New Breakthroughs in Assuring Affordable IPV Options for Low-Income Countries in the Post-Eradication Era

Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE), Geneva, 5-7 April 2011
Requests DG/WHO to:

…develop appropriate strategies and products for managing risks, including safer processes for IPV production & affordable strategies for its use…
Affordable IPV Strategy: Different Approaches

- Enable IPV production in lower-cost
doses/vial or micro-needle patches to reduce required dosage

- Reduce amount of dose
- Reduce amount of antigen content
- Reduce production cost

- Enable IPV production in lower-cost
Operational Definition of Affordable IPV

- A price of $0.50 or less per "immunizing*" dose of IPV


*An immunizing dose can be adjuvanted or fractional.
Oman Trial
Doses Given at 2, 4, 6 Months, Oman

<table>
<thead>
<tr>
<th></th>
<th>n=187</th>
<th>n=186</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>seroconversion, %</td>
<td>228 (144-287)</td>
<td>724 (575-912)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>[median titer]‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>seroconversion, %</td>
<td>288 (228-456)</td>
<td>1149 (912-1149)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>[median titer]‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[median titer]‡</td>
<td>362 (287-456)</td>
<td>≥1448 (≥ 1448)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Randomized Controlled Clinical Trial of Fractional Doses of Inactivated Poliovirus Vaccine Administered Intradermally by Needle-Free Device in Cuba

Sonia Resik,1 Alina Tejeda,2 Pedro Mas Lago,3 Manuel Díaz,4 Ana Carmenat Belkis Galindo,1 Anthony Burton,3 Martin Friede,1 Mauricio Landaverde,9 and
1Pedro Kouri Institute, Havana, and 2Provincial Health Office, Camaguey, Cuba; 3World Health Organization, Washington, DC

Background. As part of an evaluation of strategies to make inactivated poliovirus vaccine administered intradermally by a needle-free jet injector device comparably effective to conventional delivery, we conducted randomized clinical trials of fractional doses of inactivated poliovirus vaccine in a cohort of healthy young adults.

Methods. We compared the immunogenicity and reactogenicity of full dose of vaccine administered intradermally using a needle-free jet injector device compared with full dose administered by standard intramuscular needle. Subjects were randomized at birth to receive IPV at 6, 10, and 14 weeks.

Results. A total of 471 subjects were randomized to the 2 study groups. The 2 study groups were comparable in terms of age, sex, and other demographic characteristics. The primary endpoint of the study was the seroconversion rate to each of the 3 poliovirus serotypes at 4 weeks after the last dose of vaccine. The seroconversion rates were similar in the 2 study groups. The incidence of local and systemic reactogenicity was also similar in the 2 study groups.

Discussion. These results suggest that intradermal delivery of poliovirus vaccine using a needle-free jet injector device is a feasible and effective alternative to intramuscular delivery. Further studies are needed to determine the optimal dose and interval for immunization with this delivery method.

Fractional Doses of Inactivated Poliovirus Vaccine in Oman

S. M. D. Shyam Bawikar, M. D., M. P. H., M. D. Mir, M. D., M. P. H., Mahmoud M. A. Shaban, M. D., and A. A. Avoort, Ph. D., M. A. Pallansch, Ph. D., B. S. Meghana Sreevatsava, M. P. H., and M. D., M. P. H. T. M.

Background. As part of an evaluation of strategies to make inactivated poliovirus vaccine delivered at risk areas in developing countries and the World Health Organization, we conducted a randomized clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by a needle-free jet injector device to improve the effectiveness of the poliovirus vaccine. The study was conducted in the Sultanate of Oman, which has a high incidence of vaccine-preventable diseases and a high prevalence of polio-like illnesses. The project was funded by the World Health Organization and the United Nations Children's Fund.

Methods. The study was conducted in a cohort of healthy young adults. The primary endpoint of the study was the seroconversion rate to each of the 3 poliovirus serotypes at 4 weeks after the last dose of vaccine. The seroconversion rates were similar in the 2 study groups. The incidence of local and systemic reactogenicity was also similar in the 2 study groups.

