 80–85% chance to have an HPV infection, which means it is a widespread sexually transmitted disease. Speaking of sexually transmitted, 99% of all types are transmitted via sex, and using condoms do not protect from it (although some studies show that it protects up to 60%, theoretically any contact between testicals and the vulva is enough for transmission); it can spread even if a finger that had contact with the infected organ touches the opposite gender's genetelia (less than 0.1% of all cases), and since the virus requires body heat; it cannot be transmitted via pools, toilets, baths, saunas, or any other non-living surface.

So is HPV a cervical cancer factor, and are there other HPV-related diseases? HPV-related diseases are: cervix, anus, vulva, penis, oropharynx, and oral cavity cancers. The main reason for cervical cancer is HPV. In other words, cervical cancer cannot happen without HPV. HPV is also related to other diseases to some extent (**Figure 3**).

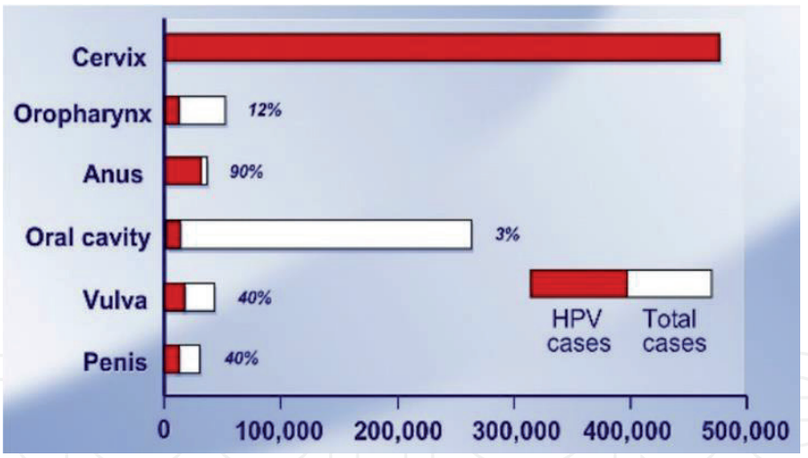

Figure 3.
HPV-related cancers and their HPV prevalence [3].

Recently, its association with lung cancer has been shown. In a study by Xiong et al. in 17 countries with 6890 cases and 7474 control groups, squamous cell carcinoma, adenocarcinoma and small-cell carcinoma types showed an increase post-HPV infection (Total OR 3.64 (95% CI: 2.60–5.08) for HPV 16: 3.14 (95% CI: 2.07–4.76) for HPV 18: 2.25 (95% CI: 1.49–3.40)) [4].

Apart from cancer, anogenital wart is one of the most important social problems. As seen in **Figure 4** for England and the Wales, anogenital wart increases with a country's level of development.

In Turkey, anogenital wart prevalence was found as 154/100,000 and in another study that was adjusted for age, point prevalence (lifetime incidence rate) was 3.8% for the full group, and 2.4% for the pregnant population. Prevalence study revealed similar results of recurrence with USA and Europe by 15–37% [5, 6].

The question, then, arises: Is HPV only for females? What about HPV in males? HPV has been shown to be associated with anogenital wart, anal and penile cancers in men [7, 8].

