A SHORT HISTORY OF VACCINATION AGAINST VARICELLA-ZOSTER VIRUS

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VZV infection presents a paradox

VZV is highly infectious *in vivo*.

But *in vitro* VZV spreads only slowly by cell-to-cell contact.

*Media contains no infectious virions.*
VZV proliferates in the epidermis during varicella and zoster.

- Infectious virions are produced in and shed from the suprabasal epidermis, which lacks MPRs.
VZV in history

- Varicella-zoster virus (VZV) is a very old virus (60-70 million years ago)
- Historically varicella confused with smallpox and syphilis
  - Presumably led to name “chickenpox”
- “Shingles” comes from Latin word for belt
- No one seemed to worry about VZV in early 20th century, although there was occasional mortality
- Weller isolated VZV in cell culture in 1953
- Weller and Coons developed the fluorescent antibody technique in 1954, using VZV
Cheatham, Weller, et al. reported fatal varicella in one child being treated for neuroblastoma and another on steroids for rheumatic fever in Boston, in 1956.

This child was my patient at Bellevue Hospital in about 1970.
Zoster is common in immunosuppressed patients and may be severe.

Zoster may disseminate in immunocompromised hosts but is rarely fatal.
Saul Krugman had a 60th birthday party at NYU in 1971

- Philip Brunell, Anne Gershon, and Mike Gershon attended.
- Brunell’s work on VZV sparked my interest in the virus.
  - VZV had the fascinating characteristic of latency
Big heroes dropped by and talked with little fellows at NYU in the ‘70s
FAMA is the “gold standard” for assessment of varicella immunity (immune correlate)

- This fluorescent antibody test, developed with tools learned at Oxford, was introduced in 1974.
- After a household exposure to VZV, fewer than 2% of persons with a titer of $\geq 1:4$, develop varicella (n=131).
- Attack rate after household exposure in persons with a titer of $<1:4$ is 59% (n=68).

In the early 1970s there were 3 potential approaches to fight VZV infections

- **Passive immunization (VZIG) in US, Canada**
- **Antiviral therapy**
  - Not available
- **Active immunization:**
  - Early attempts unsuccessful
  - Attenuated vaccine, developed by Takahashi.
  - Highly controversial.
Takahashi published numerous small studies of varicella vaccine from Japan (1974-7)

- Vaccinated 70 VZV-exposed hospitalized children without history of varicella (Lancet 1974)
  - 17% receiving steroids
  - 2 developed mild rash after 10-14 days
  - no cases of chickenpox
  - Was rash indicative of wild or vaccine type VZV?

- Varicella occurred in 0/26 vaccinated but in 19/19 non-vaccinated (control) children with family exposures to VZV
  - Children with malignancy in remission were vaccinated (chemotherapy interrupted)
  - little efficacy information
American virologists greeted Takahashi observations with controversy

- **Anti**
  - Too little was known about VZV latency
  - Immunity to VZV was not understood—would infection be postponed to later life?
  - VZV is a DNA virus and what would be the consequences of putting modified viral DNA into human hosts?

- **Pro**
  - Something had to be done to prevent varicella.
  - Seasonal epidemics were unstoppable.
  - Children were being cured of leukemia only to die of varicella.
  - Available data highly encouraging
“In my judgment, the elimination of the varicella-zoster problem is a desirable objective. I believe that the Takahashi varicella vaccine deserves more extensive study and clinical trials on an increasingly larger scale. If the reports of the successful tests already carried out by Takahashi and his associates can be independently confirmed, the prospects for success are very good.”

Albert Sabin, JAMA, October 1977
The FDA, BOB, NCI, and NIAID convened a workshop to discuss whether studies on varicella vaccine should be carried out in the United States.

Participants included: Drs. Jordan, Galasso, LaMontaigne, Plotkin, Krugman, Hilleman, Takahashi, Brunell, and Gershon.
The first adult recipient of varicella vaccine was immunized at NYU

- Pediatric intern, an only child, had never had varicella
- Developed very mild rash after injection.
- Vaccine had an unintended effect.
  - That intern devoted his life to the study of pediatric infectious disease (including varicella and zoster).
Immune responses to VZV in an adult vaccinee indicated protection and boosting.
Numerous studies of varicella vaccine followed

- **Open label collaborative clinical trial of children with ALL in remission** (Gershon et al, JAMA 1984)
  - On maintenance chemotherapy for at least 1 year (in remission)
  - Chemotherapy stopped for 3 weeks for vaccination
  - Two doses proved necessary
  - Some rashes due to Oka but nothing serious
  - 85% completely protected from varicella; rest had mild disease

- **Two double blind studies in healthy children**
  - One from USA (Weibel, 1984), one from Finland (Varis, 1996)
  - Highly protective, especially after large vaccine doses

