Human papillomavirus vaccine trials and tribulations

Clinical perspectives

Marc Z. Handler, MD,[a] Nancy S. Handler, BA,[a,f] Slawomir Majewski, MD,[g] and Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP (Edin)[a,b,c,d,e]
Newark, New Jersey; Omaha, Nebraska; and Warsaw, Poland

Learning objectives
After completing this learning activity, participants should be able to state the recommended human papilloma virus immunization schedule for females and males; list the oncogenic and nononcogenic human papilloma virus types for which each of the three human papilloma virus vaccines provide immunity; and discuss the evidence that the human papilloma virus vaccination does not encourage unsafe sexual behavior in children and adolescents.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Human papillomavirus (HPV) affects hundreds of millions of people worldwide and is associated with both benign and malignant neoplasms in men and women. It is a double-stranded DNA virus with an icosahedral capsid. Forty HPV types are known to infect mucosal keratinocytes. If not cured by the immune system, the infection can lead to genital warts, mucosal dysplasia, or cancer. The most common oncogenic types are 16 and 18. The vaccine to prevent HPV and its associated morbidity and mortality has existed since 2006. Several variations protect against an increasing number of HPV types. The recommended vaccination age is before sexual exposure; administration of the vaccine to children has been controversial. This continuing medical education review evaluates the current HPV vaccines available to clinicians. Part I focuses on the debate over who should be vaccinated, at what age, and in which populations. (J Am Acad Dermatol 2015;73:743-56.)

Key words: anal cancer; Cervarix; cervical cancer; condylomas; Gardasil; human papillomavirus; vaccine.

INTRODUCTION

Key points

- **Not all human papillomaviruses are oncogenic**
- **Existing vaccines target human papillomavirus types that cause benign and oncogenic neoplasms**
- **Most human papillomavirus infections are suppressed by the body's immune system**

Human papillomavirus (HPV) is transmitted by skin-to-skin or mucosa-to-mucosa contact. There are >150 HPV types, with approximately 60% causing benign neoplasms (warts) on locations

From Dermatology,[a] Pathology,[b] Pediatrics,[c] and Preventive Medicine and Community Health,[d] Rutgers University New Jersey Medical School, and the School of Public Affairs and Administration,[e] Rutgers University, Newark; University of Nebraska Medical Center, College of Medicine, Omaha[f]; and the Department of Dermatology and Venereology,[g] Medical University of Warsaw.

Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication May 23, 2015.

Reprint requests: Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP (Edin), Department of Dermatology, Rutgers University New Jersey Medical School, 185 S Orange Ave, Newark, NJ 07103-2714. E-mail: roschwar@cal.berkeley.edu.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.05.040
Date of release: November 2015
Expiration date: November 2018

Abbreviations used:

AIN:	anal intraepithelial neoplasia
CDC:	Centers for Disease Control and Prevention
CHMP:	European Committee for Medicinal Products for Human Use
FDA:	US Food and Drug Administration
HPV:	human papillomavirus
MSM:	men who have sex with men
MSW:	men who have sex with women
OPSCC:	oropharyngeal squamous cell carcinoma
USPSTF:	US Preventive Services Task Force
VLP:	virus-like particle
SCCA:	squamous cell carcinoma of the anus

such as the hands and feet, and 40% that infect mucosal surfaces, including the genitals, anus, and oropharynx, usually by sexual activity.[1] Most HPV infections are asymptomatic; those affected are typically not aware that they have the virus. Each year, 14 to 20 million people in the United States are infected with the virus; 79 to 110 million Americans are currently infected.[2-4] While most HPV infections are resolved by the body's immune system and never result in human health problems, some people develop benign genital warts, while others, affected by specific oncogenic types of HPV, develop cancer of the cervix, oropharynx, anus, vulva, vagina, and penis.[2] In 2006, the US Food and Drug Administration (FDA) and the European Committee for Medicinal Products for Human Use (CHMP) approved the first HPV vaccine—a quadrivalent HPV vaccine—marketed as Gardasil (Merck and Co, Kenilworth, NJ). Gardasil targets oncogenic HPV types 16 and 18, as well as types 6 and 11, which produce genital warts. HPV type 16 causes about 50% of cervical cancers; HPV type 18 causes an additional 20% of cervical cancers.[5] In certain circumstances, HPV types 6 and 11 are responsible for condylomas that have the potential to become squamous cell carcinomas, such as Buschke–Lowenstein tumor,[6] oral florid papillomatosis,[7] and epithelioma cuniculatum.[8] Approved by Australia in May 2007, the CHMP in September 2007, and the FDA in October 2009, a bivalent HPV vaccine, marketed as Cervarix (GlaxoSmithKline, New York, NY), is designed to prevent infection from oncogenic HPV types 16 and 18 only.[1,9] On December 10, 2014, the FDA approved a 9-valent HPV vaccine for the prevention of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, which has been marketed as Gardasil-9 (Merck and Co; Fig 1).[11]

CERVICAL HUMAN PAPILLOMAVIRUS SCREENING

Key points

- **In the United States, it is recommended that women receive screening examinations for cervical dysplasia**
- **The Papanicolaou smear detects dysplasia of epithelial cells, not direct human papillomavirus infection**
- **Examination intervals may be extended from 3 to 5 years if a human papillomavirus test is added to the Papanicolaou smear**

The US Preventive Services Task Force (USPSTF) recommends that women between 21 and 65 years of age with a cervix be screened with a Papanicolaou (Pap) smear every 3 years, or every 5 years between 30 and 65 years of age, with a combination of a Pap smear and HPV testing, for cervical cancers and precancers.[12] Pap smears are performed at the recommended intervals in the majority of developed countries[13]; low- and middle-income countries (eg, India, China, South Africa, Nigeria, and Indonesia) do not have organized cervical cancer screening programs. Although it is unclear how representative California is with respect to Pap smears in the United States, a 2005 survey in California asked women if they had received a Pap smear in the previous 3 years. The results revealed that cervical cancer screening rates were similar among black, Hispanic, and non-Hispanic white women, with rates ranging from 74% to 80%. Asian American women had lower rates (60%) of screening in the previous 3 years.[14] Although screening raters are similar among the populations, treatment delay does exist for black women as compared to white or Hispanic women.[14-17]

HUMAN PAPILLOMAVIRUS EPIDEMIOLOGY

Key points

- **Human papillomavirus infection rates vary by country**
- **Infection by human papillomavirus is the most common sexually transmitted infection**
- **More than 600,000 cancers are attributed to human papillomavirus infection worldwide**

The worldwide HPV infection rate among women of all ages is 12%, with a peak of 24% among those who are tested after they become sexually active and who are also under 25 years of age.[18] The prevalence is highest among women in sub-Saharan Africa (24%), Central and Eastern Europe (21%), and the Caribbean (35.4%).[18] HPV infection is the most