



# Update on HPV Vaccination Policy, 2019

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Current Issues in Immunization Webinar

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# Changes in HPV vaccination policy, 2019

- Harmonization of catch-up recommendations through age 26 years for all persons
- Shared clinical decision-making for adults soon age 27 through 45 years

Morbidity and Mortality Weekly Report

## Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices

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### Introduction

Vaccination against human papillomavirus (HPV) is recommended to prevent new HPV infections and HPV-associated diseases, including some cancers. The Advisory Committee on Immunization Practices (ACIP)<sup>1</sup> routinely recommends HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-up vaccination has been recommended since 2006 for females through age 26 years, and since 2011 for males through age 21 years and certain special populations through age 26 years. This report updates ACIP catch-up HPV vaccination recommendations and guidance published in 2014, 2015, and 2016 (1–3). Routine recommendations for vaccination of adolescents have not changed. In June 2019, ACIP recommended catch-up HPV vaccination for all persons through age 26 years. ACIP did not recommend catch-up vaccination for all adults aged 27 through 45 years, but recognized that some persons who are not adequately vaccinated might be at risk for new HPV infection and might benefit from vaccination in this age range; therefore, ACIP recommended shared clinical decision-making regarding potential HPV vaccination for these persons.

### Background

HPV is a common sexually transmitted infection, with HPV acquisition generally occurring soon after first sexual activity (1). Most HPV infections are transient and asymptomatic. Persistent infections with high-risk (oncogenic) HPV types can lead to development of cervical, anal, penis, vaginal, vulvar, and oropharyngeal cancers, usually after several decades (1). Most

new HPV infections occur in adolescents and young adults. Although most sexually active adults have been exposed to HPV (4), new infections can occur with a new sex partner (5).

Three prophylactic HPV vaccines are licensed for use in the United States: 9-valent (9vHPV, Gardasil 9, Merck), quadrivalent (4vHPV, Gardasil, Merck), and bivalent (2vHPV, Cervarix, GlaxoSmithKline) (6–8). As of late 2016, only 9vHPV is distributed in the United States. The majority of HPV-associated cancers are caused by HPV 16 or 18, types targeted by all three vaccines. In addition, 4vHPV and 9vHPV target HPV 6 and 11, types that cause anogenital warts. 9vHPV also protects against five additional high-risk types: HPV 31, 33, 45, 52, and 58.

In October 2018, using results from 4vHPV clinical trials in women aged 24 through 45 years, and bridging immunogenicity and safety data in women and men, the Food and Drug Administration expanded the approved age range for 9vHPV use from 9 through 26 years to 9 through 45 years in women and men (6). In June 2019, after reviewing evidence related to HPV vaccination of adults, ACIP updated recommendations for catch-up vaccination and for vaccination of adults older than the recommended catch-up age.

### Methods

During April 2018–June 2019, the ACIP HPV Vaccines Work Group held at least monthly conference calls to review and discuss relevant scientific evidence regarding adult HPV vaccination using the Evidence to Recommendations framework (<https://www.cdc.gov/vaccines/acip/recs/grade/downloads/ACIP-evidence-rec-frame-508.pdf>). The Work Group evaluated the quality of evidence for efficacy, safety, and effectiveness for HPV vaccination for primary prevention of HPV infection and HPV-related disease using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (<https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html>).

Scientific literature published during January 1, 2006–October 18, 2018, was searched to identify clinical trials of any licensed HPV vaccine in adults aged 27 through 45 years. Detailed search methods and results for the GRADE tables are available at <https://www.cdc.gov/vaccines/acip/recs/grade/HPV-adults.html>. Benefits were based on per-protocol analyses

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# Recommendations for HPV vaccination in the United States - before June 26, 2019

- **Routine vaccination**
  - Age 11 or 12 years
  - Vaccination can be started at age 9 years
- **Catch-up vaccination**
  - Females through age 26 years
  - Males through age 21 years
  - Certain populations through age 26 years\*
- **Males aged 22 through 26 years may be vaccinated**