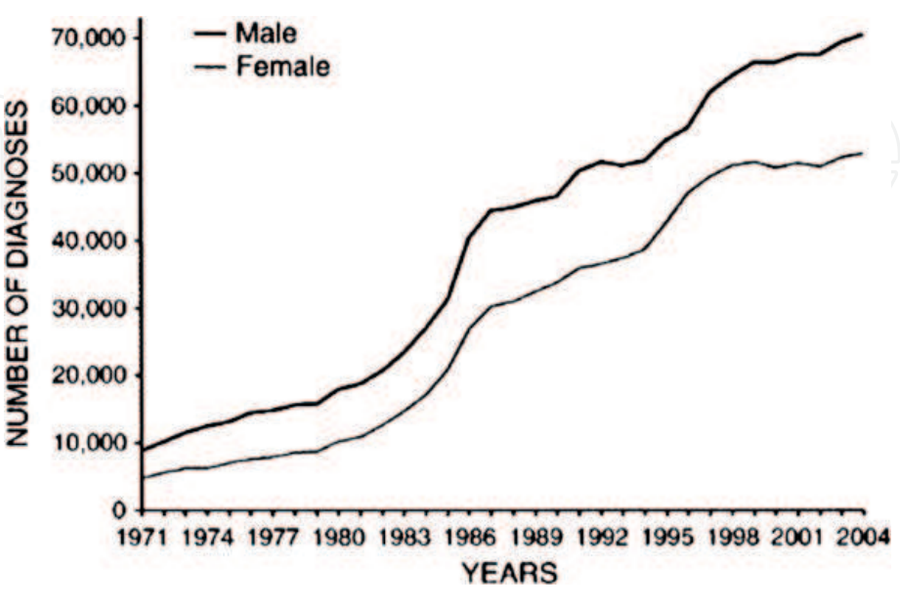

Figure 4.
Prevalence of anogenital wart in England and the Wales throughout the years (Health Protection Agency of England and Wales).

Males are the carriers of this sexual-transmitted disease; however, the disease burden is mostly present in females.

So, is there any vaccine developed against this infectious disease, can this disease be eliminated?

First ever vaccination study was developed as a monovalent (for a single type) against 16 with a 100% protection rate [9]. This vaccine was not commercialized.

A bivalent (for 2-types) vaccine against the most cancer-linked types 16 and 18 based on the previous study, as well as a quadrivalent (for four-types) vaccine based on recombinant virus-like particle (VLPs) were developed by the world-leader companies GSK and MSD [10, 11]. Then, a nonavalent (for nine-types) vaccine was developed and commercialized in order to protect against even more cancer-linked HPV types [12].

Since anogenital warts are one of the substantial social problems, it has not been available and bivalent vaccine against HPV 6 and 11 is still in progress. The current vaccines in use do not provide protection against HPV types associated with non-wart anogenital warts and non-melanoma skin cancers (NMSC). Therefore, vaccination studies against L2 proteins are in progress in the phase of animal experiments.

The International Papillomavirus Society, in an excerpt in the Guardian, pointed to Australia as a model for eradicating cervical cancer; they discussed results in between 2005 and 2015 and showed vaccination rates at 78.6% for girls below the age of 15 and 72.9% for boys below the age of 15, since 2016 [13].

World Health Organization (WHO) has developed a strategy plan to eliminate cervical cancer. According to the strategy, to provide a total elimination from cervical cancer, up to 15 years of age 90% of the girls should be vaccinated, 70% of females aged between 35 and 45 should be screened via high sensitivity tests and 90% of women should be successfully treated of cervical diseases (precancerous lesions and invasive cancers). World Health Organization stated that if these goals are reached by 2030, the elimination of cervical cancer would be possible in 2090 (**Figure 5**) (https://www.who.int/docs/defaultsource/documents/cervical-cancer-elimination-draft-strategy.pdf?sfvrsn=380979d6_4).

In Turkey, however, the situation is highly controversial. As of the last months of 2019, nonavalent is not licensed let alone being included in a vaccination programme. Unfortunately, two of our worst examples for vaccination; polio and hepatitis B; shows a 17-year delay in adapting vaccination programs behind the rest of the world. In 1955, there were statements on Milliyet Journal's columns such as

