



HPV VACCINE

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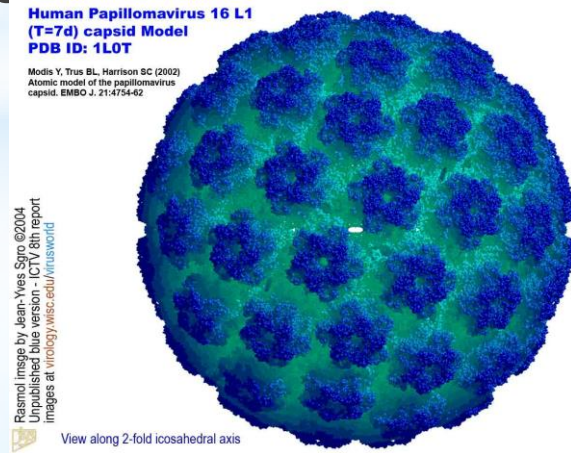


Objectives

1. WHAT IS HPV
2. HPV RELATED INFECTIONS
3. PREVELANCE IN U.S AND SAUDI ARABIA
4. TYPES OF VACCINES AVILABLE
5. TIME OF VACCINATION
6. DOSES AND ADMINISTRATIONS
7. DURATION OF PROTECTION
8. SAFETY OF THE VACCINE

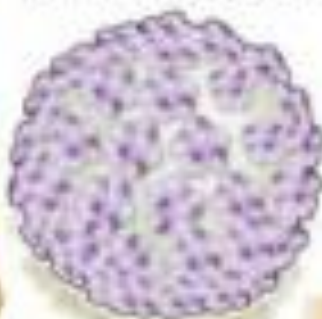
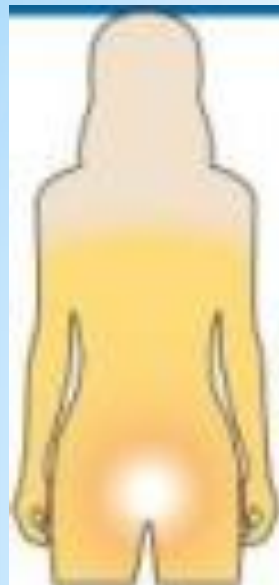
Human papillomavirus

- ✓ DNA virus from the papillomavirus family
- ✓ over 150 types are known
- ✓ More than 40 types are transmitted through sexual contact and infect the anus and genitals.
- ✓ spread by sustained direct skin-to-skin contact with vaginal and anal sex
- ✓ It does not spread via common items like toilet seats
- ✓ cannot be cultured without living tissue



Human papilloma virus (HPV)

Sexually transmitted HPV infections are common and often asymptomatic, untreated cases in women are the main cause of cervical cancer