\*Men who have sex with men, transgender persons, and persons with certain immunocompromising conditions  
MMWR 2014;63 (RR05) MMWR 2015;64:300-4 MMWR 2016; 65:2105-8

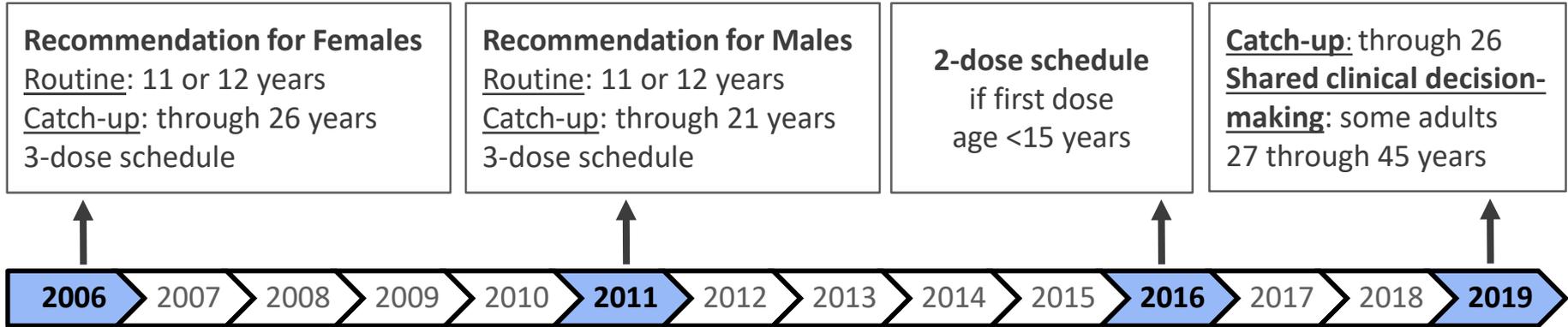
# Current recommendations for HPV vaccination in the United States

- **Routine vaccination**
  - Age 11 or 12 years
  - Vaccination can be started at age 9 years
- **Catch-up vaccination**
  - Through age 26 years, if not adequately vaccinated

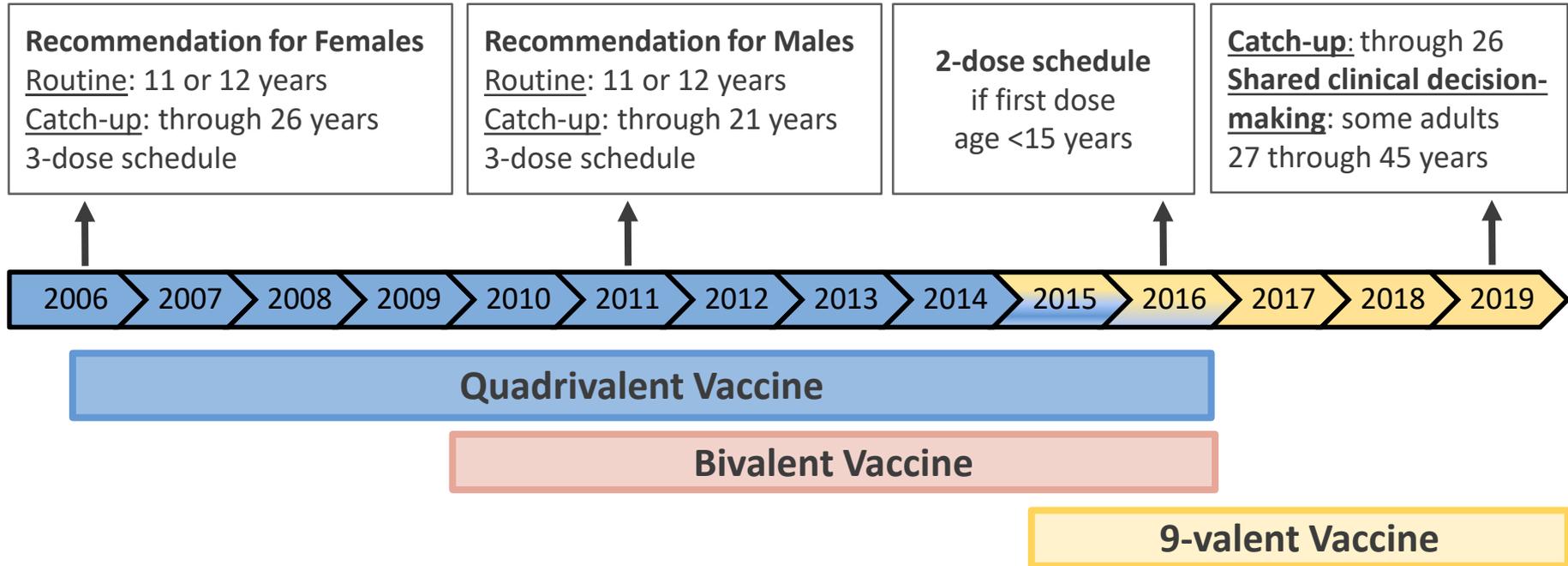
# Current recommendations for HPV vaccination in the United States

