Beneficence and Non-maleficence for Pediatric Research that Poses More than Minimal Risk and Uncertain Benefit

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2002 OHRP Review of Protocol Smallpox Vaccine in Children
Smallpox Vaccine in U.S. General Population

- 1800’s – 1972 Universal for ≥1 year
- 1972 Vaccine risks > risk smallpox
- 1980 Smallpox declared eradicated
- 2001 9/11, Anthrax, Fear of additional bioterrorism
Variola Major

30% Case-fatality rate
Exercise Overview

June 22-23, 2001

The Dark Winter exercise portrayed a fictional scenario depicting a covert smallpox attack on U.S. citizens. The scenario is set in three successive National Security Council (NSC) meetings (Segments 1, 2 and 3) which take place over a period of 14 days. Former senior government officials played the roles of NSC members responding to the evolving epidemic; representatives from the media were among the observers of these mock NSC meetings and played journalists during the scenario’s press conferences (see Players List). The exercise itself was held at Andrews Air Force Base, Washington, D.C., on June 22-23, 2001.
Dec 2001 survey: 75% of adults would take vaccine
Original Diluent

DILUENT FOR SMALLPOX VACCINE DRIED
Calf Lymph Type DRYVAX® WITH BRILLIANT GREEN

50% glycerin, 0.25% phenol and 0.005% brilliant green in Sterile Water for Injection, U.S.P.
Smallpox Vaccine Supply and Production

- **Dryvax**
  - 15 million doses – undiluted
  - 75 million @ 1:5 dilution

- **AvP Vaccine**
  - 70-90 million doses

- **Acam 1000**
  - ~54 million doses

- **Acam 2000**
  - ~155 million doses

Sources:
- Orenstein and Margolis
- CDC
# Response to Smallpox Vaccine by Dilution in Adults

<table>
<thead>
<tr>
<th>Dilution</th>
<th>No. Vac</th>
<th>% Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiluted</td>
<td>106</td>
<td>97.2 (92.0-99.4)</td>
</tr>
<tr>
<td>1:5</td>
<td>234</td>
<td>99.1 (97.0-99.9)</td>
</tr>
<tr>
<td>1:10</td>
<td>340</td>
<td>97.1 (94.7-98.6)</td>
</tr>
</tbody>
</table>

Frey et al NEJM 2002; 346: 1265-74
A Multicenter, Randomized, Dose Response Study of the Safety, Clinical and Immune Responses of Dryvax Administered to Children 2 to 5 Years of Age

- Protocol prepared June 2002
- Sponsor: National Institutes of Health
- Under FDA IND
- 40 children: 20 undiluted, 20 diluted 1:5
- Compare “take” rates and side effects

Approved by IRBs at Cincinnati Children’s and Kaiser Permanente
Harbor UCLA IRB Review

• CFR 46.405:
  – 5 for, 5 against, 1 abstention
  – Chair voted to break tie - 6 against
• CFR 46.407
  – 11 for, 0 against
• Aug 5, 2002 Referred to Secretary HHS
Robust Take
ERYTHEMA MULTIFORME

COMMON, IMPRESSIVE, BUT BENIGN; RARELY CAN SEE STEVENS-JOHNSON SYNDROME

Vincent A. Fulginiti, M.D.
Adverse Reactions: Eczema Vaccinatum
Progressive Vaccinia

Vincent A. Fulginiti, M.D.
Lesions during the first week of disseminated disease (day 5) Extensive scarring of the resolving lesions after 9 weeks of passive immunotherapy.

# Complications* from Smallpox Vaccine 10 State Survey 1968

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;1</th>
<th>1-4</th>
<th>5-9</th>
<th>&gt;20</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadvertent inoculation</td>
<td>507</td>
<td>577</td>
<td>371</td>
<td>606</td>
<td>529</td>
</tr>
<tr>
<td>Generalized vaccinia</td>
<td>394</td>
<td>233</td>
<td>140</td>
<td>212</td>
<td>242</td>
</tr>
<tr>
<td>Eczema vaccinatum</td>
<td>14</td>
<td>44</td>
<td>35</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Progressive vaccinia</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>42</td>
<td>10</td>
<td>9</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>

* Per million primary vaccinations

 Lane JM J Infect Dis 1970; 122:303
### Adverse Events Following Smallpox Vaccination* Among 665 Healthy Adults 18-32 Year Old Adults

<table>
<thead>
<tr>
<th>Event</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp $\geq 101^\circ$</td>
<td>3.0</td>
</tr>
<tr>
<td>Erythema $&gt;10$ cm</td>
<td>10.0</td>
</tr>
<tr>
<td>(mean =51mm)</td>
<td></td>
</tr>
<tr>
<td>HA mod-severe</td>
<td>13.9</td>
</tr>
<tr>
<td>Rash</td>
<td>14.3</td>
</tr>
<tr>
<td>Pain mod-severe</td>
<td>33.9</td>
</tr>
<tr>
<td>Missed work/school/recreation</td>
<td>36.5</td>
</tr>
</tbody>
</table>

*Most received a reduced dose

Frey et al NEJM 2002; 346: 1265-74
2002 Pediatric Protocol Review Issues

• Risk understated:
  – Encephalitis risk is higher in children
  – Serious complications not “remote”
  – Transmission

• Potential benefit overstated

• Consent from both parents

• Safety monitoring

• Alternatives
Non-maleficence

- Careful screening
- Minimize Exposure
- Undiluted vaccine known to result in high take rates in children
- Study diluted vaccine first: if high take rate, no need to expose additional children to undiluted vaccine
Beneficence

• Select children whose parents have received smallpox vaccine:
  – Maximize parental knowledge of vaccine
  – For parents working in laboratories with the vaccine, some theoretical potential for inadvertent exposure
45 CFR 46.404, 405, 406, and 407

• Not approvable under 404, 405, or 406
• CFR 46.407
  – Greater than minimal risk, no or uncertain benefit
  – Reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
Since initiating this regulatory review process, bioterrorism preparedness plans have evolved such that, under current plans, the potential to use diluted Dryvax® in children will no longer exist. In the absence of plans to use diluted Dryvax® in children, the Secretary, HHS, and the Commissioner, FDA, have determined that there is no justification for this particular clinical investigation to proceed. Please note that this determination applies only to the above-referenced study involving Dryvax® in children, and does not pertain to future research involving smallpox vaccines in children.

Statement issued January 25, 2003 from Secretary and Commissioner
Monkeypox in a Child
Wisconsin 5/27/03

Smallpox Vaccine given to exposed children and adults
Monkeypox is Preventable with Smallpox Vaccine

Monkeypox Transmission Cycle in Central Africa

Primary hosts: Rodents (squirrels, rats)

Incidental hosts: Non-human primates (low prevalence)

Bushmeat hunting

Humans

Secondary transmission

Other humans

www.environment.ucla.edu/ctr/news/
Developments Since 2002

- Myocarditis risk ~1/10,000
- Dryvax not available
- ACAM2000 licensed
- MVA? - in stockpile, not licensed
What Constitutes Sufficient Estimated Risk to Justify Studies in Children for Countermeasures?

- Pediatric Rule: Need to study vaccines and drugs in children when there is anticipated use in children
www.hhs.gov/ohrp/archive/children/dryvax.html