▶ A sexually transmitted virus that causes cancer

▶ More than 100 types of HPV have been found so far

▶ 15 have been identified as putting women at high risk for cervical cancer

Cervical cancer

Virus in cervix enters cells through micro-abrasions

1



Infects cells

2

HPV replicates

90 percent of cases heal within two years

Several weeks later



Infection spreads

3

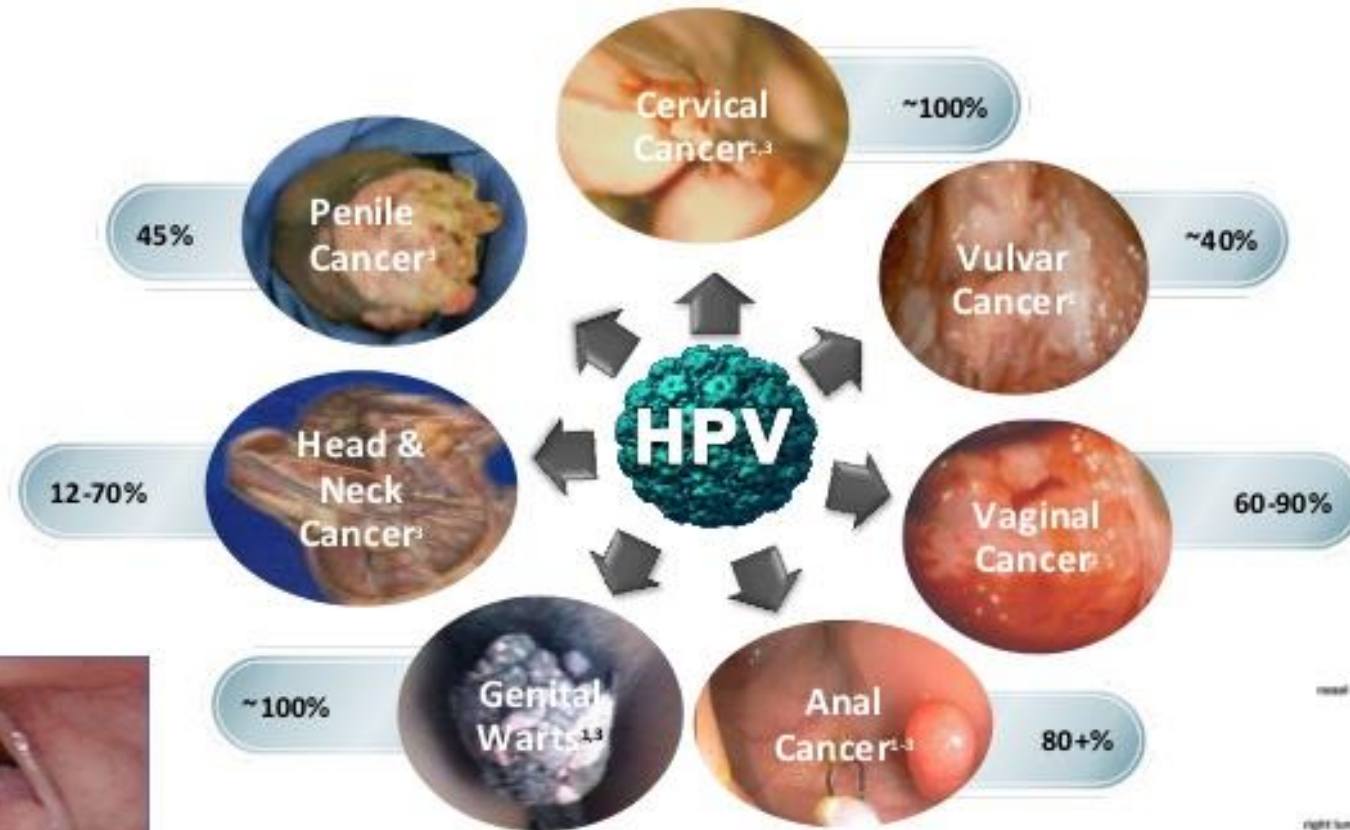
0.8 percent of cases develop cancer

10-30 years later



HPV invades deeper layer of tissues and turns cancerous

HPV causes more than cervical cancer



Percentages represent cases attributable to HPV infection



Braaten KP et al. Rev Obstet Gynecol. 2008;1:2-10.

Hoots BE et al. Int J Cancer. 2009;124:2375-2383.

IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Human papillomaviruses. Vol 90. Lyon, France: IARC, 2007.

DISEASE ASSOCIATIONS:

❖ HPV-related disease in females

➤ Cervical cancer and precursor lesions

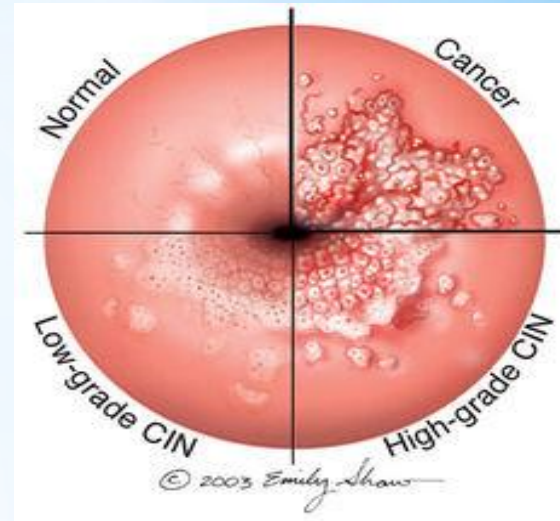
-is the third most common female cancer worldwide

