

# Vaccines: Science & Application

Gary A. Richwald, MD, MPH

Communicable Disease Specialist

Clinical Virologist

Consultant in HSV & HPV Infections,

American Social Health Association

# Vaccine Preparations

## *Live Attenuated Vaccines*

- Uses weakened form of pathogen, which elicits an immune response
- Compared to inactivated vaccines, have higher rates of adverse effects and longer lasting immunity
- Examples: Herpes Zoster, Intranasal Influenza

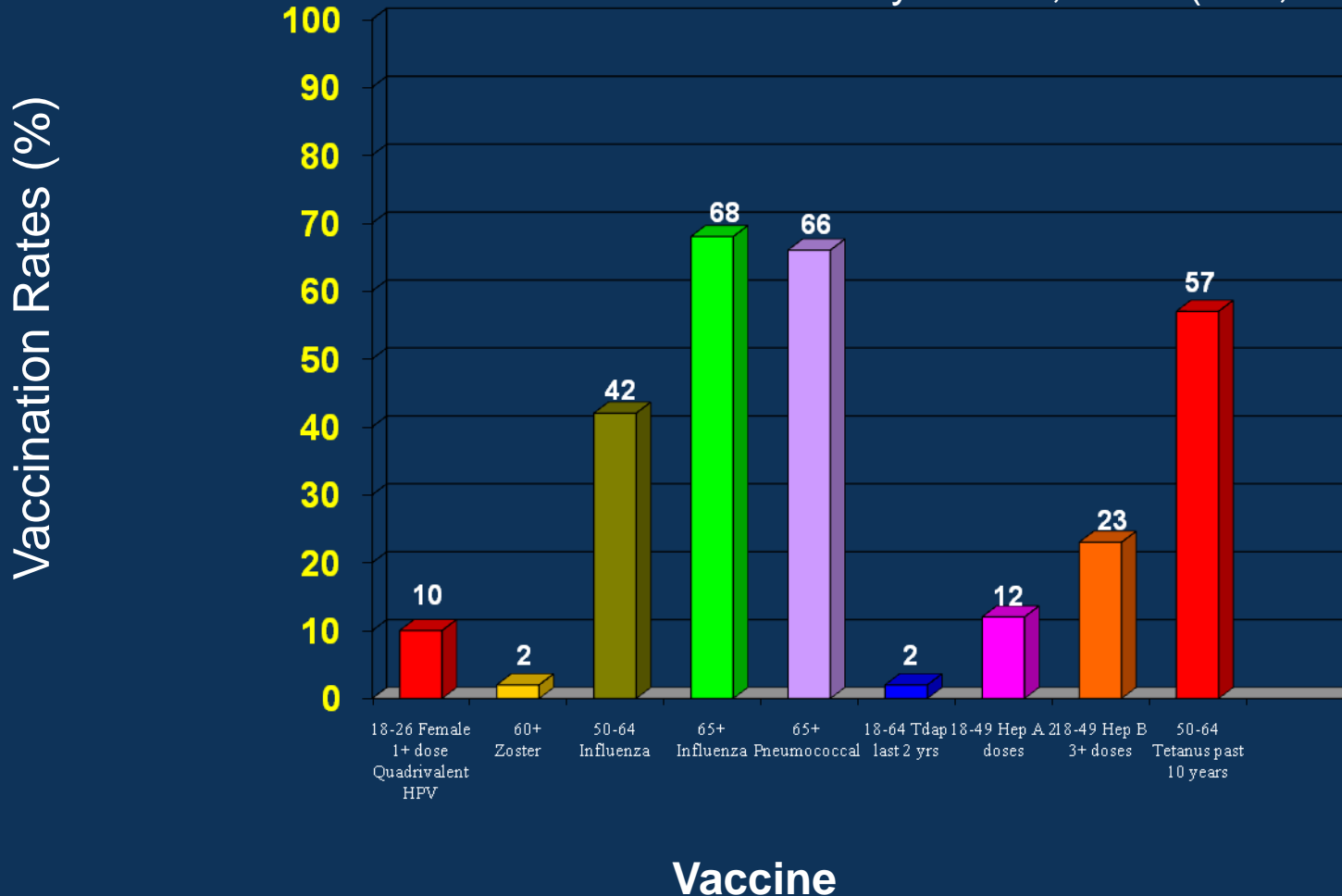
# Vaccine Preparations

## *Inactivated Vaccines*

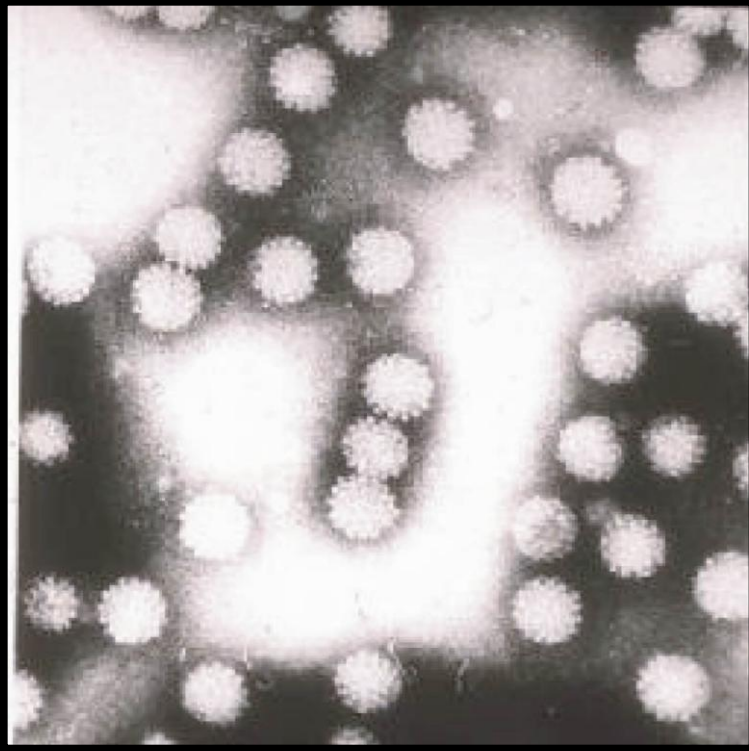
- Prepared from whole pathogen (bacteria or virus), part of a microbiologic protein or inactivated bacterial toxins (toxoids)
- Compared to live attenuated vaccines, may be less immunogenic, especially polysaccharide-based vaccines
- Can require multiple shots (series) with deep intramuscular injection
- Examples: Whole pathogen: Hepatitis A  
Polysaccharide: Pneumococcal  
Protein: HPV, Influenza, Pertussis,  
Tetanus, Diphtheria, Hepatitis B