Results. A total of 471 subjects were randomized to the 2 study groups. The 2 study groups were comparable in terms of age, sex, and other demographic characteristics. The primary endpoint of the study was the seroconversion rate to each of the 3 poliovirus serotypes at 4 weeks after the last dose of vaccine. The seroconversion rates were similar in the 2 study groups. The incidence of local and systemic reactogenicity was also similar in the 2 study groups.

Discussion. These results suggest that intradermal delivery of poliovirus vaccine using a needle-free jet injector device is a feasible and effective alternative to intramuscular delivery. Further studies are needed to determine the optimal dose and interval for immunization with this delivery method.
Cuba Trial
Study Objectives

• To evaluate whether a schedule of two fractional 0.1 ml IPV doses administered intradermally (intervention) provides comparable seroconversion with a two-dose schedule of full 0.5 ml IPV doses (control) administered intramuscularly at 4- and 8-month of age

• To assess the contribution to seroconversion in each group after the first, and second dose of study vaccines

• To determine the proportion of subjects that responded with a priming immune response after the first dose of IPV

• To assess whether each study arm has comparable adverse events (systemic and local)
Definitions

• **Seroconversion:**
  – Non-detectable (<8) to detectable (≥8) reciprocal antibody titer; if not, then
  – A four-fold increase in reciprocal antibody titer in consecutive samples with detectable titers

• **Seroprevalence:**
  – Detectable (≥8) antibody titer

• **Priming:**
  – No seroconversion after 1st dose of IPV and seroconversion within 7 days after 2nd dose
## Study Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Before month 4</th>
<th>Month 4</th>
<th>Month 8</th>
<th>A week after month 8</th>
<th>9 month</th>
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<tbody>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sample</td>
<td>Heel</td>
<td>Heel</td>
<td>Heel</td>
<td>Heel</td>
<td>Heel</td>
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<td>Safety assessment</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Potentially eligible subjects N=611

Not Screened N= 244

Signed Informed Consent N=367

Not Enrolled N=47

Enrolled N=320

Randomization

47 not enrolled

- Consent withdrawal 16
- Did not meet entry criteria 27
  - 1 low weight
  - 1 low apgar
  - 1 low 10 percentile
  - 16 infectious disease
  - 3 immunosuppression treatment
  - 2 allergy
  - 1 convulsive seizure
  - 1 congenital illness
- Moved out of study area 4

Fractional dose N=160

Completed study N=157 (98.1%)
  3 OPV exposure

Full dose N=160

Completed study N=153 (95.6%)
  3 out of study area
  1 respiratory illness
  3 OPV exposure

3 OPV exposure
### Demographic & Study Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Fractional (n=157)</th>
<th>Full-dose (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>52.2%</td>
<td>56.9%</td>
</tr>
<tr>
<td>Birth weight (kg) median + 95% CI</td>
<td>3.40 (3.35-3.50)</td>
<td>3.42 (3.40-3.54)</td>
</tr>
<tr>
<td>Age at dose 1 (days)</td>
<td>122 (121-122)</td>
<td>122 (121-123)</td>
</tr>
<tr>
<td>Age at dose 2 (days)</td>
<td>241 (241-242)</td>
<td>241 (241-242)</td>
</tr>
<tr>
<td>P1 seropositivity + median titer (95% CI)</td>
<td>30.2% &lt;8 (&lt;8-&lt;8)</td>
<td>33.8% &lt;8 (&lt;8-&lt;8)</td>
</tr>
<tr>
<td>P2 seropositivity + median titer (95% CI)</td>
<td>35.2% &lt;8 (&lt;8-9)</td>
<td>46.8% &lt;8 (&lt;8-9)</td>
</tr>
<tr>
<td>P3 seropositivity + median titer (95% CI)</td>
<td>8.8% &lt;8 (&lt;8-&lt;8)</td>
<td>9.1% &lt;8 (&lt;8-&lt;8)</td>
</tr>
<tr>
<td></td>
<td>Fractional (n=157)</td>
<td>Full-dose (n=153)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>1st dose seroconversion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4-8 mos)</td>
<td>16.6% (26/157)</td>
<td>46.4% (71/153)</td>
</tr>
<tr>
<td><strong>Priming (8 mos – 8 mos + 7 days)</strong></td>
<td>90.8% (119/131)</td>
<td>97.6% (80/82)</td>
</tr>
<tr>
<td><strong>Seroconversion between 8 mos + 7 days &amp; 9 mos</strong></td>
<td>16.7% (2/12)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td><strong>2nd dose seroconversion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8-9 mos)</td>
<td>92.4% (121/131)</td>
<td>100% (82/82)</td>
</tr>
<tr>
<td><strong>Cumulative two-dose seroconversion</strong></td>
<td>93.6% (147/157)</td>
<td>100% (153/153)</td>
</tr>
</tbody>
</table>
Immunity Contribution by Dose