- **Routine vaccination**
  - Age 11 or 12 years
  - Vaccination can be started at age 9 years
- **Catch-up vaccination**
  - Through age 26 years, if not adequately vaccinated
- **Shared clinical decision-making**
  - Some adults age 27 through 45 years, if not adequately vaccinated

# Evolution of HPV vaccination recommendations – United States



# Evolution of HPV vaccination recommendations, vaccine availability and use – United States



# HPV vaccines licensed and age ranges, United States

## Before October 2018

Vaccine	HPV types	Licensure ages
Bivalent (2vHPV)	16,18	Females 9–25 yrs
Quadrivalent (4vHPV)	6,11,16,18	Females and males 9–26 yrs
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	Females and males 9–26 yrs

- After the end of 2016, only 9vHPV has been distributed in the United States
- In April 2018, 9vHPV manufacturer filed an application to expand age indication through age 45 years

# HPV vaccines licensed and age ranges, United States

## Since October 2018

Vaccine	HPV types	Licensure ages
Bivalent (2vHPV)	16,18	Females 9–25 yrs
Quadrivalent (4vHPV)	6,11,16,18	Females and males 9–26 yrs
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	<b>Females and males 9–45 yrs</b>

- After the end of 2016, only 9vHPV has been distributed in the United States
- HPV vaccines have been licensed through age 45 years or older in other countries

# Licensure of 9vHPV for use in expanded age range

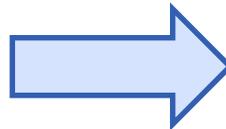
## FDA Summary Basis for Regulatory Action

- Results of a randomized, double-blind, placebo-controlled trial (base study) of 4vHPV that included women aged 27–45 years
- Observational follow-up through 10 years in a subset of women in the base study
- A cross-study immunogenicity analysis showing non-inferiority of immune responses to 4vHPV in males aged 27–45 years vs aged 16–26 years
- Extrapolation of data to 9vHPV in individuals aged 27–45 years

# ACIP uses *Evidence to Recommendations* framework

## Evidence to Recommendations Framework

- PICO question and background
- Problem
- Benefits and harms
- Values
- Acceptability
- Resource use
- Feasibility of implementation
- Balance of consequences
- Type of recommendation and recommendation text



Recommendation options

PICO: population, intervention, comparison, outcomes

<https://www.cdc.gov/vaccines/acip/recs/grade/downloads/ACIP-evidence-rec-frame-508.pdf>

# *Evidence to Recommendations: Benefits and Harms*

- 4vHPV efficacy trial in women ages 24–45 years (n=3,819)
  - Efficacy against endpoint of persistent HPV infection, extragenital lesions, CIN1+
    - Per-protocol efficacy: **88.7%** (95% CI: 78.1–94.8)
    - Intention-to-treat efficacy: **47.2%** (95% CI: 33.5–58.2)
- 9vHPV immunogenicity trial in women ages 27–45 years (n=640)
  - Antibody titers non-inferior compared to women ages 16–26 years
  - >99% of women in both age groups seroconverted to all 9vHPV types

Castellsagué X et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011

Luxembourg A. 9vHPV immunogenicity and safety trial in mid-adult females. Presentation to ACIP, Atlanta, GA. June 26, 2019.