# Adults Often Fail to Receive Recommended Vaccinations

Vaccination coverage among United States adults  
National Immunization Survey –Adult, 2007 (n=7,055)



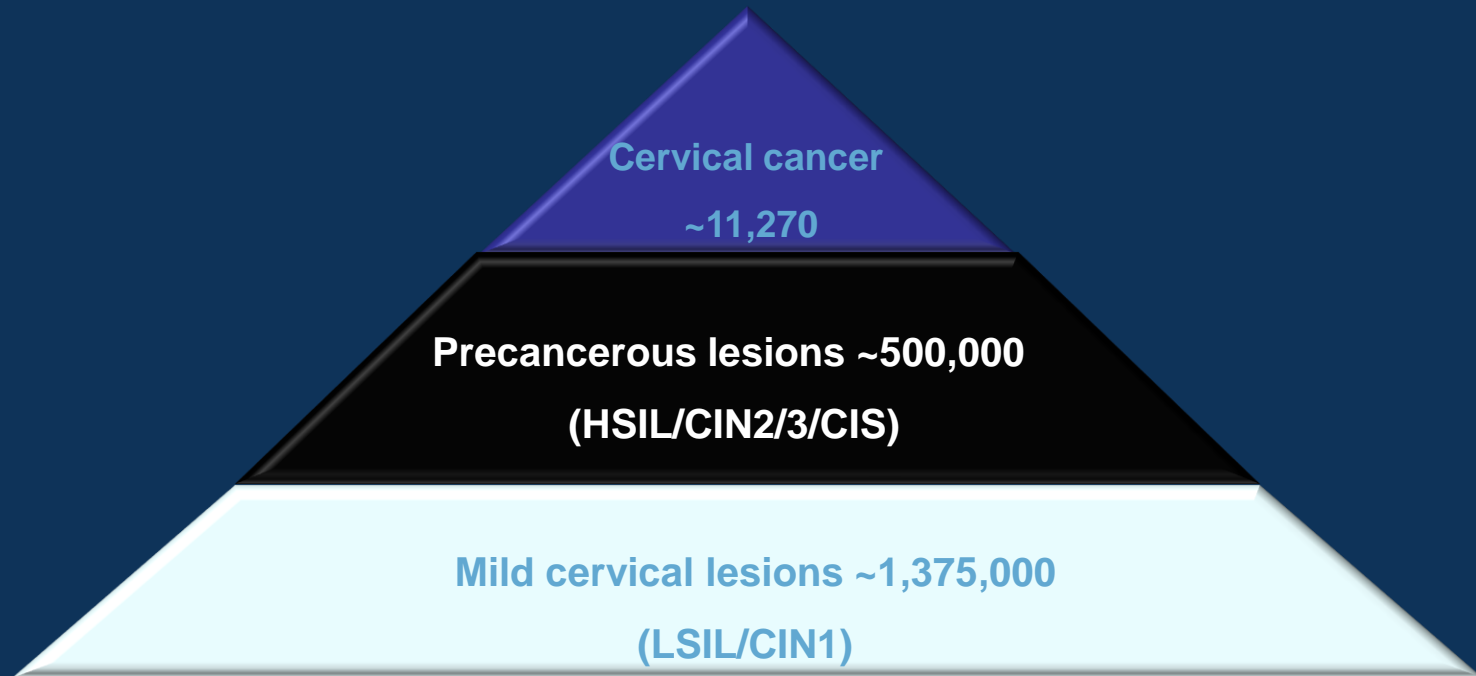
# Human Papillomavirus (HPV)



- ~100 HPV types have been identified that infect humans
- Of these, 13-15 are oncogenic and, therefore, may cause cervical cancer
- HPV infection is common; as many as 80% of all women will acquire an HPV infection by 50 years of age

# Cervical Abnormalities in the United States

## Estimated Number of Cases Per Year



HSIL=high-grade SIL; LSIL=low-grade SIL; CIN=cervical intraepithelial neoplasia; CIS=carcinoma in situ

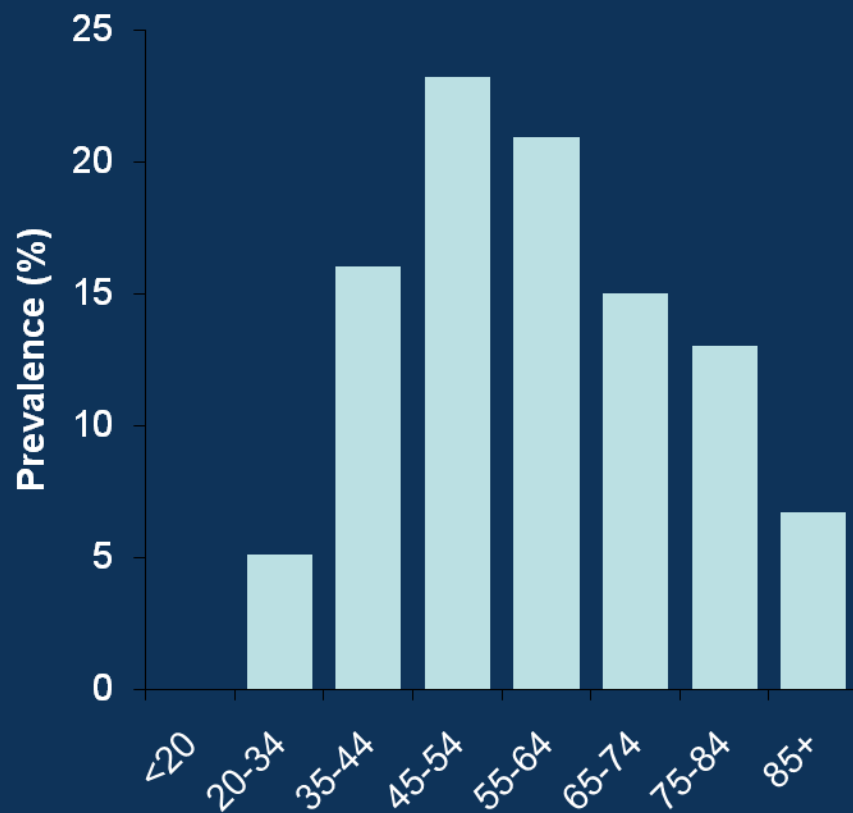
Schiffman M, et al. *Arch Pathol Lab Med.* 2003;127:946–949.