-IN U.S

-THE ESTIMATED ANNUAL INCIDENCE OF CIN AMONG FEMALE WHO UNDERGO CERVICAL CANCER SCREENING IS 0.4 % FOR CIN 1 AND 0.5% FOR CIN 2/3

-HPV TYPE 16 AND 18 cause approximately 70% of cervical cancer and 50 % of precancerous cervical lesions

-HPV types 31, 33, 45, 52, and 58 are estimated to cause an additional 19 % of invasive cervical cancers



in Saudi Arabia:

- In Saudi Arabia which has a population of 8 million women over the age of 15 years, approximately 152 new cases of CC are diagnosed every year
- 55 women die from the disease annually
- ranking number 12 between all cancers in females
- Accounts for 2.4% of all new cases, despite the lack of national screening programs.

RESEARCH ARTICLE

Open Access

Human papillomavirus prevalence and type distribution among women attending routine gynecological examinations in Saudi Arabia

Abdulaziz AlOubaid¹, Ismail A Al-Badawi^{2*}, Hanan Al-Kadri³, Kusuma Gopala⁴, Walid Kandeil⁵, Wim Quint⁶, Murad Al-Aker^{2,7} and Rodrigo DeAntonio⁵

Abstract

Background: Cervical cancer (CC) is caused by persistent infection with high-risk (HR) human papillomavirus (HPV) types. In Saudi Arabia which has a population of 6.5 million women over the age of 15 years, approximately 152 new cases of CC are diagnosed and 55 women die from the disease annually. Nevertheless current epidemiological data for HPV in this population are limited. This study evaluated the prevalence and type distribution of HPV and documented the awareness of HPV infection and health-related behavior among Saudi and non-Saudi women attending routine examination.

Methods: This was an observational, epidemiological cross-sectional study conducted between April 2010 and December 2011 at three hospitals in Saudi Arabia. Cervical samples from women aged ≥ 15 years, who were attending routine gynecological examinations were collected and tested for HPV-DNA by polymerase chain reaction and typed using the SPF₁₀ DEIA/LiPA25 system. Two questionnaires on health-related behavior and awareness of HPV infection were completed.

Results: A total of 417 women, mean age (standard deviation) 41.9 (± 10.4) years, were included in the final analysis, of whom 77% (321/417) were Saudi nationals. HPV-DNA was detected in 9.8% women (41/417, 95% confidence interval [CI]: 7.1-13.1). The prevalence of any HR-HPV by age was: 25–34 years: 3.0%; 35–44 years: 4.5%; 45–54 years: 3.2%; >55 years: 10.9%. The most prevalent HR-HPV-types were: HPV-68/73 (5 cases); HPV-18 (4 cases); HPV-16 (3 cases). The most prevalent low risk (LR) types were HPV-6 (4 cases); HPV-42, HPV-53 and HPV-54 (2 cases each). The prevalence of HPV was higher among non-Saudi nationals vs. Saudi nationals (16.7% vs. 7.8%, $P = 0.0234$). No statistically significant risk factors were identified: 32.2% (101/314) women were aware of HPV and 89.9% (285/317) showed an interest in HPV vaccination.

Conclusion: The overall prevalence of HPV was 9.8% in Saudi Arabia, but was higher in women over 55 years, as well

- This was an observational, epidemiological cross-sectional study conducted between April 2010 and December 2011 at three hospitals in Saudi Arabia

- **Result :**

1. The overall prevalence of HPV was 9.8% in Saudi Arabia, but was higher in women over 55 years, as well as in non-Saudi nationals.

2. The most prevalent HR-HPV-types were:

HPV-68/73 ---(5 cases)

HPV-18 ----(4 cases)

HPV-16 (3 cases)

The most prevalent low risk types were

HPV-6-- (4 cases)

HPV-42, HPV-53 and HPV-54 (2 cases each).