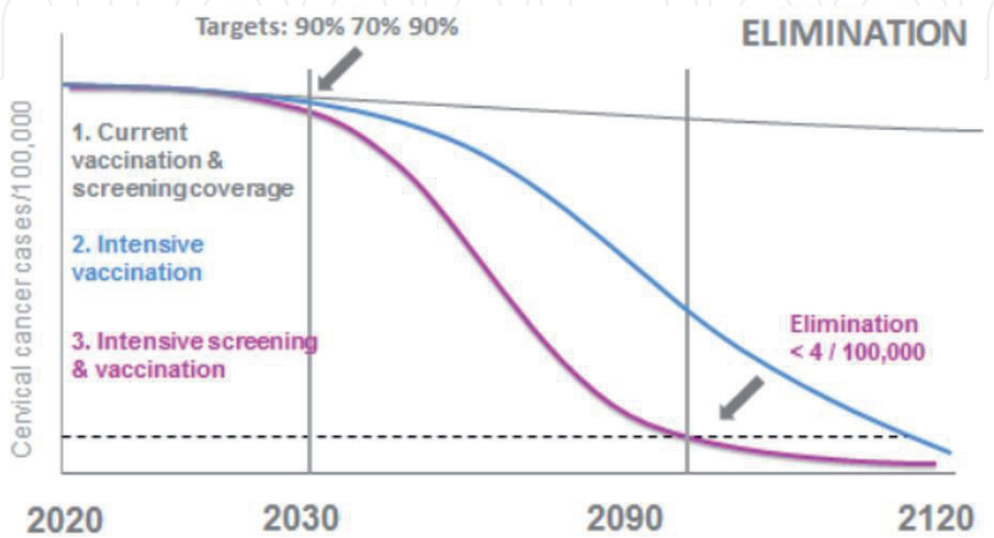

Figure 5.
Timeline for eliminating cervical cancer.

"The discovery of Polio vaccine caused a stir in Turkey" and "The news of Polio caused an excitement in our country but Turkish practitioners do not want to make any statement before getting informed from authorities." Seventeen years after these statements, polio was eliminated to be included in the vaccination programme of Turkey.

2. Myths

- Natural infection protects so there is no need for vaccination.
- Vaccinated children never experience HPV infection and never have HPV associated cancer throughout their lives.
- Vaccination cures their related disease.
- Antibody levels in blood are quite important; the protection loses its effect if the levels drop.
- Herd immunity (protection of the unvaccinated population) does not exist.
- Vaccinations are not effective when done at later ages.
- Smear or other HPV tests should be performed before the vaccination.
- If a pregnancy occurs during vaccination, it should be terminated.
- Vaccinated young girls have higher rates of sexually transmitted diseases since they feel more sexually comfortable.
- Autoimmune diseases such as primary ovarian deficiency and Guillain-Barre have higher rates among the vaccinated girls.
- There is cross-protection so vaccinations of HPV 16 and 18 are sufficient.
- If there is total protection against types in vaccinations, then cancer prevalence of other types will increase.
- Vaccines are not safe, there are deaths associated with the vaccine.
- Vaccines are not cost-effective, protected patients are not worth the cost.

3. Facts

3.1 Natural infection protects so there is no need for vaccination

HPV slithers through the cervical cracks and reaches basal cells in about 30 minutes and enters the cells to infect them. Since it does not stay in the vascular system, the antibody response does not form. Inside the cell, DNA is located episomally at first. Episomally located DNA causes a temporary infection and gets excreted with the cell when the cell is visible on the surface. If the DNA of the HPV gets integrated into the cell DNA, persistent infection will occur and some of them advance to

preinvasive lesions. Only 15 of 100 HPV-infected women will develop cervical intraepithelial neoplasia (CIN) while 60% of them will have regression and 25% of them continue as infection.

In a study by Viscidi et al. with the National Cancer Institute (NCI) on the "Guanacaste, Costa Rica NCI Program," that included 10,049 women examined for over a 5-year period; natural HPV infection occurred on women independent of the type-based serological state. HPV infections from types 16, 18, and 31 rates were equal for both seronegative and seropositive cases. This is the clearest evidence which proves that natural infections do not protect against HPV [14].

3.2 Vaccinated children cannot get HPV or HPV-linked cancer in the future

Many patients as well as physicians have misinterpreted this issue. HPV-vaccinated patients that develop HPV-related diseases are shown as exemplary cases. What is the right information, then? Considering the cervical cancer, only 15 high-risk types can cause cancer. Types 16 and 18 that are included in the vaccines are responsible for 71–76% and the seven high-risk types in the nonavalent vaccines are responsible for 88–90% of all cervical cancer. Naturally, even nonavalent vaccines do not protect against all HPV types, and HPV infection can develop in the rest. Furthermore, we know that LSIL (low-grade squamous intraepithelial lesion) may develop not only through high-risk HPV types but also it can be caused by other types of HPV.

In the end, naïve (no prior contact with HPV) group children are protected close to 100% against *the types included in the vaccine*. Adults who have not developed the same type HPV before are also protected close to 100%. If they developed it before, they are instead protected against the other included types.

