9-valent Human Papillomavirus Vaccine Provides Further Protection Against Anogenital Cancers and Genital Warts

Elizabeth R. Howe
New Zealand

Please Note: This continuing medical education review example has been written as if it were November 2015 to give an accurate representation of what a CME for the 9-valent HPV vaccine may have looked like. We now have further information about this vaccine that was not available at the time, and as, such has been excluded from this review. For example, in December 2015 the FDA approved use of the vaccine for males up to 26 years of age. Prior to this, it was only approved for males 9-15 years of age, as is stated in this review.

Learning Objectives:
List the available HPV vaccines recommended for the differing populations.
Summarise the patient groups the 9-valent vaccine is not recommended for.
List the cancers and lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.
Explain the recommended spacing of the 9-valent vaccine doses.

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Infection with oncogenic types of human papillomavirus (HPV), such as high-risk subtypes HPV16 and 18, can cause anogenital and oropharyngeal cancers in both women and men. As of December 2014, there are 3 vaccines that protect against HPV types 16 and 18: bivalent, quadrivalent and 9-valent vaccines. The bivalent vaccine provides protection against oncogenic HPV types 16 and 18. The quadrivalent vaccine provides protection against HPV types 6 and 11, 16 and 18. In addition to these four HPV types, the 9-valent vaccine prevents infection with HPV types 31, 33, 45, 52 and 58. The vaccines are composed of virus-like particles (VLPs) derived from the L1 proteins of the HPV types. This continuing medical education review evaluates the importance of the additional 5 HPV types in the 9-valent vaccine, the efficacy and safety of the 9-valent vaccine, and the recommended time frames of administration of the vaccine.

Key words: anogenital cancer; cervical cancer; HPV; human papillomavirus; vaccine.

INTRODUCTION

Prior to December 2014, there were two preventative vaccines available against human papillomavirus (HPV) infection: bivalent and quadrivalent vaccines. These vaccines are administered in a 3-dose series and are recommended for women (bivalent and quadrivalent) and men (quadrivalent only). The bivalent vaccine provides protection against oncogenic HPV types 16 and 18. The quadrivalent vaccine provides protection against HPV types 6 and 11, 16 and 18. HPV subtypes 6 and 11 have a causal role in most anogenital warts and recurrent respiratory papillomatosis (RRP).[1-2] The vaccines are composed of virus-like particles (VLPs) derived from the L1 capsid proteins of each of the HPV types in the respective vaccines.[2]

Cervical cancer is the 5th deadliest cancer in women[3]; 70% of which is caused by HPV types 16 and 18.[1,4-5] 20% of cervical cancers and 10% of all invasive cancers are caused by 5 other HPV types: 31, 33, 45, 52 or 58.[1,6-7]

Abbreviations:

AASH:	amorphous aluminium hydroxyphosphate sulfate
ACIP:	Advisory Committee on Immunisation Practices
AIN:	anal intraepithelial neoplasia
AIS:	adenocarcinoma in situ
CIN:	cervical intraepithelial neoplasia
FDA:	US Food and Drug Administration
HPV:	human papillomavirus
MS:	multiple sclerosis
MSM:	men who have sex with men
PV:	Papillomavirus
RRP:	recurrent respiratory papillomatosis
VaIN:	vaginal intraepithelial neoplasia
VIN:	vulvar intraepithelial neoplasia
VLP:	virus-like particle

Neither the bivalent nor quadrivalent vaccines provide effective cross-protection against these five oncogenic HPV types. Cervical screening (smear tests) is performed to detect abnormal tissue in the cervix and prevent most cervical cancers when appropriate further treatment is obtained; however, this does not prevent HPV infection.[2] Although physical presentations of an HPV infection, such as genital warts, precancerous lesions, RRPs and cancers, are treated, HPV infections themselves are not.[8]

This highlights the need for prevention of HPV types other than HPV 6, 11, 16 and 18.