RESEARCH ARTICLE

Open Access

HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia

Ghazi Alsbeih^{1,4*}, Najla Al-Harbi¹, Medhat El-Sebaie² and Ismail Al-Badawi³

Abstract

Background: Cervical cancer incidence is low in Saudi Arabian women, suggesting low prevalence to HPV infection due to environmental, cultural and genetic differences. Therefore, we investigated HPV prevalence and genotype distribution in cervical cancer as well as the association with 9 genetic single nucleotide polymorphisms (SNPs): *CDKN1A* (*p21*) C31A, *TP53* C72G, *ATM* G1853A, *HDM2* promoter T309G, *HDM2* A110G, *LIG4* A591G, *XRCC1* G399A, *XRCC3* C241T and *TGFβ1* T10C, presumed to predispose to cancer.

Methods: One hundred cervical cancer patients (90 squamous cell carcinoma and 10 adenocarcinoma) and 100 age/sex-matched controls were enrolled. SNPs were genotyped by direct sequencing and HPV was detected and typed in tumors using the HPV Linear Array Test.

Results: Eighty-two cases (82%) were positive for HPV sequences. Seven HPV genotypes were present as single infections (16, 18, 31, 45, 56, 59, 73) and five double infections (16/18, 16/39, 16/70, 35/52, 45/59) were detected. Most common genotypes were HPV-16 (71%), 31 (7%), and 18, 45, 73 (4% each). Only *XRCC1* SNP was significantly associated with cervical cancer ($P=0.02$, $OD=1.69$; 95% $CI= 1.06-2.66$). However, nested analysis revealed a preponderance of HPV-positivity in patients harboring the presumed risk allele *TP53* G ($P=0.06$). Both *XRCC1* and *TP53* SNPs tended to deviate from Hardy-Weinberg equilibrium (HWE; $P=0.03-0.07$).

Conclusions: HPV prevalence (82%) in cervical cancer is at the lower range of the worldwide estimation (85 - 99%). While *XRCC1* G399A was significantly associated with cervical cancer, *TP53* G72C showed borderline association only in HPV-positive patients. Deviation from HWE in HPV-positive patients indicates co-selection, hence implicating the combination of HPV and SNPs in cancer predisposition. Thus, SNPs could be more relevant biomarkers of susceptibility to cervical cancer when associated with HPV infection.

Keywords: Cervical cancer, Human papillomavirus (HPV), Predisposition, Single nucleotide polymorphism (SNP)

- 100 patients with histo pathologically proven, locally advanced, cervical cancer were enrolled in this study out of 218 patients followed at KFSHRC from 2009 to 2012.
- There was no restriction on patients' age or histological type of cervix cancer

Conclusions

- The prevalence of HPV infection in invasive cervical cancer in Saudi Arabia (82%) is at the lower range of that observed in the world (85%-99%)
- the most common HPV genotype was HPV-16 (71%), followed by HPV-31 (7%), HPV-18, 45, and 73 (4% each)
- double infections were present in 8.5% of HPV-positive patients.

- ❖ The Departments of Obstetrics and Gynecology, and Histopathology at KKUH conducted A retrospective study.
- ❖ reviewed all cervical pap smears obtained from Saudi women between the years of 2004 and 2014.
- ❖ found that the frequency of epithelial cell abnormalities in the cervix among Saudi women is relatively low.
- ❖ The mean age of cervical carcinoma was 61 years, which is higher than the one reported in western countries.
- ❖ relatively high incidence of invasive Cancer, which is found in older Saudi women, suggest that the starting age of cervical screening in our society should be from 25 years with continuation of the screening till after 65 years of age.

- **Vulvar and vaginal cancer and precursor lesions –**
- Relatively rare cancers globally

IN U.S

- estimated incidence of 27,000 vulvar cancers and 13,000 vaginal cancers in 2008
- the attributable fraction due to HPV infection has been estimated to be 43 % for vulvar and 70 % for vaginal cancer

❖ HPV-related disease in females and males

➤ Anal cancer and precursor lesions –

- Relatively rare cancer globally
- HPV types 16 and 18 cause around 70 to 85 % of anal cancers and precancerous lesions (ie, anal AIN grade 2 and grade 3)



➤ Genital warts —

- HPV types 6 and 11 cause 90 percent of genital warts.
- IT is associated with physical and psychological morbidity and have a high rate of treatment failure AND treatment of recurrent episodes is costly



➤ Oro-pharyngeal cancer —

- HPV infection may also play a role in the pathogenesis of squamous cell carcinomas of the head and neck.
- primarily found in the oropharynx and base of the tongue , tonsil AND larynx

❖ HPV-related diseases in males

➤ Penile cancer and precursor lesions —

- It is rare globally
- HPV 16 and HPV 18 cause approximately 35 to 40 % of penile cancers and 70-80 % of HPV-positive penile cancers

1989

HPV VACCINE?



