VARICELLA-ZOSTER VIRUS: DISEASE AND VACCINATION

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Varicella Zoster Virus (VZV)
The rash of VZV is vesicular.

- Vesicular fluid is highly infectious.
  – Well-formed virions are suspended in it.
Natural History of VZV

• **Primary infection: varicella**
  – Highly contagious (airborne)
  – Complications: bacterial superinfection, encephalitis, pneumonia, congenital syndrome

• **Secondary infection: zoster**
  – Due to reactivation of latent VZV
  – DNA, RNA, proteins in ganglia at autopsy
  – Zoster in vaccinees caused by Oka strain (1/3 due to wild type virus)
  – Due to low cell-mediated immunity (CMI) to VZV

• No asymptomatic shedding of infectious VZV as with HSV
Varicella is a generalized illness. Infectious virions are produced in the skin vesicles.
Zoster is initially localized

- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.
In the body VZV spreads from cell-to-cell

- In varicella, VZV is transported from the respiratory mucosa (tonsils) to the blood in T cells (viremia), where virus is not accessible to antibodies.
  - Because of cell-to-cell spread, and innate immune responses, early viral spread is slow, so the incubation period of varicella is long (~2 weeks).
  - Slow spread prevents host from being overwhelmed before the adaptive immune response develops

- T helper (TH1) and cytotoxic T cells are required for host control of virus by adaptive immunity
VZV is highly cell-associated but spreads in two ways.

VZV latency is established by free virions that infect sensory nerve endings, and also by viremia.
Congenital varicella syndrome
Fatal neonatal varicella
Zoster in a 3 month old
VZV In the Immunocompromised

- Varicella is likely to be severe
  - Prevent or modify with pre-formed antibodies just after exposure (VZIG)
  - Virus spreads from cell-cell in body
    - requires CMI (cellular immunity) for host defense
  - Treat most immunocompromised patients immediately with acyclovir

- The frequency of zoster is increased
  - Probably related to low CMI response
  - Likely to suffer post-herpetic neuralgia (PHN) (also elderly)
Latent Infection with VZV

- VZV becomes latent in DRG, CNG, enteric ganglia (ENS)
- 6 of 68 genes (also RNA and proteins) are expressed during latency
- Suggests regulatory proteins are blocked from normal action, leading to inhibition of cascade of gene expression preventing lytic infection from occurring (latency)
- Latency is established when cell-free VZV in skin vesicles invades neurons and also by viremia
Gene expression in latent & lytic VZV infection

Latency genes

62 → 61?
4 →
21 →
29 →
63 →
66 →

E genes
6 →
16 →
28 →
51 →
52 →
55 →
etc →

L genes
68 →
31 →
37 →
67 →
14 →
10 →
e17 →
eetc →

Latent infection

Lytic infection

Hay and Ruyechan, Semin Virol 1994
Varicella Vaccine and Zoster Vaccine

- Same vaccine (Oka strain) is used to prevent VZV primary infection (varicella) and reactivation (HZ)
  - Dose of VZV is 15 times greater in HZ vaccine than in varicella vaccine
  - HZ vaccine for those over age 50 years is a therapeutic vaccine
  - Mechanism of action for HZ vaccine: stimulate CMI to VZV

- VZV becomes latent in DRG, CNG, enteric ganglia (ENS) after varicella vaccine
Varicella Vaccine (Oka)

- Live attenuated vaccine
- Most common complaint: mild rash in 5%
  - 1 month after vaccination; transmission rare
- Vaccine extremely safe; given as 2 doses
  - 1 dose: 85% completely protected; 15% partial immunity
  - 2 doses 98% effective in preventing varicella disease
- Little evidence for waning immunity
- Subsequent zoster is rare/unusual
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


Marin et al, Pediatrics, 2011
Varicella vaccine effectiveness over time (case-control study): little or no waning of immunity

Adapted from Vásquez et al. *JAMA* 2004;291:851-855. Yale-Columbia study
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
Numerous factors regarding VZV seem important for varicella vaccine’s success

- Varicella has an incubation period of 2-3 weeks
- Early innate immune responses in skin (Arvin) and cell-to-cell spread slow viral multiplication
- Viremia results in infection of organs
- VZV immune evasion occurs but is not well developed
- Can distinguish between vaccine and wild type VZVs
- Availability of an immune correlate for varicella (FAMA)
- Live attenuated vaccine
FAMA is the “gold standard” for assessment of varicella immunity (immune correlate).

In persons with a titer of $\geq 1:4$, fewer than 2% develop varicella after a household exposure ($n=131$).

Attack rate after household exposure in persons with a titer of $<1:4$ is 59% ($n=68$).

