Outline

- Varicella-Zoster Virus (VZV)
- Varicella
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  - Epidemiology and Impact of the Varicella Vaccination Program
  - Vaccine Information
  - Varicella Vaccination of Healthcare Personnel
- Herpes Zoster
  - Clinical Description
  - Epidemiology and Vaccination Coverage
  - Vaccine Information
- VZV Laboratory Testing
- Contact Information and Additional Resources
Varicella-Zoster Virus (VZV)

- Human alpha-herpesvirus
- Causes varicella (chickenpox) and herpes zoster (shingles)
- Primary VZV infection leads to varicella
- VZV establishes latency in dorsal root ganglia after primary infection
- VZV can reactivate at a later time, causing herpes zoster
- There are 3 licensed vaccines to prevent varicella (Varivax®, Proquad®) and herpes zoster (Zostavax®) in the US:
  - Varivax® (licensed 1995)
  - Proquad® (licensed 2005)
  - Zostavax® (licensed 2006)
VARICELLA
VARICELLA: CLINICAL DESCRIPTION
Varicella: Clinical Features in Unvaccinated Cases

- Persons with varicella may develop prodrome of fever, malaise, headache, and abdominal pain 1-2 days before rash
- Rash involves 3 or more successive crops over several days; each crop usually progresses within less than 24 h from macules to papules, vesicles, pustules and crusts so that on any part of the body there are lesions in different stages of development
- Rash usually starts on face and trunk, then spreads to extremities
- Rash usually involves 250-500 lesions that are pruritic
- Lesions are typically crusted 4-7 days after rash onset

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4); Arvin Clin Microb Rev 1996; Vaccine 5th Edition
Varicella: Clinical Features in Vaccinated Persons (“breakthrough varicella”)

- Breakthrough varicella is defined as infection with wild-type varicella disease occurring > 42 days after vaccination
- Approximately 15-20% of 1-dose vaccinated persons may develop varicella if exposed to VZV
- Usually milder clinical presentation than varicella in unvaccinated cases
  - Usually low or no fever
  - Develop < 50 lesions
  - Experience shorter duration of illness
  - Rash predominantly maculopapular rather than vesicular
- 25-30% of breakthrough varicella cases are not mild and have clinical features more similar to varicella in unvaccinated persons

Varicella: Complications

- Secondary bacterial infection of skin lesions
- Central nervous system manifestations (meningoencephalitis, cerebellar ataxia)
- Pneumonia (viral or bacterial)
- Hepatitis, hemorrhagic complications, thrombocytopenia, nephritis occur less frequently
- Certain groups at increased risk for complications
  - Adults
  - Immunocompromised persons
  - Pregnant Women
  - Newborns

CDC. Prevention of Varicella. *MMWR* 2007; 56(No. RR-4); Arvin *Clin Microb Rev* 19
Varicella: Transmission

- Transmitted person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster, or aerosolized respiratory tract secretions
- Average incubation period: 14-16 days after exposure to rash (range: 10-21 days)
- Period of contagiousness: 1-2 days before rash onset until all lesions crusted or disappear if maculopapular rash (typically 4-7 days)
- Varicella in unvaccinated persons is highly contagious (61-100% secondary household attack rate)
- Varicella in 1 dose-vaccinated persons half as contagious as unvaccinated cases
  - One study indicated that varicella in 1-dose vaccinees with < 50 lesions was 1/3 as contagious as unvaccinated persons although contagiousness in vaccinees with ≥ 50 lesions was similar to unvaccinated persons

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4); Arvin Clin Microb Rev 1996; Seward JAMA 2004; Vaccines, 5th edition
VARICELLA: EPIDEMIOLOGY AND IMPACT OF THE VARICELLA VACCINATION PROGRAM
Varicella Disease Burden in the United States Before Introduction of Varicella Vaccine in 1995

- 4 million cases/year
- 11,000 - 13,500 hospitalizations/year
- 100 - 150 deaths/year
- Greatest disease burden in children
  - >90% cases
  - 70% hospitalizations
  - 50% deaths

