Varicella Vaccine (Oka)

- Most common complaint: mild rash in 5%
  - Vaccine extremely safe; given as 2 doses
  - 1 month after vaccination; transmission rare
- 1 dose: 85% protected; 15% partial immunity
- 2 doses 98% effective in preventing varicella
- Little evidence for waning immunity
- Subsequent zoster is rare/unusual
- Same vaccine (15x higher dose) also used to prevent zoster in the elderly (different mechanism of action... stimulates CMI to VZV)
- Also have MMRV formulation (high titer) for children age 1-12 years
Varicella in Immunocompromised Children May Be Fatal
Reported Varicella and Annual Vaccine Coverage Antelope Valley* CA, U.S., 1995-2004

*Varicella Active Surveillance Project site

Varicella hospitalization rates (NHDS) by year and age declining in U.S., 1988–2006

(ACIP Recommendation 1 dose)

ACIP Recommendation (2 doses)

CDC DATA, COURTESY JANE SEWARD
The incidence of zoster in vaccinees is low

Adult incidence is extremely low (0.9/1000 P-Y) (Hambleton JID 2000)

Lower rates in leukemic vaccinees than in leukemias following natural infection (4 studies in 1980s)

Healthy vaccinated children: 0.33/1000 person-years (P-Y) (2008); risk decreased ~ 10 times (Tseng, Civen, PIDJ 2009)

1/3 of cases are due to wild type virus

Rate of zoster in vaccinated HIV-infected children

no cases reported
Vaccination Prevents Varicella in HIV-infected Children

Rate Per 1000 person years

- Unvaccinated Pre-Vaccine Era: 103.3
- Unvaccinated Post-Vaccine Era: 36.82
- Vaccinated: 6.76

*p<0.001*

*P=0.012*
Vaccination Prevents Zoster in HIV-infected Children

Rate Per 1000 person years

VZV rash was rare in vaccinees

\( p = 0.49 \)

\( p < 0.001 \)
Varicella vaccine effectiveness over time (case-control study): no waning of immunity

Adapted from Vásquez et al. *JAMA* 2004;291:851-855.
Two Vaccine Doses Were Highly Effective in a Case Control Study

<table>
<thead>
<tr>
<th>Number of doses received</th>
<th>Cases, N = 71 (%)</th>
<th>Controls, N = 140 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 doses</td>
<td>5 (7)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>66 (93)</td>
<td>117 (83.6)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>0 (0.0)</td>
<td>22 (15.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The effectiveness of 2 doses of varicella vaccine vs 1 dose was 98.3%

Shapiro et al. JID 2011; Yale-Columbia Study
FAMA is the “gold standard” for assessment of varicella immunity (immune correlate)

- Presence indicates protection
- 113/138 (76%) of healthy child vaccinees seroconverted after 1 dose of vaccine (3 locations)
- Suggests 24% primary vaccine failure after 1 dose

Severe varicella vaccine reactions are rare

- 19 yo w cholangitis, lymphopenia
- 13 mo w ADA deficiency
- 16 mo w HIV and 8 CD4 cells per mm3
- 5 yo w asthma, steroids
- 11 yo NK cell deficiency
- 8 yo w Di George syndrome
- 24 yo hypopuitarism w steroids
- 3 yo w acute leukemia
- Vaccination, cancer, severe zoster (2)
- HZ with meningitis nd recovery w no sequelae (9)
Latent VZV (DNA/RNA) was found (PCR) in ganglia at multiple levels.

Distribution of VZV DNA/RNA in ganglia of vaccinated patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Vac</th>
<th>Trigeminal</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>1.75</td>
<td>1.75</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

DNA detected: ORF 4, 62. 63, 68; RNA detected: ORF 4, 29, 62, 63
VZV RNA is found in surgical specimens of gut from patients with a history of varicella or vaccination.