VZV DNA can be identified as WT or vOka

Amplify ORFs 54, 38 look for Bgl1, Pst1

vOka is Bgl1+, Pst1-

US WT is Bgl1-/+ , Pst1+

ORF 62, position 106262

– Oka has Sma1 site, WT does not

– sequencing of the segment 106035-106303 to determine whether T (WT) or C (Oka) is present at position 106262

– also positions 10811, 105705, and (107252) (Quinlivan JCM, 2012)
The incidence of zoster in vaccinees is low

Adult incidence extremely low (0.9/1000 person-years) (P-Y) (Hambleton JID 2008)

Lower rates in leukemic vaccinees than in leukemics after natural infection (4 studies in 1980s)

Healthy vaccinated children: 0.3/1000 P-Y; risk decreased ~4 times (Tseng 2008, Civen, 2009: PIDJ)

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

\[ p < 0.001 \]

\[ p = 0.012 \]
Vaccination Prevents Zoster in HIV-infected Children

Rate Per 1000 person years

$p=0.49$

$p<0.001$
Sensory ganglia were obtained from autopsied children.

- Autopsies were performed on 9 children soon after death (mean: 17.0 ± 1.5 hrs). 2/9 controls; 6/9 vaccinated.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Vaccination</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (control)</td>
<td>no</td>
<td>seizure</td>
</tr>
<tr>
<td>1 (control)</td>
<td>no</td>
<td>MVA</td>
</tr>
<tr>
<td>1.75</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>MVA</td>
</tr>
<tr>
<td>2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>4</td>
<td>yes</td>
<td>MVA</td>
</tr>
<tr>
<td>8</td>
<td>yes</td>
<td>Gunshot</td>
</tr>
<tr>
<td>10</td>
<td>yes</td>
<td>Operative comp</td>
</tr>
</tbody>
</table>

No VZV DNA or RNA was found (PCR) in patients who were \( \leq 1 \) year old and lacked history of varicella and VZV vaccination*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Trigeminal</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DNA examined: ORF 4, 31, 63, 68; RNA examined: ORF 4, 29, 62, 63

* These patients were considered to be controls.
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 Age</th>
<th>Vac</th>
<th>Trigeminal Right</th>
<th>Trigeminal Left</th>
<th>Cervical Right</th>
<th>Cervical Left</th>
<th>Thoracic Right</th>
<th>Thoracic Left</th>
<th>Lumbar Right</th>
<th>Lumbar Left</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.75</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>Oka</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>WT</td>
</tr>
<tr>
<td>2</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>WT</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>WT</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>WT</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>WT</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>WT</td>
</tr>
</tbody>
</table>

DNA detected: ORF 4, 62, 63, 68; RNA detected: ORF 4, 29, 62, 63
Severe varicella vaccine reactions are rare. *estimate 100 million doses distributed*

- 19 yo w cholangitis, lymphopenia
- 13 mo w undiagnosed ADA deficiency
- 16 mo w undiagnosed HIV and 8 CD4 cells per mm³
- 5 yo w asthma, steroids
- 6 yo, 11 yo w undiagnosed NK cell deficiency (2 patients)
- 8 yo w Di George syndrome
- 24 yo hypopuitarism on steroids
- 3 yo w acute leukemia
- HZ with meningitis, ACV, and recovery with no sequelae (9)
  - Vaccination, cancer, severe zoster (2)
- 16 yo with VZV ulcer; VZV reactivation in ENS
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
Immune Responses to VZV in an Adult Vaccinee

VZV FAMA Titer

VZV CMI

Vaccine
Rash
Exposure 3 yr
Exposure 7 yr
Exposure 20 yr
Will the incidence of zoster increase in the unvaccinated?

- Modeling predicted doubling of incidence of zoster for next 40 years, increased mortality: (2-4 to 4-8/1000 p-y)
- A number of studies show increase in zoster (since 1950s)
- Other recent studies show stable rates
- No diagnostic standardization
- Lack of good baseline data on incidence in pre-vaccine era
- Need to consider impact of other variables such as increasing age of population, immunocompromising illnesses, diabetes, stress
- Recent French study showed same incidence of HZ in isolated populations and general public (Gilliat et al, CID 2011)
- Asymptomatic reactivation may stimulate immunity to VZV
VZV DNA has been detected in saliva after space flight


<table>
<thead>
<tr>
<th>VZV DNA Shedding</th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>In saliva (PCR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Comments and Conclusions

• Varicella is a disease worth preventing
• Varicella vaccine is safe and effective in healthy hosts and as 2 doses
• When studies with varicella vaccine were initiated, its success in preventing disease was not really predicted (GAS); many said varicella was too mild a disease to be worth preventing
• In the early 1980s it was underappreciated that HZ could be prevented by vaccination
  • Recent information on HZ complications such as vasculopathy (Gilden) makes preventing HZ even more compelling
• Many investigators thought the vaccine would not work well because of viral latency; however lack of sterilizing immunity (reinfection and reactivation) have not presented a serious obstacle to success of VZV vaccines