Experience with 1-dose Varicella Vaccination Program

- 1-dose varicella vaccination coverage in 19-35 month-olds increased from 26% to 91% from 1997 to 2008
- Varicella disease incidence declined by 90% in two varicella active surveillance sites by 2005 as compared to 1995
- Varicella hospitalizations declined 88% during 1994-2002
- Varicella mortality rate declined 93% from 1990-1994 to 2005-2006 in persons aged <50 years

National Immunization Survey (www.cdc.gov/vaccines/stat-surv/default.htm#nis); Guris J Infect Dis 2008; Marin Pediatrics 2008; Zhou JAMA 2005; National Center for Health Statistics
Varicella and Measles Vaccine Coverage (1+ doses)*, Children 19-35 Months
National Immunization Survey, 1997-2008

*National Immunization Survey (NIS), coverage available at http://www.cdc.gov/vaccines/stats-surv/default.htm#nis
Varicella Cases and 1-Dose Vaccine Coverage
Varicella Active Surveillance Project Sites, 1995-2005

Antelope Valley, California

90% decline in varicella incidence in both sites

Guris J Infect Dis 2008
Varicella-Related Hospitalization Rates
U.S., 1994-2002

Decline 1994-95 to 2002
Overall 88%
< 10 yrs 91%
10-19 yrs 92%
20-49 yrs 78%

Zhou et al, JAMA, 2005
Reduction in Varicella Health Care Costs

- Total estimated direct medical expenditures for varicella hospitalizations and ambulatory visits
  - 1994-1995 $85 million
  - 2002 $22 million
- 74% decline in total estimated direct medical expenditures for varicella hospitalizations and ambulatory visits from 85 to 22 million

Zhou JAMA 2005
Decline in Reported Varicella Deaths
<50 years of age, US, 1990-2006

No. of Deaths


YEAR

average=85

93% decline in deaths in 2005-2006 compared to pre-vaccine era 1990-1994

average=8

National Center for Health Statistics
Impressive Achievements with the 1-Dose Varicella Vaccination Program
But Challenges to Varicella Control Remained...

• 15-20% of children vaccinated with 1 dose remain at risk for varicella due to lack of immune response or partial protection
  — Concern about accumulation of susceptible individuals

• Vaccinated persons with breakthrough varicella disease are contagious

• Outbreaks continued during the 1-dose program
Varicella Vaccines

- Two live attenuated varicella virus vaccines licensed for use in US: Varivax® and Proquad®
- Both vaccines may be used for first and second doses of varicella vaccine
- Varivax® (1,400 pfu) is the single-antigen varicella vaccine licensed in 1995 for use among healthy persons aged ≥ 12 months
- Proquad® or MMRV (9,800 pfu) is a combination measles, mumps, rubella, and varicella vaccine licensed in 2005 for use among healthy children aged 12 months-12 years

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Current Varicella Vaccination Policy in the United States

Implemented routine 2-dose childhood varicella vaccination program in 2006

- 1st dose at age 12-15 months
- 2nd dose at age 4-6 years
- Catch-up vaccination of children and adolescents who had previously received one dose
- 2 doses for all adolescents and adults without evidence of immunity
- Pre-natal screening and post-partum vaccination

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Criteria for Determining Persons Who Can Be Considered Immune to Varicella

- Documentation of age-appropriate vaccination with varicella vaccine
- Laboratory evidence of immunity† or laboratory confirmation of disease
- Birth in the US before 1980§
- Diagnosis or verification of history of varicella disease by a health-care provider
- Diagnosis or verification of history of herpes zoster by a health-care provider

†Commercial assays may lack sensitivity for detecting vaccine-induced immunity
§For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Rationale for Timing of 2nd Dose of Varicella Vaccination at 4-6 Years of Age

- Varicella epidemiology during 1-dose program
  - Low incidence among 1-4 year old children
  - Outbreaks in elementary and middle schools
- Similar immune response to 2nd dose with intervals 3 months or 3-4 years after 1st dose
- Programmatic harmonization with MMR vaccine and availability of MMRV vaccine

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Post-licensure One-Dose Vaccine Effectiveness in US*

- 17 studies with 20 estimates
  - Study designs: case-control, cohort (outbreaks, other), household contact
- Prevention all varicella
  - Median 85% (range 44% - 100%)  Mean 81%
- Prevention of combined moderate and severe varicella
  - Median 97% (range 86% - 100%)  Mean 96%
- Prevention of severe varicella*
  - Median 100% (range 97% to 100%)  Mean 99%