Saslow D, et al. *CA Cancer J Clin.* 2007;57:7-28.

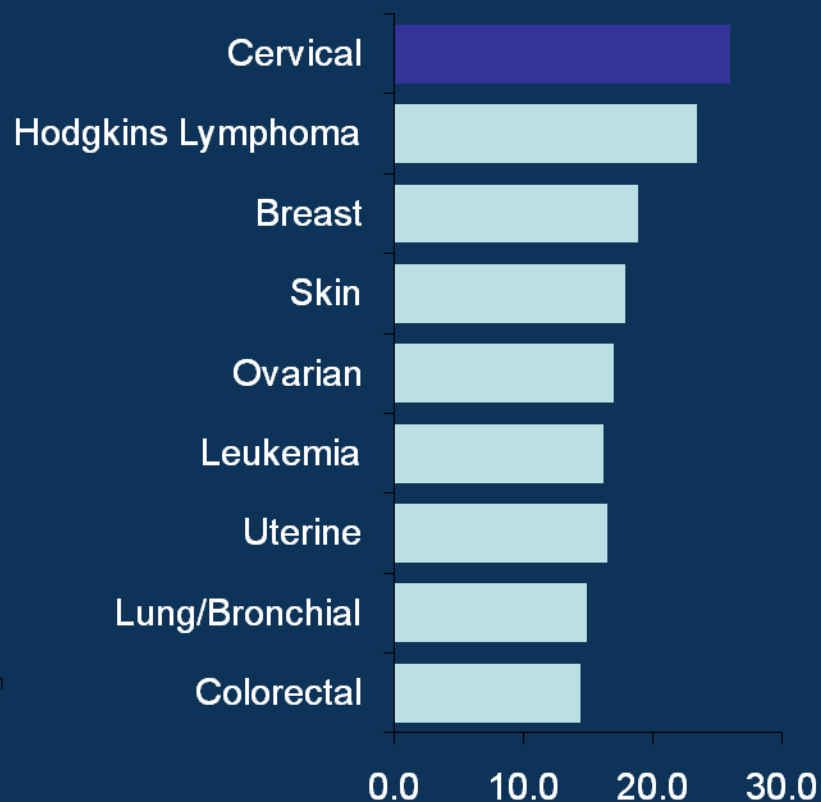
American Cancer Society. *Cancer Facts & Figures 2009.* Atlanta: 2009.