HPV DISEASE AND EPIDEMIOLOGY

The human papillomavirus is of the papillomaviridae family. PVs have a circular, covalently closed, double stranded DNA genome of 8 genes, encoding the early (E) and late (L) proteins.[2,9-10] Of these 8 genes, L1 and L2 are the major and minor proteins of the capsid, respectively.[2] The major capsid protein is used to produce the VLPs that form the active component of the vaccines.[10]

Of the >150 HPV types that have been identified, there are 40 that infect the genital area.[10]

Replication

Once the virus enters the basal cells of the epithelium, the E2 protein regulates transcription of the viral genome using host cell replication machinery.[2,9] The host cell cycle is deregulated and cell division is promoted by interaction of E6 and E7 proteins with p53 and retinoblastoma protein, respectively, causing the epithelium to thicken.[2,9] The capsid proteins (L1 and L2) are then produced and encapsidate the genome.[9] HPVs can persist here asymptomatically or cause neoplasms.[10]

HPV is transmitted via genital contact and is likely to be more frequently transmitted from females to males.[2,11] The prevalence of HPV in women aged 18-25 years increases with the number of sexual partners. The prevalence of HPV infection in women who have only have one sexual partner is 14.3%. This increases with two sexual partners to 22.3%, and 31.5% with 3 or more sexual partners.[12]

HPV infections are often self-limited and asymptomatic; however, if infection is persistent anogenital warts, and cancers can develop.[2] Persistent HPV infection has a casual role in many different cancers and is responsible for 5% of cancers worldwide.[13-14] There are approximately 20 different high risk types of HPV; including subtypes 16 and 18 which cause 64% of invasive HPV-associated cancers.[1,4] Cancers associated with HPV infection include oropharyngeal and anal cancers, which occur in both men and women; vaginal, cervical, and vulvar cancers, occurring in females; and penile cancers in males.[1,15] Approximately 90% of cervical cancers can be attributed to infection of HPV subtypes 16, 18, 31, 33, 45, 52 or 58.[1,4-7] Precancerous cervical lesions such as high grade cervical intraepithelial neoplasia 2 and 3 (CIN2 and CIN3), as well as cervical adenocarcinoma in situ (>CIN2) are most often caused by HPV infection; 50% are caused by HPV types 16 or 18, and 25% by types 31, 33, 45, 52 or 58.[1]

HPV types 6 and 11 are low-risk types and cause >90% of anogenital warts and the majority of recurrent respiratory papillomatosis (RRP).[1,16]

AVAILABLE HPV VACCINES

The quadrivalent HPV vaccine was approved by the FDA in 2006.[17] This vaccine is safe for both males

and females and provides protection against HPV types 6, 11, 16 and 18. In 2009, the FDA approved the bivalent HPV vaccine for use in females.[18] This vaccine is not approved for use in males and provides protection against HPV types 16 and 18.

On December 10, 2014, the FDA approved a 9-valent HPV vaccine for use in both males and females.[19] This vaccine protects against the same four HPV types as the previous vaccines, as well as an additional five: HPV 31, 33, 435, 52, and 58.[1,7,19]

All three vaccines consist of the same type of active component. Non-infectious virus-like particles (VLPs) are derived from the L1 protein of the HPV types, which induce the appropriate immune response in the body.[1-2,6]

Vaccine Mechanism

The protection provided by the 9-valent HPV vaccine is thought to be mediated by the humoral immune response induced by the vaccine; however, the exact mechanism is unknown.[6]

APPROVED 9-VALENT VACCINATION GROUPS

The FDA has approved the use of the 9-valent HPV vaccine for females from ages 9 through 26 and males aged 9 through 15, in a 3 dose vaccination series.[19] The ACIP recommends the vaccination series be started at the age of 11-12 for both males and females,[1] but can also be started for females aged 13-26 and males aged 13-21 if they have not previously been vaccinated or have not received all 3 doses.[1]

Special populations

The 9-valent vaccine is also recommended for men who have sex with men (MSM) through to the age of 26, as well as immunocompromised patients.[1]

The 9-valent vaccine is not recommended for:

- pregnant women,
- persons with hypersensitivity to any components of the vaccine, and
- persons with immediate hypersensitivity to yeast [1]

For further information regarding contraindications of the 9-valent vaccine, refer to page 4.