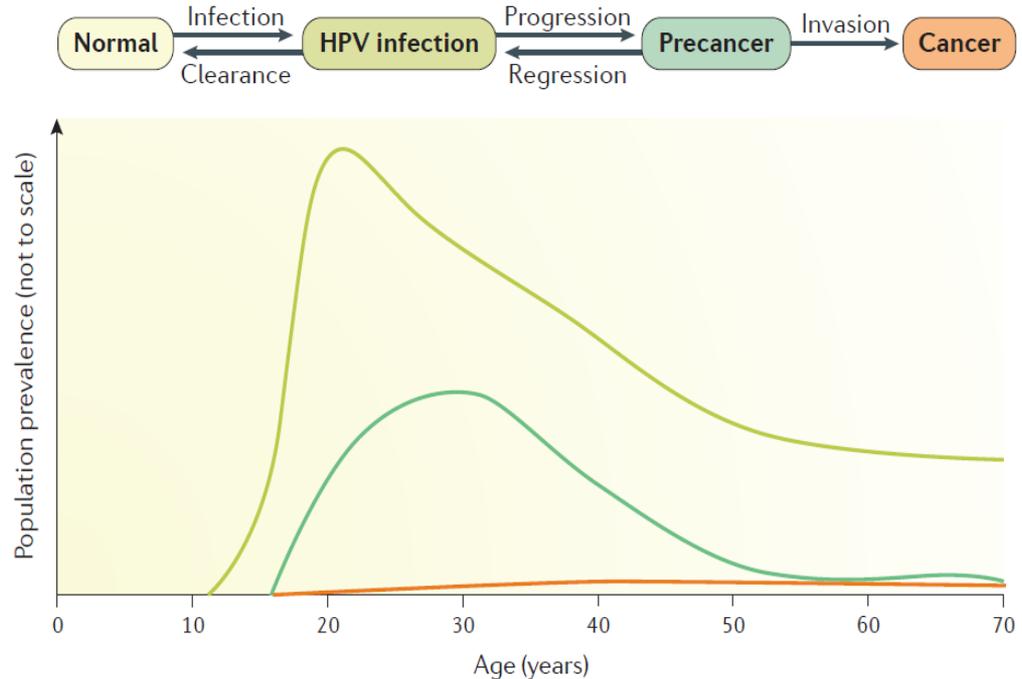
CIN, cervical intraepithelial neoplasia

# ***Evidence to Recommendations: Benefits and Harms***

- Evidence on benefits:
  - Efficacy: 3 RCTs of 4vHPV and/or 2vHPV
  - Immunogenicity: 3 RCTs, 6 observational trials
- Evidence on harms:
  - Safety: 5 RCTs, 4 observational trials

# Conceptual model of HPV infection leading to cervical cancer

- First HPV infection occurs soon after onset of sexual activity
- HPV infection highest in late teens/early 20s
- Most infections clear or become undetectable within 1-2 years
- Many precancers clear
- Precancers can progress to cancer after many years/decades



# Understanding the burden of disease due to incident HPV infection in adults

- HPV incidence highest in late teens and early twenties
- New HPV infections do occur in mid-adults
  - New partner is risk factor; new partners decrease with increasing age
- Epidemiology of HPV infection differs for males and females
- Some uncertainty about immunity after clearance of natural infection
  - Immunity thought to be low; higher for females than males
- Progression to cancer occurs over years/decades
  - Some high risk HPV types more likely to progress to cancer