- Ian Hector Frazer
- born 6 January 1953
- is a Scottish-born Australian scientist
- He met with virologist Jian Zhou the two considered the problem of developing a vaccine for HPV



U.S FDA Approved ?

2006

Saudi Food and Drug Administration approved prophylactic HPV vaccine in 2010

**Three different vaccines
have been developed
against HPV :**



FDA licensed Gardasil in June 8, 2006.

- ✓ a quadri-valent HPV vaccine, targets HPV types 6, 11, 16, and 18
- ✓ It is approved for the prevention of cervical cancer and cervical and vulvar intra epithelial neoplasia in young women
- ✓ approved for both men and women from the ages of 9 to 26 for the prevention of genital warts, anal cancers, and anal intraepithelial neoplasias.

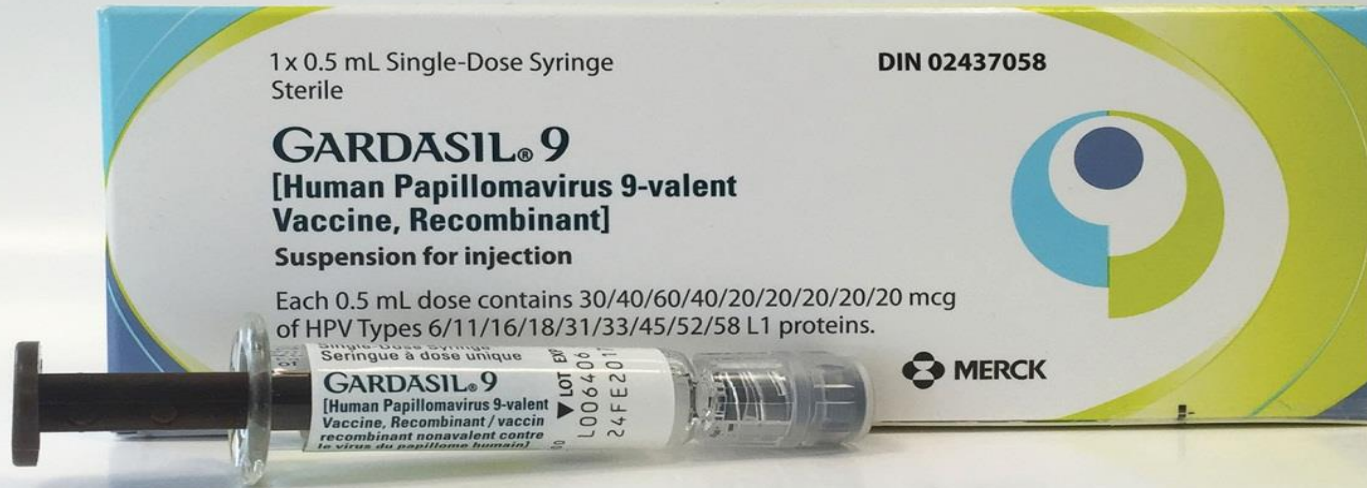
➤ Two large, randomized, double-blind, placebo-controlled trials have evaluated the efficacy of this vaccine in more than 17,000 adolescents and young females :

1. Among HPV-naïve populations, the efficacy for preventing CIN2 or more severe disease due to HPV types included in the vaccine, was 97 to 100 %

* The National Cancer Institute
Reviewed: November 2, 2016

2. In the overall population of study participants (with or without prior HPV infection), the efficacy of the vaccine for preventing CIN2, or more severe disease due to HPV types included in the vaccine was significantly lower at approximately 44 % after a mean follow-up period of 3 years.

This reduction in efficacy reflects the fact that the vast majority of enrollees in this trial were already sexually active and many had been previously infected with vaccine HPV types



is approved In December 2014, the United States' Food and Drug Administration (FDA) for women and girls aged 9 to 26 and men and boys aged 9 to 15.