However, FUTURE III study shows us that the chance of developing both types 16 and 18 infections is less than 1% [15]. In addition to this, Kang et al. studied the efficacy of quadrivalent vaccines in 737 cases treated for CIN 3 over the course of 3 years. In this randomized controlled study, 360 vaccinated cases and 377 non-vaccinated cases were monitored in terms of recurrent diseases associated with certain HPV types. In the vaccinated group, recurrent infection rate was 2.5% while in the non-vaccinated group, the rate was 8.5% (HR = 2.840; CI: 1.335–6.042; $p < 0.01$) [16].

As a summary, both vaccinated girls and boys can develop HPV infections, which can lead to cancer, with types that are not included in the vaccine. Anogenital warts can occur with HPV types other than 6 and 11, hence the quadrivalent and nonavalent vaccinated group can develop anogenital warts at a rate lower than 10%.

3.3 Vaccination cures their related disease

Vaccines do not treat HPV-associated diseases. They are not therapeutic. However, as stated in previous section, vaccines are effective in preventing recurrent infections.

3.4 Antibody levels in blood are quite important; the protection loses its effect if the levels drop

Both bivalent and quadrivalent HPV vaccines' fundamental studies, FUTURE [15] and PATRICIA [17], recorded related blood antibody levels. In these studies, neutralizing antibody levels were measured for four different age groups: 15–25, 26–35, 36–45, and 46–55 years old. For per protocol groups, both HPV 16 and 18 neutralizing antibodies separately showed a peak at 7 months (after the third dose).

Antibody levels were found to be at least 8 times higher compared to natural infections, even in the youngest age group. HPV vaccines were found to have a general characteristic to be effective when done in both childhood and later ages. Neutralizing antibody level of 4V HPV vaccine for type 18 started to fall starting at 24 months and fell to the natural infection level at 55 months. Neutralizing antibodies showed 76% decrease at 24 weeks and 56% at 36 weeks.

Does this decrease in antibody level correspond to a decrease in protection level against type 18? In a 2008 RCT study by Joura et al., the protection level against HPV type 18 was steady at 98.4% (95% CI: 90.5–100) even when the antibody levels fell [18]. Ault et al. also showed that at 4 years mark, CIN 2/3 protection levels were at 100% even when seropositivity dropped to 60% [19]. When we consider the HPV vaccinated population that did not follow the full protocol; or had one or two doses only, by the 15th year mark hepatitis B vaccine shows a similar result. One or two dose vaccination was shown to provide comparable protection to three-dose regimes [20]. Even though hepatitis B vaccinated population's neutralizing antibody level was not measurable, the protection level was known to be still at 100%. This goal is presumed to be reflected on HPV vaccination soon. As in, changes in the neutralizing antibody levels do not affect the protection, which will stay at 100%.

3.5 Herd immunity does not exist

Herd immunity, or the increase in protection rate of the unvaccinated population as the overall vaccination rate increases, is a well-known fact for all types of vaccines. In Sweden, even though quadrivalent HPV vaccination rates are very low, 15–44 years old unvaccinated men and women had significant decrease on the annual rate-of-change percentage [21]. Therefore, as the community vaccination rate increases, those who are not vaccinated with HPV-related vaccines will develop HPV-related diseases at a lower rate.

3.6 Vaccinations are not effective when done at later ages

It was shown that HPV vaccination generates high neutralizing antibody levels when done in early childhood as well as at later ages. PATRICIA and FUTURE studies, at four age groups of 15–25, 26–35, 36–45 and 46–55 years old, shows consistent antibody levels for all of them. Even if there is not a statistical significance on vaccination of the naïve population, it is expected to be more effective. However, for all three vaccinations, EMA (European Medicine Agency) does not provide a set age limit. After considering the available data and studies, EMA decided to lift the age limit on women. However, there is a soft 25 years-old upper limit for men. This age limit is due to follow-up case series not being available yet.