# Years of Life Lost Due to Cervical Cancer

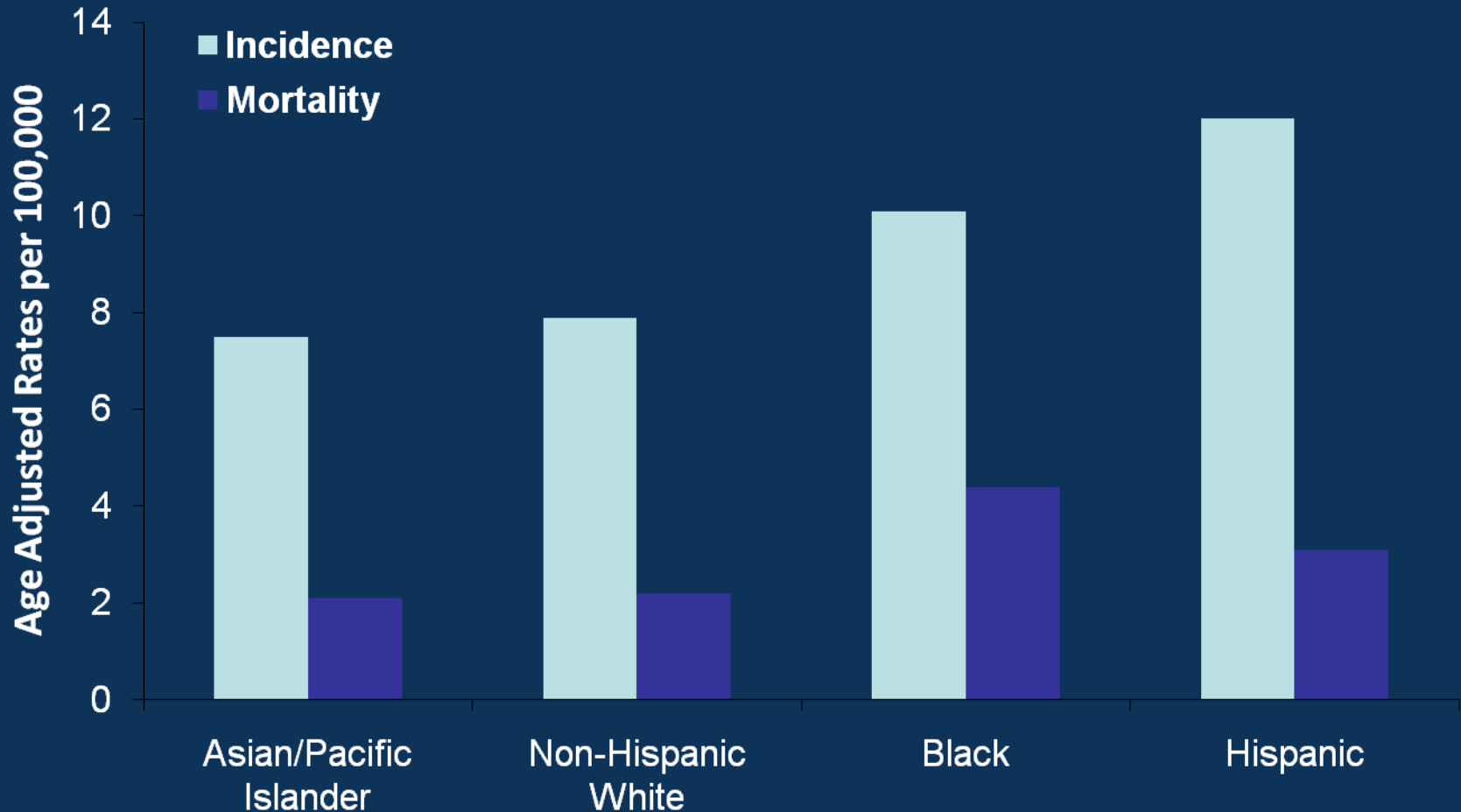
The median age at death is 48 years



The estimated life lost for each woman who dies of cervical cancer is 26 years



# Cervical Cancer Incidence and Mortality Rates by Race/Ethnicity, United States, 2003-2007



# Characteristics of HPV Vaccines for Females

Characteristic	HPV 4	HPV 2
Manufacturer	Merck & Co, Inc.	GlaxoSmithKline
Vaccine composition	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	20 µg HPV 16 20 µg HPV 18
Manufacturing	Bread Yeast (Saccharomyces)	Insect Cells (baculovirus)
Adjuvant	225 µg aluminum hydroxyphosphate sulfate	500 µg aluminum hydroxide with 50 µg 3-deacylated monophosphoryl lipid A (AS04)
Preservatives	None	None

# Efficacy of HPV 2 and HPV 4 in Females: CIN 2/3 or AIS

Vaccine/Endpoint/HPV Type	Vaccine Efficacy (confidence intervals)
<b>Bivalent vaccine (HPV 2)</b>	
CIN 2/3 or AIS	
HPV 16 and/or 18	92.9 (79.9-98.3)
HPV 16	95.7 (82.9-99.6)
HPV 18	86.7 (39.7-98.7)
<b>Quadrivalent Vaccine (HPV 4)</b>	
CIN 2/3 or AIS	
HPV 16 and/or 18	98.2 (93.3-99.8)
HPV 16	97.6 (91.1-99.7)
HPV 18	100.0 (86.6-100.0)

AIS=adenocarcinoma in situ

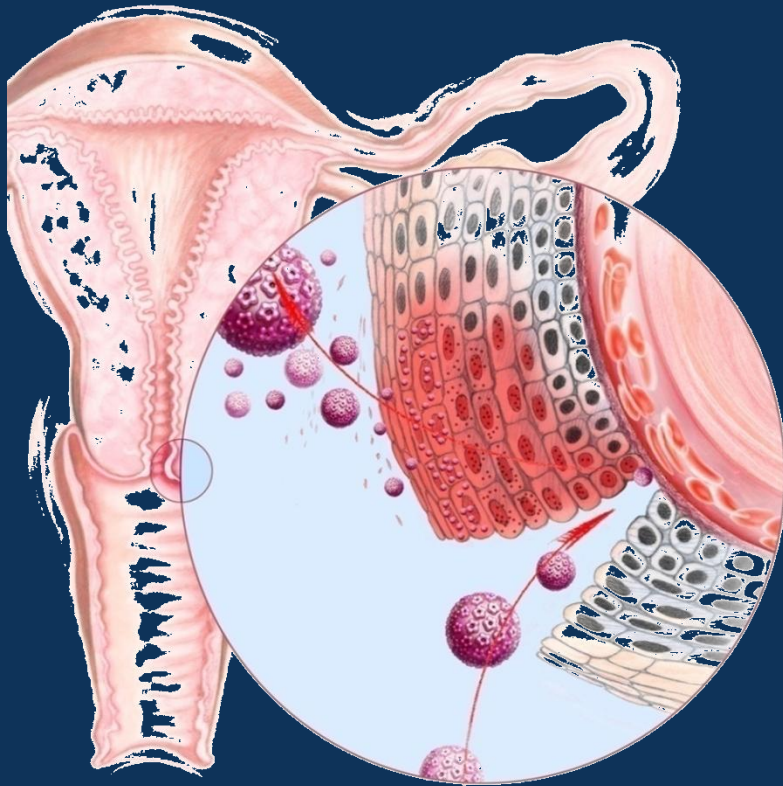
MMWR. May 28, 2010;59:626-629. FDA. Product approval-prescribing information [current package inserts]. HPV 4 and HPV 2 vaccines.

# HPV Vaccine Indications

## ACIP, May 2010

- Routine vaccination of females ages 11-12, ideally before sexual debut
- As early as age 9, also recommended for unvaccinated ages 13-26
- For women with previous cervical abnormalities or genital warts, vaccine may have reduced benefits. Vaccine still recommended for prevention of HPV vaccine types not already acquired
- Pre-vaccination assessments are not recommended at any age (e.g., Pap, HPV, and pregnancy tests)
- No therapeutic effect of HPV vaccination

# The Benefits of Vaccinating Younger-aged Females



**Transformation zone**

- In young females, the transformation zone of the cervix is particularly vulnerable to HPV infection, and is the most common site for cervical cancer development
- HPV infection is most prevalent in females <25 years of age; therefore, vaccination should be prior to sexual debut
- Induced neutralizing antibodies are higher in younger girls (10-14 years), as compared with 15-25 year olds

Moscicki AB. *J Adolesc Health*. 2005;37(6 Suppl)S3-S9.

Dunne EF, et al. *JAMA*. 2007;297:813-819.

Castle PE, et al. *Cancer Res*. 2006;66:1218-1224.

# HPV Vaccine Administration

## ACIP, May 2010

### 0.5 mL administered as IM injection in deltoid muscle

- 1 inch needle for female/male <130 lbs
- 1-1.5 inch needle for females 130-200 lbs and males 130-260 lbs
- 1.5 inch needle for females >200 lbs
- Using too short a needle may cause inadequate immune response



# HPV Vaccine Special Situations

## ACIP, May 2010

- HPV 2 and HPV 4 are not live vaccines and are recommended for immunosuppressed persons. Efficacy likely attenuated

- **Co-administration with other vaccines**

Permitted simultaneously or at any time before or after HPV vaccine

Simultaneous administration of Tdap, MCV4, or influenza vaccines increases the likelihood that these vaccines are received on schedule and without additional delivery cost and inconvenience

# HPV Vaccine Pregnancy Considerations

## ACIP, May 2010

- Category B: No evidence of impaired fertility/harm to fetus in animal studies
- If pregnant after initiation of vaccination, delay remainder of series until completion of pregnancy
- Avoid pregnancy until 2 months after vaccination
- Pregnancy testing not needed before vaccination
- Lactating women can receive HPV vaccine
- Vaccine exposure during pregnancy, provider/patient report to:
  - HPV 4: Merck, 800-986-8999
  - HPV 2: GlaxoSmithKline, 888-452-9622