- ✓ a 9-valent vaccine, targets the same HPV types as the quadri-valent vaccine (6, 11, 16, and 18) as well as types 31,33, 45, 52, and 58 .

- ✓ An international trial reported the efficacy of this vaccine in approximately 14,000 females aged 16 to 26 years who were randomly assigned to receive the vaccine :
 1. Among HPV-naïve populations, the efficacy of 9-valent vaccine for preventing CIN2 or more severe disease, VIN2 or 3, and VaIN2 or 3 associated with HPV types 31, 33, 45, 52, and 58 was 97 %

2. In the overall population of study participants (with and without prior HPV infection), the rates of high-grade cervical, vaginal, and vulvar disease were the same among women who received the 9-valent vaccine and those who received the quadri-valent vaccine (14 cases/1000 person years in both groups).



- a bivalent vaccine, targets HPV types 16 and 18
- is approved for girls and women aged 9 to 25 for the prevention of cervical cancer and CIN.

➤ One large randomized clinical trial in more than 18,000 young females aged 15 to 25 years demonstrated the efficacy of bivalent HPV vaccine .

• Among HPV-naïve patients, the efficacy of the vaccine for preventing CIN2 or more severe disease due to HPV types included in the vaccine was 93 %

- In the overall population of study participants (with and without prior HPV infection), vaccine efficacy for preventing CIN2 or more severe disease due to HPV types included in the vaccine was significantly lower at 53 % after a mean follow-up period of approximately 3 years.

* The National Cancer Institute
Reviewed: November 2, 2016

When?

American Cancer Society (ACS) guidelines

should be routinely offered to

1. females aged 11 to 12 years; immunization may begin at 9 years of age .

2. catch-up vaccination for females aged 13 to 18 who have not been previously vaccinated or completed their vaccine series.

3. The ACS notes that there is insufficient evidence to recommend for or against vaccination of females aged 19 to 26 years.

The World Health Organization (WHO)

1. suggests that girls within the age range of 9 through 13 years should be the primary target population for HPV immunization.
2. local public health programs should recommend vaccination of older females **only if** it is affordable and cost effective and does not divert resources from vaccinating the primary target population or screening for cervical cancer.

Attitudes and perceptions towards HPV vaccination among young women in Saudi Arabia

Aneela N. Hussain, Abdullah Alkhenizan, [...], and Ahmed Abdulkarim

[Additional article information](#)

Abstract

Background:

Rising incidence of human papillomavirus (HPV) infection and cervical cancer can be reduced by effective vaccination. Saudi Food and Drug Administration approved prophylactic HPV vaccine in 2010 for females of 11–26 years.

Objectives:

To determine the awareness of HPV infection, its health sequel and the attitude and barriers to the acceptance of HPV vaccine by young women in Saudi Arabia. Dynamics influencing the decision of patients and parents regarding vaccination were assessed to foster effective and strategically focused interventions.

Materials and Methods:

All patients of Family Medicine department, King Faisal Specialist Hospital and Research Center, Riyadh were invited to participate in this study from January 2012 to June 2014. A culturally sensitive and specially designed questionnaire was administered using an interview-based model to assess the knowledge, perception, and associated sociodemographic factors of HPV.

Results:

Conclusion:

Knowledge and perception of HPV infection as an STDS and its vaccine was significantly low in this cohort of patients.

Higher age and educational levels directly correlated with increased knowledge of HPV infection and its complications.

It is recommended that awareness should be raised, and access to HPV vaccination increased to help reduce the health care burden of HPV sequelae in the Kingdom.

IMMUNIZATION IN SPECIAL PATIENT POPULATIONS

What about ? Pregnant females?



According to CDC RECOMMENDATIONS

✓ not recommended

given that safety in this setting has not been thoroughly evaluated .