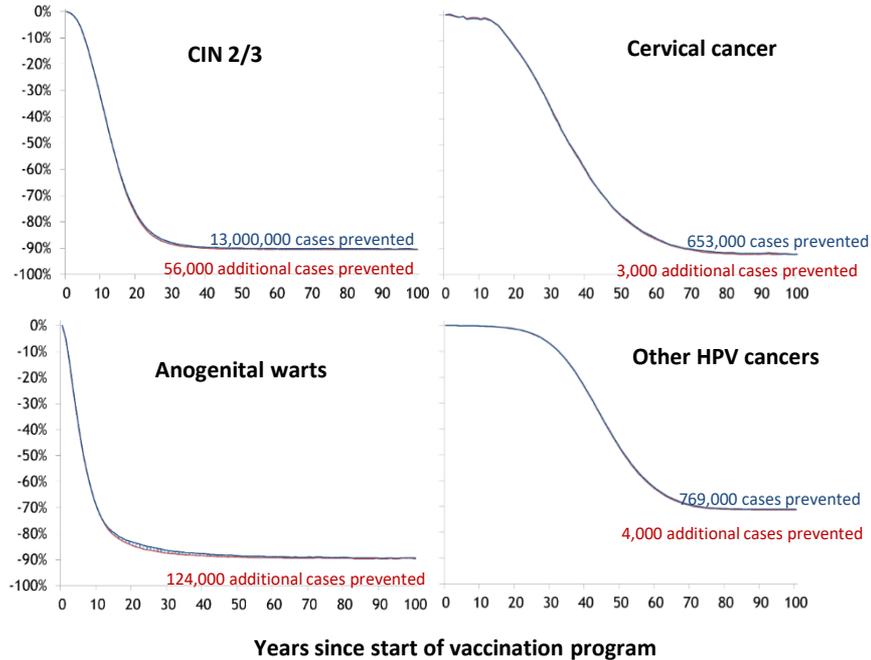
# *Evidence to Recommendations: Resource use*

- **5 health economic models of HPV vaccination in the U.S. were reviewed**
  - The cost-effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about \$35,000 per QALY gained
  - In the context of the existing program, expanding vaccination through age 30, 35, 40 or 45 years would provide relatively small additional health benefits
  - The incremental cost per QALY for also vaccinating adults through age 30 years exceeded \$300,000 in 4 of 5 models
  - Variation in results across models was due to factors such as uncertainties about HPV natural history

# Estimated impact of HPV vaccination: HPV-ADVISE results

Current recommendation

Current recommendation plus adults through age 45 years



- In the context of the existing HPV vaccination program, expanding vaccination to adults through age 45 years would produce relatively small additional health benefits and less favorable cost-effectiveness ratios

# Estimated number needed to vaccinate

- HPV vaccines are most effective when given before exposure to HPV
- Population benefit would be minimal, yet some individuals in this age range might be able to benefit from vaccination
- Estimated number needed to vaccinate (NNV) to prevent one case of **anogenital warts, cervical precancer, or cancer**, is:

NNV with existing vaccination  
program

**9, 22, and 202**

NNV with vaccination through age  
45 years

**120, 800, and 6,500**

# Evidence to Recommendations framework

## Evidence to Recommendations Framework

- PICO question and background
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## ▪ Recommendation options

- Recommend the intervention
- Recommend for individuals based on *shared clinical decision-making* (formerly “permissive” or Category B)
- Do not recommend the intervention

# Types of ACIP recommendations

ACIP does not recommend the intervention

Vaccination is not recommended

ACIP recommends intervention for individuals based on shared clinical decision-making

Recommendation relies upon guidance of clinician in the context of individual clinician-patient interactions to determine whether or not vaccination is appropriate for a patient

ACIP recommends the intervention

Vaccination recommended for all persons in the age group or group at increased risk for vaccine preventable disease

# Changing ACIP terminology over time for similar type of recommendation

## Permissive Recommendation

- 2009 HPV vaccine for boys

“HPV4 may be given to males aged 9 through 26 years...”

## Category B Rec/ Clinical Decision Making

- 2015 Men B for adolescents and young adults

“...adolescents and young adults may be vaccinated with a serogroup B meningococcal (MenB) vaccine...”