CANCER AND LEISON PREVENTION

The 9-valent HPV vaccine is designed for the prevention of the following *cancers* in females, caused by HPV types 16, 18, 31, 33, 45, 52 and 58

- cervical,
- vaginal,
- vulvar, and
- anal

as well as prevention of anal cancer in males.[19]

The 9-valent HPV vaccine is designed for the prevention of the following *dysplastic or precancerous lesions*:

- condyloma acuminata (genital warts) caused by low-risk HPV types 6 and 11
- anal intraepithelial neoplasia (AIN) grades 1, 2 and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

in both males and females.[19]

Additionally, in females, the 9-valent HPV vaccine prevents against *dysplastic or precancerous lesions* such as:

- cervical intraepithelial neoplasia grade 1 (CIN1), grade 2 (CIN2) and grade 3 (CIN3),
- vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3,
- vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, and
- cervical adenocarcinoma *in situ* (AIS)

caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.[19]

Vaccination does not remove the need for cervical screening for females 21 – 65 years of age for prevention of HPV associated cancers and lesions.[20]

VACCINE EFFICACY AND SAFETY

Efficacy:

HPV types 16 and 18 cause approximately 70% of cervical cancer, and the additional 5 oncogenic HPV types in the 9-valent vaccine cause about 20% of cervical cancers; therefore, this new vaccine has the potential to prevent approximately 90% of cervical cancers.[6,21]

In a phase III trial comparing the efficacy of the quadrivalent and 9-valent HPV vaccines in females aged 9 through 26 years of age, the 9-valent vaccine showed 96.7% efficacy for prevention of the

following dysplastic or precancerous lesions caused by HPV types 31, 33, 45, 52, or 58:

- Cervical intraepithelial neoplasia >grade 2
- Vaginal intraepithelial neoplasia grade 2 and grade 3
- Vulvar intraepithelial neoplasia grade 2 or 3[22]

Another study found a 96% reduction in high grade cervical, vaginal, and vulvar lesions associated with HPV types 31, 33, 45, 52 and 58 in patients treated with the 9-valent vaccine, compared to those treated with the quadrivalent vaccine. In this same study, persistent infections of HPV 31, 33, 45, 52 and 58 were also reduced by 96%.[21]

The results of a similar study showed 97.1% efficacy of the 9-valent vaccine against the additional 5 HPV types in the 9-valent vaccine.[23]

The quadrivalent and 9-valent vaccines have equal efficacy against HPV types 6, 11, 16 and 18 in females ages 16-26 years.[24]

Site reaction:

Injection-site pain, swelling and erythema were common reactions in a study comparing the safety of the quadrivalent and 9-valent HPV vaccines. These reactions occurred in 90.2% of patients in the 9-valent group and 84.0% of the quadrivalent group and occurred more often in children under 15 years of age than in adults 16-26. [6,25,26]

New onset autoimmune:

Potential new onset autoimmune disorders were similar between the quadrivalent and 9-valent vaccines, although there was an imbalance in cases of multiple sclerosis (MS); there were only 2 cases of MS in the quadrivalent group but 5 in the 9-valent group. Due to the small number of cases, it is unclear if this imbalance is clinically significant.[6]

Pregnancy

Although no studies have been undertaken directly on the effects of the 9-valent HPV vaccine on pregnancy, during clinical studies 86% and 85% of patients in the 9-valent and quadrivalent vaccinated groups, respectively, became pregnant. These patients were assessed following completion of the pregnancy and the data did not reveal an increased risk of adverse pregnancy outcomes when vaccinated with the 9-valent vaccine in comparison to the quadrivalent vaccine.[6] Additionally, results from a study in which pregnant rats were injected with the 9-valent vaccine showed no evidence of harm to the fetus.[1]