3.7 Smear or other HPV tests should be performed before the vaccination

Vaccination will not protect against infections that occurred prior to it. FUTURE III study shows us that developing both HPV 16 and 18 together has a chance less than 1%. According to abnormal smear results, HSIL and cancer are only correlated with high-risk HPV types. On the other hand, LSIL is correlated with both high-risk HPV types as well as others. Hence, HPV DNA test prior to vaccination can only tell for less than 1% of women if the vaccine cannot protect against the most prevalent types 16 and 18. Studies also show that vaccinations help reduce reinfection rate for prior type 16 and/or 18 infections. On top of the infections, a randomized control study on LEEP treated cases due to HSIL, shows us that vaccinated group had a

reduced reinfection rate at 2.5% compared to 8.5% [16]. According to this data, smear or HPV DNA tests are not required prior to vaccination.

3.8 If a pregnancy occurs during vaccination, it should be terminated

There are limited number of cases about uses of bivalent and quadrivalent HPV vaccination during pregnancy. Both vaccines are classified as category B due to prior data. Comparison between vaccinated and unvaccinated group did not show an increase in the infant's congenital anomaly rates. However, due to unavailability of more data, vaccination during pregnancy is not recommended. This does not mean that the vaccination is done without knowledge of the pregnancy, that it should be aborted [22].

3.9 Due to decreased sexual fear, sexually transmitted disease rates increase among vaccinated girls

From a social, psychologic, and religious angle; parents of vaccinated girls wonder if the protection of the vaccine would urge them to be more sexually active at a younger age. It would be an issue if it was true. In order to answer this, a study published at Pediatrics reported sexually transmitted infections (STI) history of vaccinated girls. Mayhew et al. found that between the 42.5% cases without prior sexual relations and 57.5% cases with prior sexual relations, there was only a difference of OR 0:13 (95% CI: 0.03–0.69) which shows that vaccination did not change their sexual behavior [23].

3.10 Autoimmune diseases such as primary ovarian insufficiency and Guillain-Barre have higher rates among the vaccinated girls

In order to claim that a vaccination developed a disease, it needs to be within 3 years. At the 9th-year mark of HPV vaccines, 170,000,000 doses of vaccines had been done. Out of this large sample size, only six cases in the literature show primer ovarian insufficiency. Looking closer, we see that three of these cases had irregular periods up to 15 years before vaccination. The other three cases had their diagnosis more than 3 years after vaccination [24].

In the placebo-controlled FUTURE III (quadrivalent HPV vaccine) study, in both the vaccinated and AAHS (regular saline, placebo) groups, autoimmune disease rates were at 2.3%. This is the clearest study that shows autoimmune disease rate does not increase in vaccinated population. In addition, in a large meta-analysis study by Genovese et al. (243,289 vaccinated and 248,820 control group) there was no correlation between HPV vaccines and autoimmune diseases [25].

3.11 Vaccines that include types 16 and 18 are enough for the rest due to cross-protection effect

The difference between cross-protection and cross-reaction is an important issue. Bivalent and quadrivalent HPV vaccines both show cross-reaction. Especially in bivalent HPV vaccines, researchers argued for cross-protection due to common ancestry of types 16 and 31 as well as 18 and 45. In bivalent vaccinated girls, HPV 31 and 45 immune response, as well as GMTs and seropositivity rates were considered. Serum GMTs were 20 times higher than natural infections for HPV 31 and 45. This effect, however, is cross-reaction. Because the vaccinated girls and women lose the protection against HPV 31 and 45 by the end of 4th year in these bivalent HPV studies [26–28].

In a report by the Centers for Disease Control and Prevention (CDC) in the USA, as of 2018, there are no bivalent or quadrivalent HPV vaccines in the market; only nonavalent HPV vaccine is sold [29].

3.12 If the vaccines include full protection against some types, cancer rates in the rest of the types will increase

This is a baseless theory from anti-vaccination group. Is it necessary to prove the opposite of this theory? Even so, there have been studies on the matter. In 1180 vaccinated cases, anogenital non-vaccinated type HPV and genetic-related HPV 16 and 18 types prevalence are studied. There was no change in the non-vaccinated HPV type prevalence [30].

3.13 Vaccines are not safe; there are deaths associated with the vaccine

Three independent institutes on the CDC Website are continuously monitoring the safety of vaccines and the data is available for both experts and the community. Because in the USA, every drug that is on the market has an obligation for routine control. These vaccine-monitoring systems are: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) Network; and any person who had an adverse effect from a vaccine can report to them freely.