## Shared Clinical Decision-Making

- 2019 HPV vaccine for adults age 27-45 years

“...shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated”

# Routine HPV vaccination of adults 27 through 45 years was not brought to ACIP for consideration

ACIP does not recommend the intervention

Vaccination is not recommended

ACIP recommends intervention for individuals based on shared clinical decision-making

Recommendation relies upon guidance of clinician in the context of individual clinician-patient interactions to determine whether or not vaccination is appropriate for a patient

~~ACIP recommends the intervention~~

~~Vaccination recommended for all persons in the age group or group at increased risk for vaccine preventable disease~~

# Shared clinical decision-making

- Shared clinical decision making category addresses situations where
  - vaccination may benefit some individuals, but
  - will have relatively minimal population-level impact

Identifying who will benefit from vaccination is not always straight forward

# Shared clinical decision-making for HPV vaccination of adults age 27 through 45 years

- HPV vaccination does not need to be discussed with most adults aged >26 years
- For adults aged 27 through 45 years who are not adequately vaccinated, clinicians can consider discussing HPV vaccination with persons who are most likely to benefit
- Ideally, vaccination should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity

# Considerations for shared clinical decision-making for HPV vaccination of adults age 27 through 45 years

- HPV is a very common sexually transmitted infection. Most HPV infections are transient and asymptomatic and cause no clinical problems.
- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.
- Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.
- Most sexually active adults have been exposed to some HPV types, although not necessarily all of the HPV types targeted by vaccination.
- No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.

# Considerations for shared clinical decision-making for HPV vaccination of adults age 27 through 45 years (con't)

- HPV vaccine efficacy is high among persons who have not been exposed to vaccine-type HPV before vaccination.
- Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (e.g., adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.
- HPV vaccines are prophylactic (i.e., they prevent new HPV infections). They do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

# 2020 Adult Immunization Schedule – Draft

**Table 1** Recommended Adult Immunization Schedule by Age Group  
United States, 2020

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV) <b>or</b> Influenza live attenuated (LAIV)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td or Tdap booster every 10 yrs			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV) (preferred) <b>or</b> Zoster live (ZVL)			2 doses <b>or</b> 1 dose	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination	27 through 45 years		
Pneumococcal conjugate (PCV13)	1 dose			65 years and older
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication			1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2 or 3 doses depending on vaccine			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	19 through 23 years	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations		
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

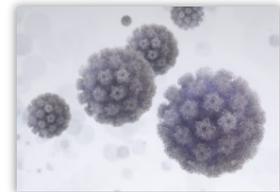
Recommended vaccination for adults with an additional risk factor or another indication

Recommended based on shared clinical decision-making

No recommendation/ Not applicable

# Other recommendations have not changed

- **Administration.** Dosing schedules, intervals, and definitions of persons considered adequately vaccinated have not changed.
- **No prevaccination testing** (e.g., Pap or HPV testing) is recommended to establish the appropriateness of HPV vaccination.
- **Cervical cancer screening.** Cervical cancer screening guidelines and recommendations should be followed.  
<https://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf>
- **Pregnancy.** For persons who are pregnant, HPV vaccination should be delayed until after pregnancy; however, pregnancy testing is not needed before vaccination.