# HPV Vaccine Safety Issues

## ACIP, May 2010

- Pooled data from clinical trials in about 60,000 recipients of HPV 2 or HPV 4
  - Most common local symptoms: injection-site pain, swelling, redness
  - Most common general symptoms: fainting, headache, nausea, fever
  - No difference between vaccine and control groups in serious adverse events, new onset chronic disease and autoimmune disorders, or deaths
- Vaccine Adverse Events Reporting System (VAERS)
  - Over 30 million doses HPV 4 distributed in US by June 2010
  - Adverse events (AE) no greater than background rates of other vaccines for this age group

# Choice of HPV Vaccines for Females

## Considerations

- HPV 4: Protects against genital warts caused by HPV 6 and HPV 11
- HPV 2: Produces HPV 16 and HPV 18 antibody levels higher than HPV 4 at 7 months after first dose
- HPV 2: Demonstrates greater protection against some nonvaccine HPV types associated with cervical precancers/cancers

## Conclusions

- Great similarities among the vaccine regarding safety, side effects, dosing, and cost
- No clear answer: Choice of HPV vaccine depends on nature of protection desired

CDC. *MMWR*. May 28, 2010;59:626-629.

Brown DR, et al. *J Infect Dis*. 2009;199:926-935.

Einstein MH, et al. *Hum Vaccin*. 2009;5:705-719.

# HPV Epidemiology in Men

- HPV infection is commonly acquired through sexual contact
- Men have similar prevalence of HPV infection, and possibly higher acquisition, compared to women
- Burden of disease and cancers in men include genital warts, recurrent respiratory papillomatosis, anal, penile, oral cavity, and oropharyngeal cancers
- Transmission high between sex partners
- Unlike HPV incidence in women, in men incidence is more or less the same from ages 18 to 44

# FDA and CDC Recommendations

- HPV 4 vaccine is effective at preventing genital warts in males and anal disease in MSM
- FDA licensure of HPV 4: Males ages 9-26 only to prevent external genital warts
- MSM are a special subset at higher risk
- The vaccine can be given to immunosuppressed patients but the immune response and efficacy could be diminished
- Syncope can occur and providers should consider watching patients for 15 minutes post vaccination
- HPV 4 is contraindicated in persons with immediate hypersensitivity to *Saccharomyces cerevisiae* (baker's yeast)

# Shannon and Marcus

## Shannon

- 18-year-old female, first sex at age 15, three male sex partners prior to current boyfriend (with him for past 6 months), occasionally uses condoms, no birth control currently
- Two years ago had very abnormal Pap test result, recalls a swab of some kind, told colposcopy was normal, also told at time that she had warts around anus
- At women's clinic a year ago, received a vaccine shot, recalls hearing something about whooping cough and also told to return in a few months, possibly for a second shot (not done)

## Marcus

- 19-year-old boyfriend, first intercourse at age 13 or 14, recalls at least 4 female and 1 male sex partners before current relationship, declined to describe further details of past sexual relationships
- Noticed flat, slightly raised dark bumps at the base of his penis for as long as he can remember, no evaluation nor treatment in past
- Recalls having HIV test a few years ago but never returned for results

# Case Management

## Shannon and Marcus

### Shannon

- Test her for chlamydia and gonorrhea
- Offer a gynecologic exam and Pap test
- Offer STI and birth control counseling, and pregnancy test

### Marcus

- Perform a thorough genital exam to evaluate for external lesions
- Offer sexually transmitted infection (STI) and birth control counseling
- Test for chlamydia and gonorrhea