Vaccines consist of VLPs (virus-like particles) made with recombinant technology, that do not include any DNA but are identical to HPV in terms of structure. They cannot develop HPV infections or HPV-related cancer, as they do not include any DNA to reproduce. On the other hand, weakened or killed bacteria or virus vaccines do have a minute risk [31].

Side effects include redness in the vaccination site, minor pain, inflammation, and mild fever; like all childhood vaccinations. It could also cause nausea and dizziness. Due to this, vaccinated people are recommended to rest for 15 minutes after. VAERS records show that when divided into critical side effects and non-critical side effects; side effect rates were on a steady decline since 2007. In theory, autoimmune diseases are the most common side effect claims. In a quadrivalent HPV vaccine in 1000 cases of 9–26 year-old girls and women, there were no differences in autoimmune diseases between the vaccine group and the adjuvant or physiologic serum group. Both groups reported a rate of 2.3%.

When nonavalent HPV vaccine was introduced after the quadrivalent vaccine, which had twice the amount of aluminum (500 μg = 0.5 mg) of the latter, several anti-vaccination physicians theorized that this would worsen the side effects. However, any side effect of the 0.5 mg AAHS in hepatitis B, which has been used for 25 years, has never been proven. In a new study on the safety of aluminum in vaccines, the aluminum in the immunity-booster adjuvants had a high safety factor and did not cause any neurotoxicity [32]. Furthermore, we ingest more aluminum from drinking water (<0.2 ml/L), from many foods such as potatoes and spinach (<5 mg/kg), from aluminum folio to preserve food, from food with aluminum supplements, and soy-based food (0.4–6 mg/L) compared to the vaccines (https://www.cfs.gov.hk/.../files/RA35_Aluminium_in_Food_e.pdf).

Theory that quadrivalent and nonavalent HPV vaccines can cause primary ovarian insufficiency (POI) has been claimed by experts in many places including the social media. As described in detail in the previous section, there have been only 6 POI cases out of 170,000,000 doses of HPV vaccines in over 9 years. What is the incidence rate of POI in a normal population? Spontaneous POI for under

30-years old is about 0.1%, and for under 40-years old is about 1%. In Australia, out of 5,800,000 doses for 83% school-age girls, there was no relation between HPV and POI [33].

In Japan, there is a two-staged national vaccine program; quadrivalent HPV vaccine was implemented to the first stage in 2010 and was moved to the second stage in April 2013. This allowed only anyone that wanted to be vaccinated. The reason was abnormal uterus bleeding, excessive uterus bleeding, and headache. To address this, 71,117 women were studied and no relation between the symptoms and vaccination were found. As a result, vaccines were reimplemented into the first stage in June 2013 [34].

Considering mortality, CDC Website reports 117 deaths for the 80,000,000 doses of vaccines from the related institutes and 51 of them had a known cause. These known causes were unrelated to vaccines. Recorded death causes included: traffic accident, homicide, epilepsy crisis for epilepsy diagnosed patients, pulmonary embolism, drug overdose for drug abuse patients, acute myocarditis, and meningoencephalitis, influenza B, and diabetic ketoacidosis. There were five reported deaths after nonavalent vaccines were introduced: car accident, suicide, acute lymphoblastic leukemia, septic shock, and an unknown cause. There are many meta-analysis and reviews about vaccine safety readily available. There are no differences in between vaccinated and unvaccinated groups in terms of critical side effects.

3.14 Vaccines are not cost-effective; protected patients are not worth the cost

This is an interesting claim. Every single patient protected is worth the effort. Looking through a scientific perspective, many studies found that even the vaccines based on HPV 6/11 related warts, HPV 16/18 related precancerous lesions, and cervical cancer are cost effective [35–37].

4. Conclusion

HPV vaccines are recommended by WHO, CDC that are the world's leading organizations, and related associations of all other developed countries, have not yet reached the deserved coverage rate. WHO described HPV vaccination as an essential part of its program when talking about the elimination of cervical cancer. The most well-known topic of all medical staff is "The worst vaccine is better than the best treatment." As such, there are numbers of myths about HPV vaccines that we mentioned above. These issues should be well known to all of our community, especially health professionals, so that HPV vaccination can become widespread. We wanted to share the truths of these myths with you in the light of the evidences of today. In this article, neither of us have any conflict of interest.

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