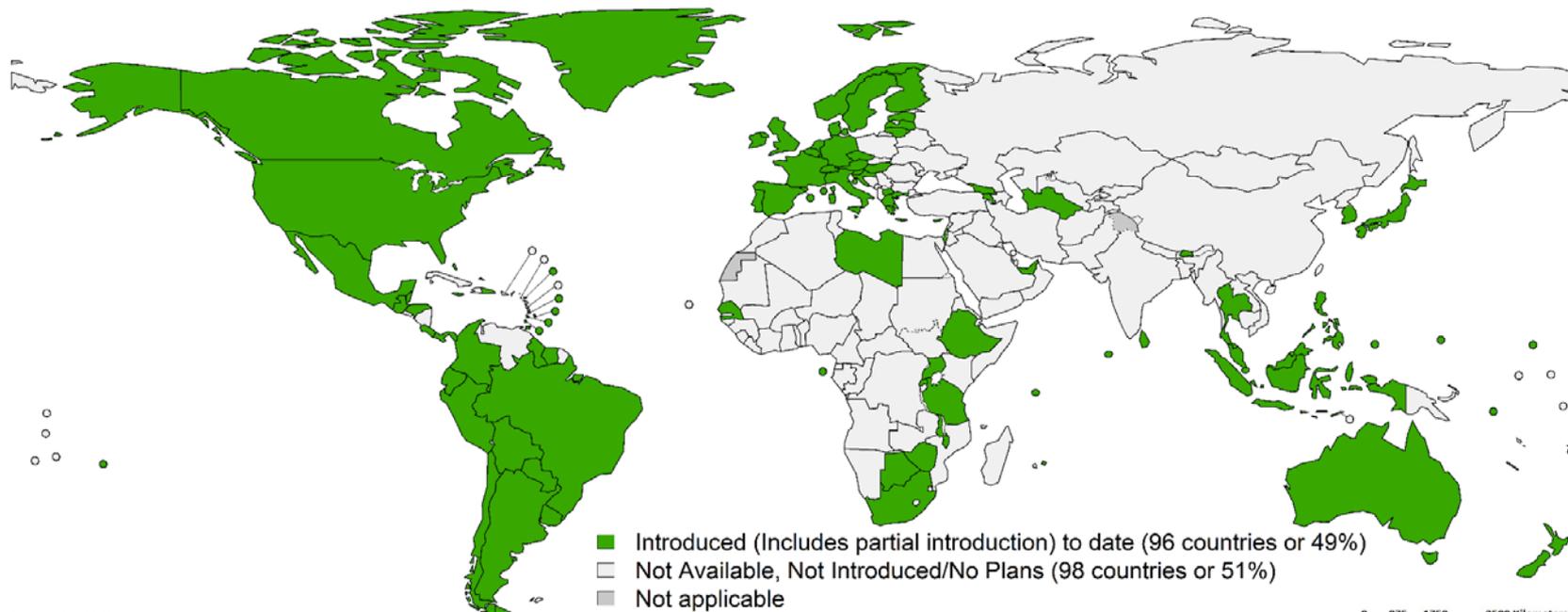


# Recommended number of HPV vaccine doses and dosing schedule, United States

Population	Number of vaccine doses	Interval between doses
Persons initiating vaccination at <b>9 through 14</b> years, except immunocompromised persons	2	0, 6–12 months
Persons in the recommended age groups initiating vaccination at <b>age 15 or older</b> and persons with immunocompromising conditions	3	0, 1–2, 6 months

- No maximum interval between doses; schedule does not need to be restarted if there is longer than recommended number of months between doses

# Countries with HPV vaccine in the national immunization program, 2019



Date of slide: 2019-08-03

Map production: Immunization, Vaccines and Biologicals (IVB), World Health Organization(WHO)

Data source: IVB database as at 3rd June 2019

## Disclaimer:

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area nor of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.  
World Health Organization, WHO, 2019. All rights reserved

# Current global HPV vaccine demand/supply imbalance

- **World Health Organization recommendations**
  - 2009 - HPV vaccination of girls for single age cohort of girls
  - 2016 - Multi-age cohort vaccination (age 9-14 years in first year)
    - Increased vaccine demand
- **HPV vaccine demand/supply imbalance**
  - Projected to last 3-5 years
  - Delay introduction in some countries
  - Prevent multi-age cohort vaccination
- **No HPV vaccine shortage anticipated in United States**
- **WHO has issued recommendations for more equitable, global allocation of the limited HPV vaccine supply**

**World Health Organization** **IMA**  
IMPROVED ECONOMICS FOR ACCESS TO VACCINES

**GLOBAL MARKET STUDY**  
HPV

**Key Takeaways**

- Twelve years after the first HPV vaccine registration, less than half of WHO Member States have introduced HPV vaccine into the routine national immunization schedule. Introductions are lowest in Gavi countries and non-Gavi, non-PRHO middle-income countries (MICs)
- Supply is currently insufficient to meet demand and some countries have or will have to postpone introductions
- WHO issued a call for action towards global cervical cancer elimination in May 2018 which, through national introductions in all countries and increased coverage, is estimated to increase total demand for HPV vaccines by at least 100M doses over the next 10 years
- To meet the expected increase in demand due to the cervical cancer elimination initiative, sizeable increases in supply will be required. Constraints are expected until at least 2024, assuming the base case supply scenario. This timing may change depending on selected vaccination strategies and investment decisions of current manufacturers, as well as on the timing of the three products in advanced stages of clinical development
- Meeting the projected demand volumes required for multi-age cohort (MAC) introductions (9-14 years of age), as per WHO recommendation, will remain especially problematic in large countries, as well as meeting additional demand generated by implementing gender-neutral HPV vaccination
- Affordability of HPV vaccines in non-Gavi MICs is a barrier which needs to be addressed to encourage introduction