- ✓ If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen should be delayed until after completion of the pregnancy

- In quadri valent HPV vaccine trials, the composite rate of adverse pregnancy outcome (spontaneous abortion, late fetal death, congenital anomaly) was similar for the 3819 females who became pregnant and controls who did not receive the vaccine (22.6 versus 23.1 percent)
- Similarly reassuring findings have been reported for the bivalent HPV vaccine and for the 9-valent HPV vaccine , although data are more limited
- Safe in lactating females as it dose not affect the infant breast feeding

Immunization in females with
pre-existing cervical
abnormalities or genital warts

- A history of genital warts, abnormal cytology, or +VE HPV DNA test result is not evidence of prior infection with any or all of the vaccine HPV types
- vaccination can still provide protection against infection with HPV vaccine types not already acquired.
- assessment with Pap testing or screening for existing HPV infection is NOT indicated as part of the determination for HPV vaccine candidacy.
- these patients should be advised that vaccination will have no therapeutic effect on pre-existing HPV infection or CIN , and the potential benefit of HPV vaccination is not as great as if they were vaccinated before they started having sex.

Transplant recipients and HIV- infected patients



According to CDC RECOMMENDATIONS

- ❖ Studies of the HPV quadrivalent vaccine in HIV-infected adult men and women aged 16 to 23 years , boys and girls aged 7 to 12 years suggest that it is both immunogenic and safe in these populations.
- ❖ efficacy data are not yet available.

❖ For solid organ transplant recipient

It is safe to be given 3 to 6 months following transplantation

PREVACCINATION ASSESSMENT

The Advisory Committee on Immunization Practices(ACIP) does not recommend serologic or HPV DNA testing prior to immunization in females or males

VACCINE DOSE AND ADMINISTRATION

According To CDC GUIDELINES ON DEC 2016

Immunization schedule – In the United States, as of 2016, the recommended dosing schedule depends on the age of the patient

- Individuals younger than 15 years should receive two doses of HPV vaccine at least six months apart.

Individuals 15 years or older should receive three doses of HPV vaccine over a minimum of 24 weeks.

- The minimum interval between the first two doses is 4 weeks and the minimum interval between the second and third doses is 12 weeks.
- The Gardasil and Gardasil 9 are typically administered in three doses at time zero, and at two and six months of follow-up.
- Cervarix follow a similar three-dose schedule for those older than 15 years, the bivalent vaccine is typically administered in three doses at time zero, and at one and six months of follow-up.

Interrupted schedules

if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series.

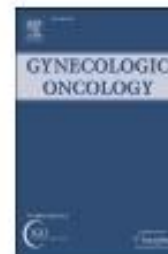
For how long ?

Duration of protection ?



- ❖ **IN ALL CLINICAL TRIALS** Persistent antibody levels and protection against HPV infection have been reported up to 10 years following vaccination .
- ❖ Of note, the precise level of antibody needed for protection against infection is unknown.
- ❖ Further data will become available in the future as female and male participants in vaccine studies are followed over time.

* CDC GUIDELINES DEC2016



Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: Modeling of sustained antibody responses[☆]

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ARTICLE INFO

Article history:

Received 30 September 2008

Available online 12 February 2009

Keywords:

HPV-16/18

VLP vaccine

Antibody persistence

Statistical models

Immunologic memory

Cervical cancer

ABSTRACT

Objectives. Strong and sustained HPV-16 and -18 antibody responses have been observed in previously unexposed women aged 15–25 years vaccinated with the AS04-adjuvanted HPV-16/18 L1 virus-like particle vaccine. While awaiting the extended results of ongoing trials, our objective was to predict the long-term persistence of anti-HPV-16/18 antibodies in vaccinees by applying three statistical models using immunogenicity data from vaccinated women with serum samples collected up to 6.4 years after first vaccination. Two different data lock-points (up to 5.5 years and up to 6.4 years) were used to assess the robustness of the models.

Methods. Three statistical models were applied to estimate the long-term persistence of anti-HPV-16/18 antibodies in 393 women vaccinated with the AS04-adjuvanted HPV-16/18 vaccine. Individual antibody levels for each study participant at each timepoint up to 6.4 years were input to previously published power-law and modified power-law models. The power-law model estimates antibody decay over time. The modified power-

Results:

- ❖ HPV-16 and -18 antibodies peaked at Month 7 and gradually plateaued at Months 18-24 and remained stable through 6.4 years
- ❖ Mean antibody levels at the last time point were several fold higher than those associated with natural infection.
- ❖ The study predict that HPV-16 and -18 mean antibody levels will remain well above those associated with natural infection for at least 20 years

Vaccine safety



All vaccines use virus-like particles (VLPs) which mimic the viral capsid.