*Definition 1) Varicella with > 500 lesions or a complication requiring physician visit
  2) disease severity scale used in clinical trials: # lesions, fever, systemic signs and subjective assessment of illness

VARIVAX® Merck and Co. Inc; Seward J Infect Dis 2008
## Pre-licensure 2-Dose Varicella Vaccine Efficacy and Immune Response

<table>
<thead>
<tr>
<th>2 Dose Vaccine Efficacy</th>
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<tbody>
<tr>
<td>-Any disease</td>
<td>98%</td>
</tr>
<tr>
<td>-Severe disease</td>
<td>100%</td>
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**Immune Response children aged 12 months-12 years, single antigen varicella vaccine***

*Measured as Geometric Mean Titer by VZV IgG gpELISA in units of μ/ml

<table>
<thead>
<tr>
<th>Time After Dose</th>
<th>Titer</th>
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<tr>
<td>-6 weeks after 1 dose</td>
<td>12.5</td>
</tr>
<tr>
<td>-6 weeks after dose 2 at age 4-6 years</td>
<td>212.4</td>
</tr>
</tbody>
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*CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)*
Simultaneous Administration of Vaccines

- Varicella vaccine, either Varivax® or combination MMRV may be administered simultaneously with other vaccines recommended for children 12-15 months and children 4-6 years.
- If varicella vaccine is not administered on the same day as MMR or live attenuated influenza vaccine, the vaccines should be separated by at least 4 weeks.
- If separated by less than 4 weeks the vaccine given second should be repeated.

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Contra-indications and Precautions for Varicella Vaccination

• Severe allergic reaction to vaccine component or following a prior dose
• Immunosuppression
• Pregnancy
• Moderate or severe acute illness
• Recent blood product (due to potential inhibition of response to varicella vaccination)

CDC. Prevention of Varicella. *MMWR* 2007; 56(No. RR-4)
Varicella Vaccination in Certain Groups of Immunocompromised Persons

- Varicella vaccine may be administered to persons with isolated humoral immunodeficiency.
- Patients with leukemia, lymphoma, or other malignancies whose disease is in remission and those chemotherapy have been terminated ≥ 3 months can receive live-virus vaccines.
- Consider varicella vaccination for HIV-infected children with CD4+ T-lymphocyte percentage of 15% or higher.
  - Eligible children should receive 2 doses of single-antigen varicella vaccine 3 months apart.
- Data on use of varicella vaccine in HIV-infected adolescents and adults lacking, but safety is likely to be similar to response in HIV-infected children. Vaccination may be considered for HIV-infected persons with CD4+ T-lymphocyte count ≥ 200 cells/μl.

CDC. Prevention of Varicella. *MMWR* 2007; 56(No. RR-4)
Post-exposure Prophylaxis

• Varicella vaccine recommended for use in healthy persons without evidence of immunity within 3-5 days after exposure to varicella
  – ≥ 90% effective in preventing varicella if vaccinated within 3 days of exposure and ~ 70% effective in preventing varicella and ~100% effective in modifying severe disease if given within 5 days
  – Vaccination still recommended for those with no other evidence of immunity even after 5 days of exposure because it will help provide protection against future exposures

• Varicella Zoster Immune Globulin (available product, VariZIG™) recommended for certain groups at high risk for severe disease AFTER EXPOSURE TO THE VARICELLA-ZOSTER VIRUS AND within 10 days of exposure.
Varicella Vaccine Storage and Handling

**Varivax**
- Store frozen at 5°F (-15°C) or colder at all times
- May be stored up to 72 hours at 35-46°F (2-8°C), but discard unused vaccine after 72 hours at this temperature
- Discard if not used within 30 min of reconstitution
- Store diluent at room temp or in refrigerator

**MMRV**
- Store frozen at 5°F (-15°C) or colder at all times
- May **NOT** be stored at refrigerator temperature **AT ANY TIME**
- Discard if not used within 30 min of reconstitution
- Store diluent at room temp or in refrigerator