**QUICK STATS**

**NUMBER OF VACCINE SUBTYPES<sup>1</sup>**  
3

**TOTAL NUMBER OF MANUFACTURERS<sup>2</sup>**  
2

**2018 ESTIMATED GLOBAL SUPPLY**  
~30 million doses (maximum)

**2018 ESTIMATED GLOBAL DEMAND**  
~30 million doses (supply constrained)

**2017 REPORTED PRICE PER DOSE (DOLLARS)**  
US \$450-\$154.28

**Purpose & Background**

Several countries across regions and income groups have notified WHO of constraints to their access of HPV vaccines. The issue of affordability has also been raised, particularly by non-Gavi MICs. Following the announcement of a call for action towards global elimination of cervical cancer by the WHO Director General in May 2018, increasing introduction and coverage of HPV vaccine worldwide will be key. Working to understand current and future global trends and drivers of supply and demand, this study aims to address the current and expected constraints and to

serve as an important resource for the development of the cervical cancer elimination strategy.

**Market Highlights**

As of May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV into the national routine immunization schedule.<sup>3</sup> Despite carrying the greatest share of disease burden, LICs and MICs are lagging in the introduction of HPV vaccine. To date, the majority of the countries have self-procured HPV vaccines (74% in 2017).

<sup>1</sup> Vaccine Subtypes differentiated by the antigen content of the various HPV vaccines. In this case there are three distinct vaccine sub-types available on the market: HPV2 (1,16), HPV4 (6, 11, 16, 18) and HPV9 (6, 11, 16, 18, 31, 33, 45, 52, 58)

<sup>2</sup> This number includes only the companies that have full manufacturing capacity and does not include formalized companies providing a portion of the manufacturing process or distributors that simply commercialize the product in some locations

<sup>3</sup> WHO Data, as of 15 May 2018

<sup>4</sup> HPV area (all countries) report, Source: IMA, Globvacc data, 2012

WORLD HEALTH ORGANIZATION / GLOBAL MARKET STUDY 1 September 2018

# Summary

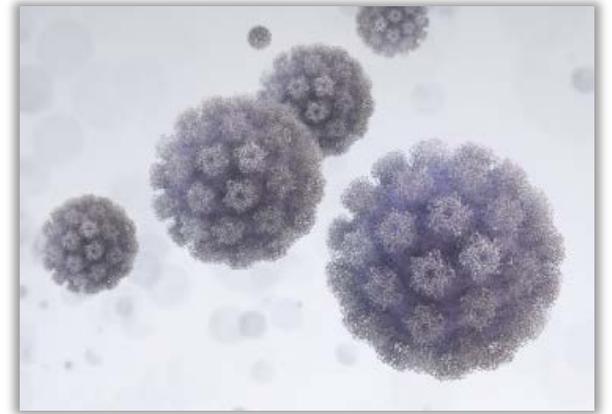


- Adolescents remain the focus of US HPV vaccination program.
- HPV vaccination is most effective when given before exposure to any HPV
- Changes in recommendations in 2019 include:
- Catch-up harmonized across genders through age 26 years.
  - Simplifies the immunization schedule and may be more feasible to implement.
- Shared clinical decision-making for some persons aged 27 through 45 years.
  - Providers do not need to discuss HPV vaccination with most adults > age 26 years.
  - CDC is not actively promoting vaccination of adults > 26 years.

# Future considerations

- ACIP reviews relevant data as they become available and updates vaccine policy as needed.

**Questions?**



# Thank You

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



# Vaccine regulatory approval and recommendations