<table>
<thead>
<tr>
<th>ORF</th>
<th>4</th>
<th>29</th>
<th>31*</th>
<th>61*</th>
<th>62</th>
<th>63</th>
<th>66</th>
<th>68*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>varicella</td>
<td>4/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>5/6</td>
<td>1/6</td>
<td>0/6</td>
<td>6/6</td>
</tr>
<tr>
<td>%</td>
<td>67%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>83%</td>
<td>17%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>vaccine</td>
<td>4/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>2/7</td>
<td>6/7</td>
<td>1/7</td>
<td>0/7</td>
<td>6/7</td>
</tr>
<tr>
<td>%</td>
<td>57%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29%</td>
<td>86%</td>
<td>14%</td>
<td>0</td>
<td>86%</td>
</tr>
<tr>
<td>No VZV</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

- The transcripts that were detected were latency-associated.
- Transcripts encoding proteins that were characteristic of lytic infection (31, 61, 68) were absent.
VZV DNA has been detected in saliva after space flight


<table>
<thead>
<tr>
<th>VZV DNA Shedding In saliva (PCR)</th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astronauts (8)</td>
<td>1% +</td>
<td>30% +</td>
<td>30% +</td>
<td></td>
</tr>
<tr>
<td>Controls (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sampled multiple times</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Cohrs et al (2008) found that 2/3 asymptomatic astronauts shed infectious VZV in saliva (no transmission).
A patient with severe gastric hemorrhage

- 16 yo male, vaccinated x 2 against varicella
  - History of asthma, obesity (100 kg)
- Sister died during a CT-scan at age 16; perforated gastric ulcer with bezoar
  - Grandmother, mother, aunt had esophageal dilatation for achalasia
- Patient: abdominal pain in morning without fever, vomiting, diarrhea
  - Developed an asthma attack with change in mental status and became unresponsive
- Emergency laparotomy to control GI bleeding; removed much of stomach
Ulcer, hemorrhage, and inflammation were found in the resected stomach.

Large area of ulceration and hemorrhage

Lymphocytic infiltrate and hemorrhage
VZV gE and ORF63p were detected in ulcerated mucosa
vOKA was detected in DNA extracted from resected stomach

- PCR used to analyze DNA in paraffin sections of resected stomach.
- Extra Sma1 site in ORF 62 (diagnostic of vOka)
- Sequencing of ORF 62 at 106262 indicated homology with Dumas WT strain, with C substitution for T (seen in vOka [VT])
There are many differences between VZV and HSV

• Pathogenesis: airborne to respiratory tract (antibody prevents or modifies), cell associated viremia, incubation period 2 weeks; immune evasion mechanisms less developed than those of HSV except at skin; T cells control reactivation

• Natural infection: lifelong protection from varicella for most (despite 7 recognized clades), very high attack rate in exposed susceptibles (helpful in evaluating vaccination efficacy)

• VZV is cell-associated (except in skin); difficult to propagate and synthesize mutants; no animal model

• Vaccine initially tested in humans
HSV presents some difficulties

• Protective immune responses not well understood, antigens uncertain, importance of mucosal immunity? CD8 at DEJ possibly important

• Might make use of new adjuvants

• Animal models available but unclear how good they are in predicting vaccine success; need human studies

• Almost constant shedding of HSV2 shows that natural immunity is not very successful; immune evasion; vaccine needs improvement on nature

• Necessary to outsmart this virus

  • “Fundamental strategy of HSV is a preemptive strike... block the cell before it can react to the virus” (Roizman)
Why should there be an HSV vaccine?

• Life threatening infections (neonatal, encephalitis, eczema herpeticum)

• Serious morbidity from genital HSV with frequent shedding, surviving neonates, keratitis, retinitis

• Might benefit certain immunocompromised patients

• Global problem: HSV increases HIV infection 3x and HIV increases transmission of HSV; these infections are synergistic

• Antivirals very useful but don’t control HSV well
What about costs?

- Cost benefit analyses ignore the effect of decreasing viral transmission
- Safe vaccines require cost analysis, but in general are cheaper than the disease
- Need vaccines against HSV 1 and HSV 2
Some candidate HSV vaccines

- DL5-29 vaccine virus (replication deficient)
  - Inactivation of immune evasion genes) (Knipe)
- Block entry; gB, gD, gH/L activation (Eisenberg, Cohen)
- gD2, gB2, (deleted gC2, gE2) Sterilizing? (Friedman)
- CD4 T cell stimulating vaccines; new targets: UL 39, UL 46 (Koele)
Additional vaccines, etc

• Animal models
• Herpevac Trial for women
• HPV