CDC. Prevention of Varicella. *MMWR* 2007; 56(No. RR-4)
Freezer Requirements for Varicella Vaccine Storage

• Acceptable Freezer Units:
  – Stand-alone freezers
  – Freezer compartments of refrigerator-freezer combinations, provided that the freezer compartment has its own separate, sealed, and insulated exterior door

• Unacceptable Freezer Units:
  – Units with an internal freezer door that is unsealed and un-insulated (e.g., small, dormitory-style refrigerators)

• Temperatures should be documented at beginning and end of each day

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
Varicella Vaccine Adverse Events

- Non-serious adverse events
  - Rash, Fever
  - Injection site reactions
  - Possible vaccine failure

- Serious adverse events are rare
  - Encephalitis
  - Ataxia
  - Pneumonia
  - Arthritis
  - Hepatitis
  - Vasculitis
  - Thrombocytopenia

Chaves J Infect Dis 2008
Reporting a Vaccine Adverse Event

• Complete VAERS form (next slide) for vaccine adverse events and if feasible, collect specimen for testing
  – CDC laboratory can conduct VZV PCR testing and genotyping
  – Genotyping may help to distinguish outcomes caused by wild-type versus vaccine strain VZV

• Additional Info: http://vaers.hhs.gov/index/ ; 1-800-822-7967
Vaccine Adverse Events Reporting System (VAERS)
VARICELLA: VARICELLA VACCINATION OF HEALTHCARE PERSONNEL
Varicella Vaccination of Healthcare Personnel

• To prevent disease and nosocomial spread of VZV, healthcare institutions should ensure that all HCP have evidence of immunity to varicella
  – Evidence of immunity = (1) laboratory evidence of immunity, (2) history of clinician diagnosed or verified varicella or zoster, (3) Documentation of age-appropriate vaccination

• Pre-vaccination serologic probably cost-effective

• Routine testing for varicella immunity after 2 doses of vaccine not recommended
  – Sensitive tests indicate 94-99% adults develop antibodies after second dose
  – VZV-specific cell-mediated immunity affords protection to vaccinated adults, even in the absence of detectable antibody response.
  – Available commercial assays may not be able to detect vaccine-induced immunity

CDC. Prevention of Varicella. MMWR 2007; 56(No. RR-4)
HERPES ZOSTER
HERPES ZOSTER: CLINICAL DESCRIPTION
Herpes Zoster (Shingles)

• Following initial infection (varicella), VZV establishes permanent latent infection in dorsal root and cranial nerve ganglia
• Years to decades later VZV reactivates and spreads to skin through peripheral nerves causing pain and a unilateral vesicular rash in a dermatomal distribution
• ~1 million cases in the U.S. annually
• Lifetime risk of developing zoster: about 30%
Clinical Features of Herpes Zoster

Prodrome: headache, photophobia, malaise, fever, abnormal skin sensations and pain

Rash:
• Unilateral, involving 1-3 adjacent dermatomes
• Thoracic, cervical, ophthalmic involvement most common
• Initially erythematous, maculopapular
• Vesicles form over several days, then crust over
• Full resolution in 2-4 weeks
• Occasionally, rash never develops (zoster sine herpete)
Complications of Herpes Zoster

- Postherpetic Neuralgia (PHN)
  - Pain ≥ 30 days occurs in 18-30% of zoster cases
  - Mild to excruciating pain after resolution of rash
  - Constant, intermittent, or triggered by trivial stimuli
  - May persist weeks, months or occasionally years
  - Can disrupt sleep, mood, work, and activities of daily living and lead to social withdrawal and depression
  - Risk factors for PHN include age ≥ 50, severe pain before or after onset of rash, extensive rash, and trigeminal or ophthalmic distribution of rash
Complications of Herpes Zoster

• Herpes Zoster Ophthalmicus
  – ~15% of HZ cases
  – Can occur when ophthalmic division of trigeminal nerve is involved
  – Untreated, 50-70% develop acute ocular complications
  – Can lead to chronic ocular complications, reduced vision, even blindness

• Neurologic complications
  – Myelitis, encephalitis, ventriculitis, meningoencephalitis, cranial nerve palsies, ischemic stroke syndrome

• VZV viremia
  – Cutaneous dissemination, pneumonia, hepatitis, disseminated intravascular coagulation