- **Because some children with ALL required antiviral therapy to treat Oka, decision was made to immunize healthy children**
  - Led to proposal for universal vaccination of healthy susceptibles
Weller presents Takahashi with award at VZV meeting in Sorrento in 1994
Varicella Vaccine was licensed for universal use in US in 1995

- **Live attenuated vaccine (Oka)**
  - Major adverse effect is mild rash in 5%
  - Vaccine is extremely safe
- **Over 80% of vaccinees are completely protected**
  - Remainder develop mild infections
- **Little evidence of waning immunity with time**
  - Incidence of breakthrough infection does not increase
  - Zoster is unusual
- **Two doses eventually proved necessary because of vaccine failures after 1 dose resulting in outbreaks at day schools.**
  - Excellent record in health care workers (2 doses)
- **Accurate tests for immunity after vaccination not widely available.**
  - FAMA not licensed.
- **Paved way for vaccine against HZ**
Varicella vaccine is very effective: varicella incidence decreased with high vaccine coverage
Antelope Valley* CA, U.S., 1995-2004

*Varicella Active Surveillance Project site
Seward J et al, JAMA 2002;287 (5):606-611
Varicella Hospitalization Rates Fell 1994–2006

Rate per 100,000 population

0 1 2 3 4 5 6

Year


(ACIP Recommendation: 2 doses in 2006)

(ACIP Recommendation 1 dose)

CDC DATA, COURTESY JANE SEWARD

Marin et al, Pediatrics, 2011
Varicella vaccine effectiveness over time (case-control study) showed 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>
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</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>
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<tr>
<td>2 doses</td>
<td>0 (0.0)</td>
<td>22 (15.7)</td>
<td>&lt;0.001</td>
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The effectiveness of 2 doses of varicella vaccine vs 1 dose was 98.3%

Shapiro et al. JID 2011; Yale-Columbia Study
Vaccination Prevents Varicella in HIV-infected children

Rate Per 1000 person years

- Unvaccinated Pre-Vaccine Era
- Unvaccinated Post-Vaccine Era
- Vaccinated

(Son et al JID 2008)
The incidence of zoster in vaccinees is low

- Adult incidence is extremely low
  - (0.9/1000 person-years; [P-Y])

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

- Lower rates in healthy vaccinees
  - 0.3/1000 P-Y  4-fold decrease in risk
  - 1/3 of cases due to wild type virus

- No zoster in vaccinated HIV-infected children
Will the incidence of zoster increase in non-vaccinated individuals?

- Modeling predicted zoster incidence will double within 40 years, with significantly increased mortality
  - Studies show zoster incidence has increased since 1950s.
  - But ascertainment, numbers of aged, individuals with immunocompromising illnesses, diabetes, stress have also increased.

- Recent study showed incidence of zoster in isolated populations and general public is similar.
  - (Gilliat et al, CID 2011)

- Asymptomatic reactivation may stimulate immunity to VZV
Asymptomatic patients may experience increases in VZV antibody titer

- Luby et al described increases in CF titer in 6/12 renal transplant patients in 1977
  - Could have resulted from exposure to VZV
    - Against this possibility were frequency of increases, lack of seasonal distribution
  - Luby proposed that the phenomenon was due to an “unstable equilibrium between the virus and the host”
    - Supported the hypothesis of Hope Simpson of subclinical release of virus with increases in VZV immunity
    - Magnified and measurable in immunocompromised hosts
Edgar Hope-Simpson studied the epidemiology of zoster in people of various ages in his medical practice.

Hope Simpson proposed that there was periodic reactivation of latent VZV that stimulated long term immunity to the virus; when this was overcome, zoster occurred.
Reactivation of VZV without rash has demonstrated by the transitory presence VZV DNA in saliva

- 1/3 of astronauts shed non-infectious VZV in saliva following space flight
- Some patients with unilateral pain syndromes have VZV DNA in saliva
- 17% of hospitalized children have VZV DNA in saliva
- Question: could latency and mild/asymptomatic reactivation help to provide long term persistence of immunity to VZV?
Collaborators

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Wanda Setlik
Jane Seward
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Sharon Steinberg
Lisa Wang
Jerry Zhu
In conclusion

- I am thrilled to have received the Sabin Gold Medal
- I have had the tremendous good fortune to have worked with wonderful colleagues, including family members
  - Varicella and zoster vaccines have profited greatly from their input
  - I was especially privileged to have personally interacted with Sabin, Krugman, Weller, and Takahashi
- Most importantly, our combined effort has helped to make lives better for children and their families
  - We can prevent the devastation and expense that VZV used to cause. VZV vaccines are a big success!