History of Cutaneous Administration of Inactivated Polio Vaccine and Novel Devices for Dose-sparing Delivery

Bruce G. Weniger, MD, MPH, Vaccine Technology, CDC

7th WHO/UNICEF Consultation with OPV/IPV Manufacturers and National Regulatory Authorities

Inconsistent Terminology

Various terms for putting antigen into or onto the skin:

Prepositional prefix | Adjectival root | Noun
---|---|---
Epi... | cutaneous... | vaccination
Endo... | Cutaneous... | immunization
Intra... | dermal... | delivery
Per... | Epithelial |...
Trans... | Needle-free... | Patch...
Skin... | Topical... |...skin

Latin origin (cutis = skin)
Greek origin (derma = skin)

Proven and Theoretical Advantages of Current and Future Methods for Cutaneous Vaccination

- Minimal invasiveness: Fewer unexpected serious adverse events than other routes
- Local reactions easier to monitor and treat
- Less dependent on patient cooperation to administer
- Relatively sure and certain delivery
- Exceptions: improper Mantoux method for classical ID
- Potentially needle-free
- Dose-sparing ability (documented for classical ID)
- Large surface area for simultaneous vaccination of competing antigens
- Disadvantages:
  - Difficult Mantoux method
  - Local reactions may rule out some adjuvants
  - High cost of newer patented technologies

Suggested Usage

- Adjectives
  - "Cutaneous" – All processes that target any part of the skin for delivery of antigen
  - "Intradermal" (aka “Classical Intradermal”) – A type of cutaneous vaccination in which a bolus of liquid is deposited into the dermis to raise a visible bleb
- Nouns
  - "Vaccination" (per Dr. Pasteur honoring Dr. Jenner) – The physical process of introducing foreign substances into the body to stimulate an immune response
  - "Immunization" – The broad field of manipulating the immune system to confer disease protection, including related programs and policies and financing, etc.

Nomenclature and advantages of cutaneous route

- Clinical trials of intradermal polio vaccination
- Traditional methods for intradermal vaccination
- New devices for classical ID delivery
- Promising technologies for cutaneous delivery
Summary of Intradermal Immunogenicity Literature for Existing Conventional Vaccines of High Interest

- Excellent results
  - Rabies (~117, already widely used ID in developing world)
- Good results worth pursuing
  - Influenza (~2 dozen)
  - Polio (IPV) (~1 dozen)
- Mixed to poor results
  - Hepatitis B (~90)
  - Measles (~15)
- No data
  - Polysaccharide vaccines (MEN, PNU, HIB)
  - Exception: Gotschlich 1972 – good results for MENps-A

### POLIPV Intradermal Vaccination – Early Salk Trials

- Aqueous formulation
- 27 children and adults at Watson School
- 2 doses 0.1 mL ID 6 weeks apart

#### Results
- Type 2 (MEF-1) = 100% 4-fold rise
- Types 1 (Mahoney) and 3 (Saukett): = 0%
- *Note: excessive inactivation*
- Later studied IM route with 1.0 mL doses of mineral oil emulsions

#### Salk JE, et al. JAMA, 23 March 1953; 151:1081-1098

### POLIPV Intradermal Vaccination – Later Salk Trials

- Aqueous formulation
- 20 children and 5 adults at Watson School and community
- 3 doses 0.1 mL ID 1 week apart

#### Results
- "+" = titer 1:4
- All responses with pre-existing antibody > 4-fold
- Types: 1 = 100% (25/25), 2 = 84% (21/25), 3 = 96% (24/25)

#### Salk JE. Pediatrics, Nov 1953; 12:471-482

### POLIPV Intradermal Vaccination – Iceland Study

- Compared American vaccine 0.2 mL SC versus Danish vaccine 1.0 mL ID
- Overall poor responses, particularly types 1 and 3
- ID titres generally lower than SC

#### Samuel, Lancet 1958;27:333-6

### POLIPV Intradermal Vaccination – Further Studies

#### Source
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Dose / Tissue / Method</th>
<th>Immune Response</th>
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<tr>
<td>Connolly, Lancet 1958:27</td>
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#### Immune Response
- 4-fold to 1024-fold booster:
  - 1:17/18 2:17/18 3:17/18
- Serum dilution, indication and erythema indicative of CMV in 1 subject

#### Samuel, Lancet 1959:133

### Notes
- ID=intradermal NS=needle/syringe PO=by mouth IM=intramuscular
- *Ab appearance or x 4 calculated titer measured 6th week

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**SUMMARY**

- Excellent results
  - Rabies (~117, already widely used ID in developing world)
- Good results worth pursuing
  - Influenza (~2 dozen)
  - Polio (IPV) (~1 dozen)
- Mixed to poor results
  - Hepatitis B (~90)
  - Measles (~15)
- No data
  - Polysaccharide vaccines (MEN, PNU, HIB)
  - Exception: Gotschlich 1972 – good results for MENps-A
**POLeIPV Intradermal Vaccination – 1998 Study**