• Dermatologic complications
  – Secondary infections of rash
  – Permanent scarring and changes in pigmentation
VZV Transmission from Zoster

- VZV can be transmitted from persons with zoster to persons with no history of varicella disease or vaccine and cause varicella
  - Risk of VZV transmission from zoster is much lower than from varicella
  - Transmission is mainly through direct contact with zoster lesions, although airborne transmission has been reported in healthcare settings
  - Localized zoster is only contagious after the rash erupts and until the lesions crust
  - Transmission from localized zoster can be decreased by covering the lesions
HERPES ZOSTER: EPIDEMIOLOGY
Risk Factors for Herpes Zoster

- Increasing age
- Immunosuppression
  - Bone marrow and solid organ transplantation
  - Patients with hematological malignancies and solid tumors
  - HIV
  - Immunosuppressive medications
- Gender: Increased risk in females
- Race: Risk in blacks less than half that in whites
- Trauma or surgery in affected dermatome
- Early varicella (in utero, infancy): Increased risk of pediatric zoster

Herpes Zoster Vaccination Coverage: U.S., Age 60 or Older, 2007-2009

HERPES ZOSTER: VACCINE INFORMATION
Herpes Zoster Vaccine

- Licensed in 1996
- Live, attenuated VZV
- Same strain used in the varicella vaccine, but 14x more potent
- Administered subcutaneously in deltoid region
Herpes Zoster Vaccine Efficacy

- Decreased zoster incidence by 51%
- Decreased risk of post-herpetic neuralgia in all participants by 67%
- Decreased burden of illness (severity x duration) in all participants by 61%

Oxman *NEMJ* 2005
ACIP Recommendations for Zoster Vaccine

• In October 2008, the Advisory Committee on Immunization Practices (ACIP) recommended a dose of the herpes zoster vaccine (HZV) for all adults ≥60 years of age unless they have contraindications.

• HZV should be offered at the patient’s first available clinical encounter.

ACIP Recommendations for Zoster Vaccine

• HZV can be administered simultaneously with influenza and pneumococcal vaccines
• HZV is recommended whether or not the patient reports a prior episode of zoster
• It is not necessary to check varicella history or titers before administering HZV
• HZV should be offered to eligible persons including those >80 y.o., frail, or with chronic illnesses

Contraindications for Zoster Vaccine

• Immunosuppression (high-dose steroids, biological response modifiers, chemotherapy, AIDS) is a contraindication for HZV
• HIV-positive status alone is not an contraindication
• Persons ≥60 y.o. anticipating immunodeficiency due to initiation of treatments or progression of illness should be offered HZV
• HZV is not recommended for persons ≥60 y.o. who have received the varicella vaccine

Zoster Vaccine Storage and Handing

• Must be stored at 5° F (-15° C) or colder AT ALL TIMES until reconstitution
• Protect from light
• Administer within 30 minutes of reconstitution
VZV LABORATORY TESTING
VZV Laboratory Testing

• Objectives of VZV Laboratory Testing
  – Confirm clinical diagnosis of varicella or herpes zoster with atypical presentation, such as varicella disease in vaccinated persons or shingles in immunosuppressed persons
  – Assess a person’s susceptibility to varicella
  – Distinguish between vaccine and wild-type strains of the virus

• Available Testing Facilities
  – Contact your local health department to check if they offer VZV testing
  – CDC’s National VZV Laboratory offers a range of VZV testing services. Please contact your local health department to determine the policy for sending specimens to CDC
Contact Information and Additional Resources

Contact Information:
• Nipinfo@cdc.gov
• 800.CDC.INFO

National VZV Laboratory:
• vzvlab@cdc.gov
• http://www.cdc.gov/shingles/lab-testing/index.html

Additional Resources:
• CDC Chickenpox (Varicella) Website: http://www.cdc.gov/chickenpox/index.html
• CDC Varicella Vaccine Webpage: http://www.cdc.gov/vaccines/vpd-vac/varicella/
• CDC Herpes Zoster Disease and Vaccine Webpages:
  http://www.cdc.gov/shingles/index.html
  http://www.cdc.gov/vaccines/vpd-vac/shingles/