It is not recommended to receive the HPV vaccination when pregnant. If a patient has begun the vaccination series, subsequent doses should be delayed until completion of the pregnancy. There is no intervention need if a patient is vaccinated while pregnant.[1]

Hypersensitivities and allergy:

The 9-valent HPV vaccine is not recommended for patients with a history of hypersensitivity to any of the vaccine components listed on page 5. Additionally, both the 9-valent and quadrivalent vaccines are contraindicated for patients with a history of hypersensitivity to yeast.[1]

Previously vaccinated with quadrivalent

The 9-valent vaccine is tolerated in patients that have previously been vaccinated with the quadrivalent vaccine.[6]

Reporting of adverse reactions

Adverse reactions to the 9-valent HPV vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS).

Concomitant administration

The 9-valent vaccine is safe to be given at the same time as, and does not interfere with, the following vaccines:

- Menactra: meningococcal
- Adacel: Tetanus, diphtheria, and acellular pertussis
- Repevax: Tetanus, diphtheria, acellular pertussis, and poliomyelitis

VACCINE ADMINISTRATION

The HPV 9-valent vaccine is administered as a 0.5mL intramuscular injection (arm or leg).[6] The 3-dose vaccination series should be completed within a year of initiation; in a schedule such as is demonstrated in table 1.

If this vaccination schedule is interrupted, there is no need to restart the series; the next vaccine dose should be given when appropriate for the patient.[2]

Dose Number	Recommended Time	Limitations
1	Preferably between ages 11-12	
2	2 months from first dose	No sooner than 1 month from first dose
3	6 months from first dose	No sooner than 3 months from first dose

Table 1: Recommended Time Frame of Administration of 9-valent HPV Vaccine. Information used in this table from Markowitz et al.[2]

If the vaccine used to start the vaccination series is not available at the time of the next appointment, any of the three vaccines may be used to complete the vaccinations for females, and either the quadrivalent or 9-valent vaccine may be used for males.[2]

VACCINE COMPOSITION AND STORAGE

Composition

The 9-valent vaccine contains VLPs composed of the L1 proteins from each of the HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. These VLPs are produced in the yeast Saccharomyces cerevisiae.[6]

The inactive ingredients in this vaccine are as follows:

- Amorphous aluminium hydroxyphosphate sulfate (AAHS)
- Sodium chloride
- L-histidine,
- Polysorbate 80,
- Sodium borate,
- Residual traces of yeast, and
- Water[25]

A summary of the vaccine ingredients in a single 5mL dose of the 9-valent HPV vaccine are displayed in table 2.

This vaccine does not contain antibiotics or preservatives.[6]

Storage

The 9-valent HPV vaccine can be stored for 30 months from the date of manufacture when stored correctly. It is to be stored in the fridge at 2-8°C as is not to be frozen.[19]

SUMMARY

The bivalent vaccine is recommended for females starting at ages 11-12 years old and the quadrivalent vaccine was recommended for both females and males from 11-12 years of age.[2] These vaccines both protect against HPV types 16 and 18, and the quadrivalent vaccine additionally protects against HPV types 6 and 11.[1,7] There are many other oncogenic HPV types including 31, 33, 45, 52 or 58, which together cause approximately 10% of invasive HPV associated cancers.[1] Because of this, there was an unmet need for protection against additional HPV types prior to the approval of the 9-valent HPV vaccine.