Not immune
2nd dose
Priming
1st dose

P1
P2
P3

ID
IM
ID
IM
ID
IM

0%
20%
40%
60%
80%
100%
<table>
<thead>
<tr>
<th>Visit</th>
<th>Fractional (n=159)</th>
<th>(n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI)</td>
<td>(&lt;8-&lt;8)</td>
<td>(&lt;8-&lt;8)</td>
</tr>
<tr>
<td>95% CI)</td>
<td>&lt;8 (&lt;8-&lt;8)</td>
<td>11 (9-14)</td>
</tr>
<tr>
<td>8-month + 7 days (median titer + 95% CI)</td>
<td>713 (566-898)</td>
<td>_ (1448-1448)</td>
</tr>
<tr>
<td>9-month (median titer + 95% CI)</td>
<td>450 (357-566)</td>
<td>_ (1448-1448)</td>
</tr>
</tbody>
</table>
Trial Summary

• High seroconversion after first dose of fractional and full-dose IPV, ranging from 15.1% (ID P3) to 63.6% (IM P2)
  – significantly lower median titer for ID arms

• Priming evident in greater than not seroconvert after first dose

• Second dose IPV closed the remaining immunity gaps and boosted antibody titers

• Drop in antibody titers between 8 mos and 7 day and 8 mos and 30 day visits

• Only minor adverse events
Immunology
Fig. 1. Memory B cell and plasma cell differentiation. Following antigenic stimulation, naïve B cells undergo clonal expansion and form clusters of activated B cells known as extrafollicular foci. These activated B cells can either differentiate into short-lived plasma cells, or they can migrate back into the follicle and initiate a germinal center reaction. After proliferation and affinity maturation, germinal center B cells produce both long-lived plasma cells that produce high affinity antibodies and memory B cells that have high affinity B cell receptors. Memory B cells presumably self-renew by homeostatic proliferation. Memory B cells may also periodically differentiate, in an antigen-dependent or antigen-independent manner, into long-lived plasma cells to maintain long-term antibody production.
Hepatitis A virus
- picornaviridae family
- non-enveloped, 27-28 nm diameter spherical virus
- single-stranded linear RNA of 7,478 nucleotides
- single serotype
- Probably using receptor to enter cell


**Figure**  Titers of anti-HAV antibodies before and 28 to 35 days after a second dose of Havrix 1440 was given to 54 vaccinees, 4 to 8 years after a single, primary dose.
Research Questions

• *Duration of priming effect*
  – hepatitis A data informative

• *Quality of priming immune response*
  – low- or high-affinity antibody

• *Translation into efficacy*
  – no VAPP after a single IPV dose (one exemption)

• *Research*
  – assess B-cells after first dose of IPV
Potential Implications

• One-dose of IPV results in >90% immune response (seroconversion and priming) regardless whether fractional or full-dose IPV

• A second dose of IPV results in high seroprevalence and high antibody titers

• Our study supports the feasibility of a one-dose IPV priming strategy

• The immunologic mechanisms for priming (and duration) should be further investigated
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- Mercedes
- Susana Madrigal
- Chavela
- Marelis
- Lea Guido

More than 100 doctors and nurses from 12 Policlinicas
Thank You!