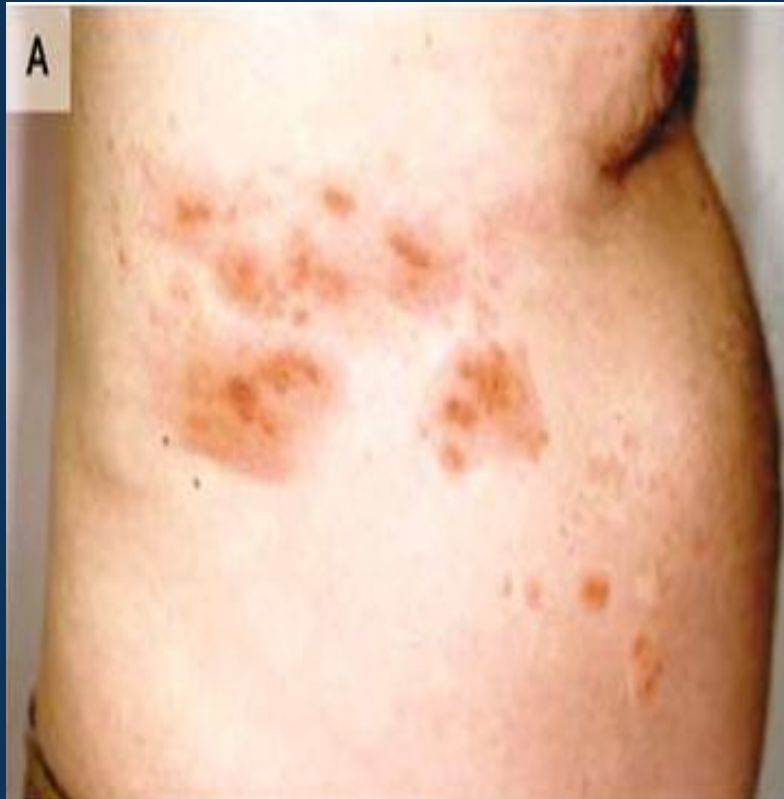


# Herpes Zoster

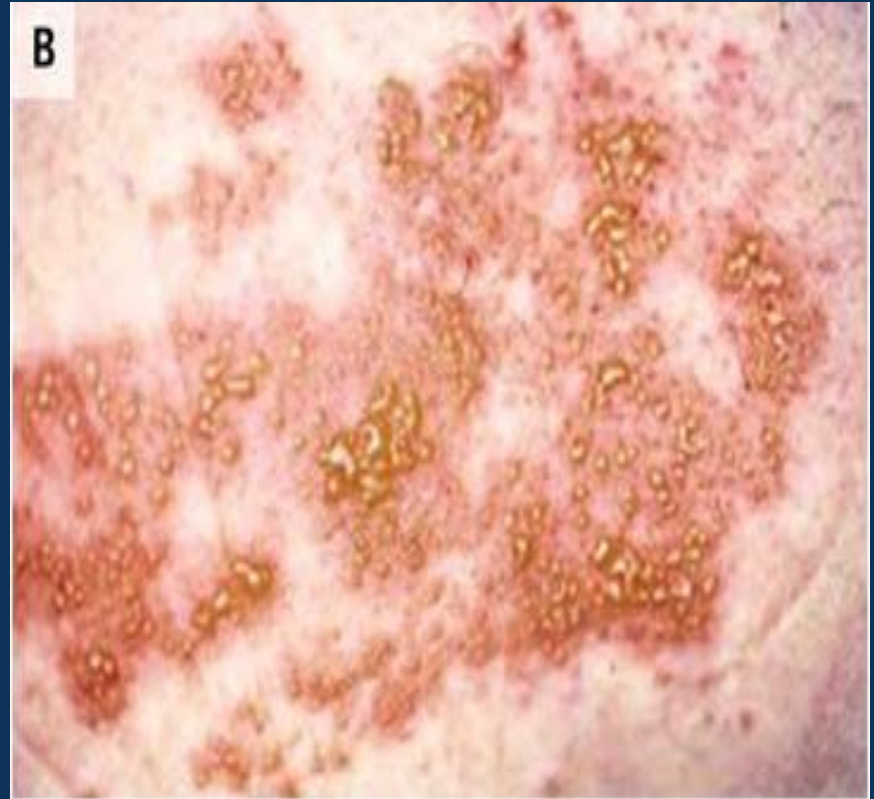
## *Epidemiology*

- About 1 million cases each year in US
- > 98% of adults in US have had VZV infection as children and are susceptible to having shingles
- One in three adults will develop shingles; severity and incidence increase with age with 50% having zoster by 85 years of age
- Recurrence of herpes zoster occurs in about 15% of patients

# Acute Herpes Zoster



Midthoracic (T4,T5)  
dermatonal distribution



Grape-like lesions clustered on  
an erythematous base

# Zoster Complications

- Post herpetic neuralgia (PHN) occurs in 15% of those with zoster and can last for months
- PHN is associated with constant pain, intermittent pain, and pain following innocuous stimuli (common in shingles as well and very common in PHN)
- Herpes zoster ophthalmicus occurs in 10-15% of zoster patients
- Zoster lesions can become super infected with bacteria leading to scarring

# Herpes Zoster Vaccine

## *Zostavax Specifics*

- Live attenuated VZV vaccine
- Zoster vaccine efficacy: 61% reduction in herpes zoster burden of illness, 67% reduction in the incidence of post-herpetic neuralgia and 51% reduction in the incidence of herpes zoster
- Zostavax has 14 times as much VZV as Varivax
- Single dose is recommended for all immunocompetent persons  $\geq 60$  years old, **whether or not they have had a previous episode of zoster**
- Must be stored frozen and administered within 30 minutes of reconstitution
- Subcutaneous administration in the upper arm
- Contraindicated in pregnant women, in those with primary or acquired immunodeficiency as a result of disease or treatment, in those with history of anaphylactic reaction to neomycin, and in those who have received varicella vaccine

CDC. Recommended Adult Immunization Schedule- United States, 2009. MMWR 2008; 57(53); Q-1-Q-4  
Adult Immunization. Treat Guidel Med Lett 2009;7:27-36.

R Harpaz et al. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57 (RR-5):1.

# Herpes Zoster Vaccine

## *Zostavax Specifics*

- Can be administered with inactivated vaccines (trivalent inactivated influenza vaccine, pneumococcal vaccine) in separate syringe at different anatomical site
- Special groups
  - Persons with history of zoster; wait 12 months to vaccinate if recent zoster
  - Persons anticipating immunosuppression: radiation, chemotherapy, those about to receive antitumor necrosis factor drugs for rheumatoid arthritis or inflammatory bowel disease; wait 2-4 weeks after immunization to start immunosuppressive therapy
  - Persons taking acyclovir and similar drugs; stop for 24 hours before immunization, resume medications 14 days later
  - Short-term, low dose corticosteroid therapy; can receive vaccine as usual
- Adverse effects: generally mild with erythema, pain, tenderness, swelling and pruritis at injection site

CDC. Recommended Adult Immunization Schedule- United States, 2009. MMWR 2008; 57(53); Q-1-Q-4  
Adult Immunization. Treat Guidel Med Lett 2009;7:27-36.

R Harpaz et al. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57 (RR-5):1.

# Seasonal Influenza

## *Annual Impact of Seasonal Influenza*

Infections	82 million
Illness	65 million
Medically attended	30 million
Hospitalizations	200,000
Deaths	36,000

Persons  $\geq$  65 years of age account for more than 90% of influenza-related deaths

CDC. Epidemiology and Prevention of Vaccine – Preventable Diseases (The Pink Book). W. Atkinson et al, eds. 11<sup>th</sup> Edition. Washington, DC: Public Health Foundation, 2009.

KL Nichol et al. Burden of influenza-like illness and effectiveness of influenza vaccination among working adults aged 50-64 years. Clin Infect Dis 2009; 48:292.

# Influenza Vaccine

## *Vaccine efficacy*

- About 70-90% effective in preventing infection in those < 65 years of age
- Annual match between vaccine containing two influenza A strains and one influenza B strain and the actual circulating viral strains determines effectiveness
- Study in 50 to 64 year olds showed 45% reduction in illness and > 60% reduction in morbidity, 30-40% reduction in illness in  $\geq 65$  years of age
- Especially for those  $\geq 65$  years of age, the major benefit of vaccine is in *reducing hospitalization (50-60%) and death (80%)*, not necessarily decreasing symptoms; reducing hospitalization reduces risk of hospital-acquired infections

# Influenza Vaccine

- Optimal time for annual vaccination is September through November; should be offered until the end of the season in late spring
- Deep IM injection or intranasal
- LAIV more efficacious than TIV in first time vaccination, but TIV more effective in previously immunized adults
- Adverse effects
  - TIV: soreness at injection site; fever, myalgia and malaise relatively uncommon
  - LAIV: rhinorrhea, nasal congestion, sore throat. Immunized contact of immunocompromised patients should avoid contact with them for 7 days based on theoretical concern of transmission of vaccine-strain virus

CDC. Recommended Adult Immunization Schedule- United States, 2009. MMWR 2008; 57(53); Q-1-Q-4.  
Adult Immunization. Treat Guidel Med Lett 2009;7:27-36.