VLPs do not contain genetic material and are produced in biologic systems, which have well-established safety records



Quadrivalent vaccine (Gardasil)



Prelicensure trial data

The safety profile of the quadri valent vaccine was evaluated in diverse populations of females from resource-rich and resource-limited settings .

Mild injection site reactions were the most commonly observed adverse events

The safety profile of quadrivalent vaccine in males was reported to be similar to that of studies in females

Postlicensure data

- ❖ In the U.S, adverse events following immunization are collected and analyzed within the Vaccine Adverse Event Reporting System (VAERS)
- ❖ Adverse events following HPV vaccine are compared with background rates following other immunizations.
- ❖ Between June 2006 and March 2013, approximately 57 million doses of quadrivalent HPV vaccines were distributed
- ❖ Reports of adverse events to VAERS have been consistent with the pre-licensure data:
 - ❖ From 2006 to 2013, VAERS received 21,194 reports of adverse events following HPV immunization among females. The vast majority (92 %) were considered mild. The proportion of events reported as serious peaked in 2008

- ❖ Among serious events, headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness were the most frequently reported.
- ❖ There is no increased risk of Guillain-Barré Syndrome compared with other vaccines in similar age groups
- ❖ Through 2011, 72 post-vaccination deaths had been reported, of which 34 were confirmed. There was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine

- ❖ VTE rates reported to the VAERS were higher for quadrivalent vaccine than other vaccines, of the 31 patients with thromboembolism reported through 2008, 90 % had a known risk factor (ie, estrogen-containing birth control pills or a family history of clotting disorder)
- ❖ Anaphylaxis had also been reported following administration of the quadrivalent vaccine

PubMed
Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials.
AUJoura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, Garland SM, Harper DM, Tang GW, Ferris DG, Steben M, Jones RW, Bryan J, Taddeo FJ, Bautista OM, Esser MT, Sings HL, Nelson M, Boslego JW, Sattler C, Barr E, Paavonen J
Lancet. 2007;369(9574):1693

9-valent vaccine (Gardasil 9)

In an analysis of seven trials in which over 15,000 individuals received at least one dose of the 9-valent vaccine, the most common adverse effects were:

1. mild or moderate injection site reactions (pain, erythema, and swelling) more frequently than with the quadrivalent vaccine.
2. systemic adverse effects (eg, headache, fever, nausea, dizziness) were similar with the 9-valent and quadrivalent vaccines.
3. Serious adverse effects occurred in <0.1 percent.



Bivalent vaccine (Cervarix)



In a phase III, multinational prospective, double-blind, placebo-controlled trial of more than 18,000 females aged 15 to 25 years, the vaccine was well tolerated and there were no differences in serious adverse events between vaccine and placebo recipients.

Because of low uptake of the bivalent vaccine in the U.S only sparse post-licensure data are available.

As of September 2011, there have been 52 VAERS reports of adverse events following administration of bivalent vaccine and the majority (98%) were considered non serious.

COST EFFECTIVENESS

Mathematical models have examined the cost effectiveness of HPV vaccination

One study suggested that vaccination of the entire United States population of 12-year-old girls would annually prevent

>200,000 HPV infections

100,000 abnormal cervical cytology examinations

3300 cases of cervical cancer if cervical cancer screening continued as currently recommended

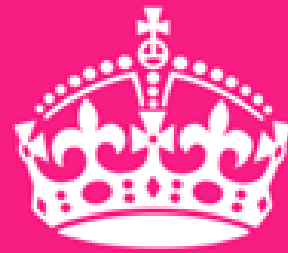


A small message to take her is

- ❖ -HPV vaccination appears to be safe and effective in preventing subsequent infection in older women, but the overall benefit is less than that in younger females
- ❖ -the need to vaccinate individuals before the onset of sexual activity to gain the greatest benefit and maximize cost effectiveness.



-None of the three vaccines treats or accelerates the clearance of pre-existing vaccine-type HPV infections or related disease.



**KEEP
CALM
AND
GET THE
HPV VACCINE**