Like the quadrivalent vaccine, the 9-valent vaccine contains VLPs formed from HPV types 6, 11, 16 and 18. Additionally, it contains VLPs from HPV types 31,33,45,52 or 58, providing protection against 9 different HPV types.[19]

The 9-valent HPV vaccine is recommended for females aged 9-26 years and males aged 9-15 years.[1,19]
It is recommended that the first dose of the 9-valent vaccine is given to both males and females around 11-12 years of age. The second dose is recommended to be given 2 months from the first, and the third should be given 6 months from the first dose.[2,25]

Patients who have a history of hypersensitivity to any of the vaccine components or yeast should not receive the 9-valent HPV vaccine. This vaccine is not recommended for pregnant women, and patients who become pregnant after the initiation of the vaccine series should delay subsequent doses until completion of the pregnancy.

Component	Quantity per 0.5mL Dose	Function	Active/Inactive Ingredients
HPV Type 6 L1 Protein	30 µg	Immunogens	Active
HPV Type 11 L1 Protein	40 µg		
HPV Type 16 L1 Protein	60 µg		
HPV Type 18 L1 Protein	40 µg		
HPV Type 31 L1 Protein	20 µg		
HPV Type 33 L1 Protein	20 µg		
HPV Type 45 L1 Protein	20 µg		
HPV Type 52 L1 Protein	20 µg		
HPV Type 58 L1 Protein	20 µg		
Amorphous Aluminium Hydroxyphosphate Sulfate	500 µg (aluminium content)	Adjuvant	Inactive
Sodium Chloride	9.56 mg		
L-Histidine	0.78 mg		
Polysorbate 80	50 µg		
Sodium Borate	35 µg		
Water	QS	Solvent	

Table 2: 9-valent HPV Vaccine Composition. Table amended from Food and Drug Administration[6]

Questions

Multiple Choice Questions – only one correct answer per question

Question 1

a) The bivalent, quadrivalent and 9-valent vaccine are all approved for use in females and males.
b) The quadrivalent and 9-valent vaccine is approved for use in both females and males, and the bivalent vaccine is approved for use in females only.
c) The bivalent and 9-valent vaccines are approved for use in both males and females, and the quadrivalent vaccine is approved for use in females only.
d) The bivalent, quadrivalent and 9-valent vaccines are all approved for use in females, none are approved for use in males

Question 2

a) The 9-valent vaccine is contraindicated for patients with a history of hypersensitivity to yeast or any of the vaccine components
b) The 9-valent vaccine is safe for patients with a history of hypersensitivity to yeast as long as they are not pregnant
c) The 9-valent vaccine is contraindicated for patients with a history of hypersensitivity to latex

Question 3

a) The 9-valent vaccine prevents cervical cancer associated with HPV, but no other cancers
b) The 9-valent vaccine does not prevent any HPV-associated cancer, but does prevent genital warts
c) The 9-valent vaccine prevents cervical, vaginal, vulvar, and anal cancers associated with HPV infection
d) The 9-valent vaccine does not prevent HPV-associated cancer or genital warts

Question 4

a) The second dose of the 9-valent vaccine may be given no sooner than 1 month from the first dose
b) The second dose of the 9-valent vaccine may be given no sooner than 3 months from the first dose
c) The second dose of the 9-valent vaccine may be given no sooner than 6 months from the first dose

Short Answer Questions

Question 5

Amelia is brought into your clinic with her mother. Amelia is 12 years old and has come to talk about receiving the HPV vaccine. She has no known allergies and is not sexually active.

a. Which HPV vaccine(s) would be safe for Amelia? (Explain all possible vaccines)
b. Amelia would like to know what the benefit is of receiving the 9-valent HPV vaccine, compared to the other vaccine options. Please list the cancers and lesions this vaccine helps to protect against.
c. Describe the vaccination series to Amelia. Include the number of appointments she needs to attend, the spacing of each appointment, and what happens if she misses an appointment.

Question 6

Sarah is a patient of yours who has already received 2 doses of the 9-valent HPV vaccine, with no complications, and she has just found out she was pregnant at the time of her second vaccination. Write a paragraph explaining the advice you would give to Sarah. Include whether any intervention is needed – if so, what would that be and when she would be able to receive her final dose.

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