KL Nichol et al. Burden of influenza-like illness and effectiveness of influenza vaccination among working adults aged 50-64 years. Clin Infect Dis 2009; 48:292.

Z Wang et al. Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel. JAMA 2009; 301:945.

# Influenza Vaccine: Guidelines: 2010-2011

- Children 6 months-8 years receive 2 doses unless previous dose of 2009 H1N1 vaccine and 1 dose of seasonal vaccine before 2009-2010 or 2 doses of 2009–2010 seasonal vaccine
- 65 years of age and older: in addition to standard-dose trivalent flu vaccine (15 mcg per strain), new Fluzone High-Dose vaccine (60 mcg per strain)
- Inactivated influenza vaccines: Fluarix (GSK) – 3 years and older, Afluria (CSL) – 6 months and older, Agriflu (Novartis) – 18 years and older

# Pneumococcal Disease in the United States

Major Syndrome	Estimated Cases/Year	Case Fatality Rate
Pneumonia “common”	500,000	5%-7% Higher in older adults
Bacteremia “less common”	50,000 Occurs in 25% of pneumococcal pneumonia cases	20% Up to 60% in older adults
Meningitis “uncommon”	3,000 represents 15% of all bacterial meningitis cases	30% Up to 80% in older adults

# Pneumococcal Vaccine (PPSV23)

## *Pneumovax Specifics*

- IM or SC injection, contains antigen from 23 serotypes of *S. pneumoniae*
- Represents 85-90% of strains that cause invasive disease
- Reduces the incidence of invasive disease such as pneumococcal bacteremia by 65-85% and decreases pneumonia-related morbidity and mortality
- Studies have not consistently identified a decrease in pneumococcal pneumonia or all-cause pneumonia
- ACIP recommends persons recommended for PPSV23 receive a dose now because of increased risk of pneumococcal disease associated with influenza

CDC. Epidemiology and Prevention of Vaccine – Preventable Diseases (The Pink Book). W. Atkinson et al, eds. 11th Edition. Washington, DC: Public Health Foundation, 2009.

Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997; 46 (RR-8):1.

# Pneumococcal Vaccine

## *Recommendations*

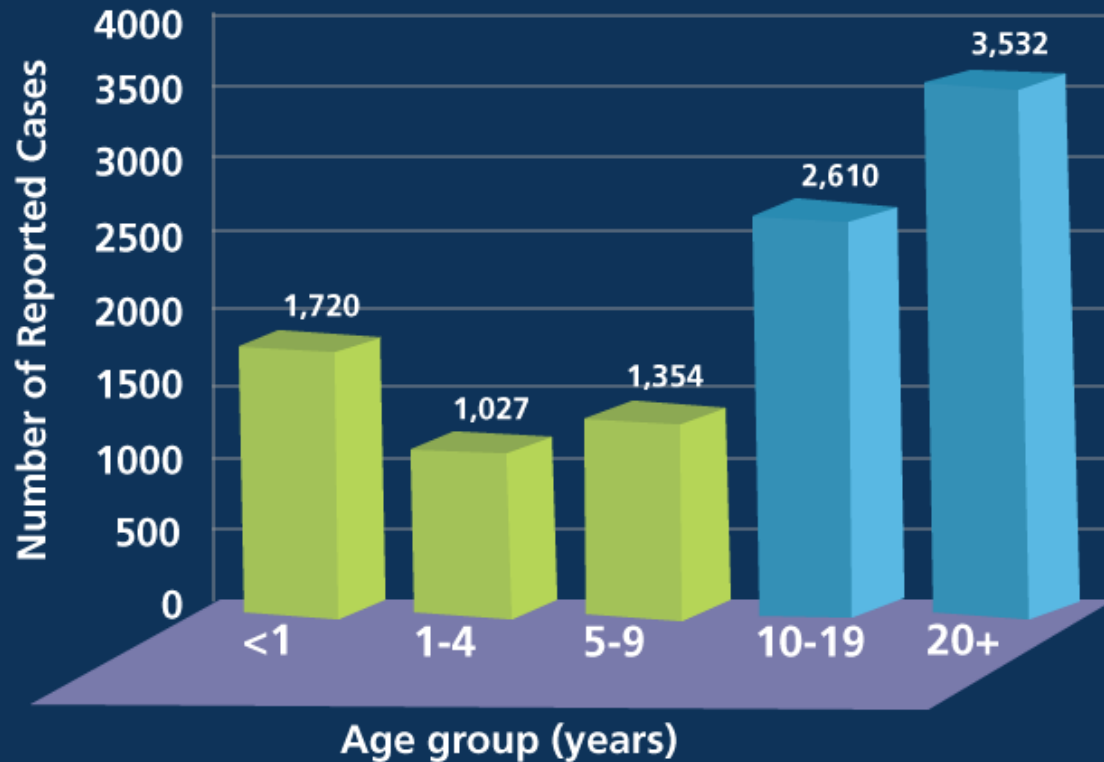
- All persons age  $\geq$  65 years
  - One time dose
  - Second dose if prior pneumococcal vaccine at  $<$  65 and at least 5 years after initial vaccination
- Age 19-64 years - Indications:
  - New indications: Asthma (16 million US adults have asthma) or cigarette smoking (1 in 5 US adults smoke cigarettes)
  - Chronic illness: Diabetes, cardiovascular, pulmonary, liver disease, or kidney disease; asplenia
  - Immunocompromising conditions including recipients of organ/ bone marrow transplants and cochlear implants
  - Long-term care residents
  - Second dose after 5 years for chronic renal failure, asplenia, and immunosuppression, regardless of age
- Adverse effects: mild to moderate soreness and redness at injection site
- Contraindications: none

# Pertussis

## *Epidemiology*

- Caused by *Bordetella pertussis*
- Transmission is person-to-person through contact with respiratory droplets (coughing and sneezing), high communicability
- Prior to availability of pertussis vaccine in the 1940s, > 200,000 cases annually with significant morbidity
- Number of cases: < 5000 in the 1980s, has increased recently to about 25,000 reported cases (2004) and about 10,400 (2007); # of cases is cyclical with substantial number of cases in adolescents and adults whose vaccine-induced immunity has fallen over time
- Reported cases of pertussis vastly underestimates the true number of adult cases due to underdiagnosis. In 2007, it was estimated that there were about 600,000 infections

# Reported Pertussis Cases, 2007



Total N = 10,454  
(211 cases with no reported age)

**60% of reported pertussis cases are in persons age 10 and older**

# Pertussis: Clinical Presentation

- Symptoms are often non-specific when presentation is not classic; this is commonly the situation in adolescents and adults
- Classic pertussis in infants and young children is associated with persistent cough, inspiratory whoop, and post-tussive vomiting
- Symptoms and signs in adolescents and adults: nasal discharge, mild cough, sneezing, hoarseness, headaches, and influenza-like symptoms
- Adults may be partially protected by previous vaccination and have milder disease; often only a few of these signs and symptoms are usually present

# Pertussis Vaccine

## *Adacel and Boostrix Specifics*

- Adults 19-64 years old should receive a single deep IM injection of Tdap to replace a single dose of Td if they received their last dose of Td  $\geq$  10 years earlier
- The following groups should receive a single dose of Tdap as soon as two years after their last Td (sooner for healthcare providers of those at significant risk)
  - Healthcare personnel
  - Adults with direct contact with infants < 12 months of age (e.g., childcare workers, parents, grandparents < 65 years of age)
  - Women anticipating becoming pregnant
  - Postpartum women
- Adverse effects: erythema and induration at injections site, occasional fever and painful swelling
- Contraindications: none

CDC. Recommended Adult Immunization Schedule- United States, 2009. MMWR 2008; 57(53); Q-1-Q-4.

TV Murphy et al. Prevention of pertussis, tetanus and diphtheria among pregnant and postpartum women and their infants: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57 (RR-4):1.

SA Gall. Vaccines for pertussis and influenza: recommendations for use in pregnancy. Clin Obstet Gynecol 2008; 51:486.

# Pertussis Epidemic in California: 2010

- 9 deaths reported, 8 (89%)
- 4017 cases reported through 9/14/2010
- In July, California health officials recommended that everyone 7 years and older, including the elderly, who is not fully immunized get the Tdap inoculation -- especially pregnant women and anyone who will have contact with them and their babies.

# Hepatitis A Virus (HAV)

## *Epidemiology*

- Frequently reported in US (> 40,000 infections annually) and endemic in certain communities in western and southwestern states and Alaska
- In adults, infection usually mild but severity and hospitalization increases significantly in older patients (>60 years of age)
- Rare fulminant hepatitis and death in those with chronic liver disease
- No chronic HAV infection; infection = life - long immunity

# Hepatitis A Immunization

- Routine childhood vaccination since 2005
- Indications for adults HAV immunization:
  - Chronic liver disease (hepatitis B and C)
  - MSM
  - IDU
  - Travelers to countries where HAV infection is endemic (all countries except Canada, Australia, New Zealand, Japan, or western Europe)
  - Any person seeking protection (immunity) from HAV infection

# Hepatitis A Immunization

- For monovalent HAV vaccine (an inactivated whole virus vaccine), administer deep IM injection in 2-dose series; second shot at least 6 months after the first
- 100% seropositivity after second dose, > 95% effective in preventing clinical hepatitis A
- Can be administered as combined with hepatitis B vaccine in 3 doses or the 4-dose accelerated schedule
- Adverse effects: pain, swelling, erythema at injection site in less than 50%; malaise, fever, and fatigue in less than 10%
- Contraindications: none

# Hepatitis B Virus (HBV)

## *Epidemiology*

- Frequently reported in US (> 50,000 infections annually), about 1.25 million in US have chronic HBV infection and are often asymptomatic yet infectious
- 3,000-5,000 died each year from cirrhosis or liver cancer due to HBV infection
- Transmission by blood or other body fluids (semen, vaginal secretions, saliva)
- Acute infection symptoms include nausea, vomiting, abdominal pain, anorexia, jaundice

# Hepatitis B Virus (HBV)

## *Epidemiology*

- Indication for vaccine use:
  - HIV infection
  - Chronic liver disease (alcoholism, hepatitis A and C)
  - Renal dialysis patients
  - MSM
  - IDU
  - Sexually active patients (2 or more sex partners in past 6 months)
  - Healthcare and public safety workers
  - Travelers to countries where HBV infection is endemic
  - **Any person seeking protection (immunity) from HBV infection**
- Vaccine use in institutional settings: STD clinics, jails and prisons, drug abuse treatment facilities, hemodialysis facilities

# Hepatitis B Immunization

- Recombinant HBV vaccine containing HBsAg protein, vaccine is non-infective
- Routine childhood vaccine since 1991
- If a combined hepatitis A and B vaccine (Twinrix) is used, administer as 3 doses (0, 1, 6 months; also the schedule for monovalent hepatitis B vaccine) or in an accelerated 4-dose schedule (0, 7, 21-30 days, followed by booster done at month 12)
- 90% seropositivity after 3 doses, lower in adults over 60 years of age or those with chronic liver disease

CDC Division of Viral of Viral Hepatitis Resources Materials for Professionals MMWR 2006; 55 (RR-16)

<http://www.cdc.gov/hepatitis/Resources/Professionals/MMWRs.htm>

Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB MMWR 2007; 56 (40): 1051 [www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm](http://www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm)

Connor BA et.al J Travel Med 2007; 14: 9-15

# Hepatitis B Immunization

- Adverse effects: pain at injection site, fever in < 10%
- Contraindications: allergy to yeast or other vaccine component, severe allergic reaction to previous dose of hepatitis vaccine

CDC Division of Viral of Viral Hepatitis Resources Materials for Professionals MMWR 2006; 55 (RR-16)  
<http://www.cdc.gov/hepatitis/Resources/Professionals/MMWRs.htm>

Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB MMWR  
2007; 56 (40): 1051 [www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm](http://www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm)

Connor BA et.al J Travel Med 2007; 14: 9-15