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<th>Immune Response</th>
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<td>Normal, vaccine 1996, 16:32b:931</td>
<td>Immune-naiive infants &amp;-thr.</td>
<td>0.1 mL @0,2 m ID NS</td>
<td>1: 100% 2: 100% 3: 100%</td>
</tr>
<tr>
<td></td>
<td>No maternal Ab+</td>
<td>0.1 mL @0,1,2 m ID NS</td>
<td>1: 100% 2: 100% 3: 100%</td>
</tr>
<tr>
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<td>Immune-naiive infants &amp;-thr.</td>
<td>0.1 mL @0,2 m ID NS</td>
<td>1: 87% 2: 68% 3: 96%</td>
</tr>
<tr>
<td></td>
<td>No maternal Ab+</td>
<td>0.1 mL @0,1,2 m ID NS</td>
<td>1: 88% 2: 74% 3: 96%</td>
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* ns: p>0.05  ** ns: p>0.01  † ns: p>0.1

**Historical controls:** types 1+3 eIPV ID > OPVx3, type 2 eIPV ID < OPVx5

**POLeIPV Intradermal Vaccination – 2000s Studies**

- WHO-sponsored trials in Cuba and Oman
- Using Biojector® 2000 needle-free jet injector
- Details and results to be reported by Roland Sutter

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**Classical Intradermal (ID) Injection**

- "Mantoux" method
  - Simultaneous invention in 1908
  - Felix Mendel (Germany), Charles Mantoux (France)
  - Originally for TB skin testing and vaccination
  - Fine-gauge needle, bevel-up, parallel into skin
  - Fluid bolus below basement membrane

**Advantages**
- Uses existing, off-the-shelf vaccines
- Enhanced immune response permits dose-sparing

**Disadvantages**
- Requires training, skill, time, needle dangers
- Local reactions from irritating ingredients

---

**Cutaneous Smallpox Vaccination Methods for Eradication**

- **Multi-use nozzle jet injectors ("MUNJIs")**
  - Invented in 1950s by U.S. military
  - High-speed devices - 600-1,000 doses/hour
  - Used in mass campaigns 1950s-1990s
  - Pox, meningitis, yellow fever, measles, influenza
  - Used for first half of eradication program
  - Special intradermal needles
  - Fine-gauge needle, bevel-up, parallel into skin
  - Fluid bolus below basement membrane

**Advantages**
- High-speed, mass vaccination
- Expanded vaccine delivery to non-traditional sites

**Disadvantages**
- Requires training, skill, time, needle dangers
- Local reactions from irritating ingredients
- Withdrawn for safety reasons. Replaced by DCJIs

- **Bifurcated needle**
  - Invented 1967 by Benjamin Rubin (Wyeth)
  - Required for WHO smallpox program
  - Replaced MUNJIs for latter half of eradication
  - Required higher-titer formulation
  - Tines hold 2.5 µL (0.0025 mL); most undelivered

**Ped-O-Jet® MUNJI Intradermal Nozzle**

- **ID nozzle:** 45° angle of injection
- Recessed to create air gap between skin and orifice
- Hundreds of millions of intradermal doses
- Smallpox
- Yellow fever (FNV)
- Some BCG
- Added spacer on IM nozzle also works for ID:
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Disposable-cartridge Jet Injectors (DCJIs)
Overcome safety concerns for blood transfer by MUNJs

Investigational Intradermal Spacer on Biojector® 2000 DCJI
- Creates 2 cm gap between nozzle and skin
- Same perpendicular injection and technique as for licensed IM and SC cartridges
- Clinical trials of intradermal delivery:
  - Cancer, HIV, lymphoma, malaria vaccines
  - Influenza (Dom. Rep.)
  - Polio (Cuba, Oman)

Intradermal Injection via Biojector® 2000 Jet Injector with Investigational Spacer

Vitavax™ DCJI
- Bioject, Inc., Portland, OR (www.bioject.com)
- Manually-wound spring, targeted for developing countries
- Autodisabling color-coded cartridges:
  - IM, SC, ID

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BD Investigational Prefilled Intradermal Syringe
- Soluvia™ Micro-delivery System, Becton, Dickinson
- Human version

• 30 gauge needle
  OD=0.305mm, projects 1.5 mm
- Clinical trial of influenza
  Belshe et al NEJM 2004
- Investigational ID CBA vaccine (flag eluate) – good responses
- Control vaccine: full dose IM of Aventis Fluzone
- Exclusive worldwide license to sanofi pasteur for many vaccine indications

BD Investigational Prefilled Intradermal Syringe

Promising Methods for Cutaneous Delivery
- Passive diffusion with or without enhancers
  Occlusion and hydration
  Plain water under occlusive patch
- Bacterial exotoxins
  • Iomai, Inc.
  - Heat-labile enterotoxin of E. coli (LT)
  - Boost elderly influenza response
  - 75% protective efficacy for mod.-sev. travelers diarrhea (ICAAC 2007, ab G-1247A)
- Other chemicals
  Acetone rubbing
  Protein and colloidal carriers
  • Bacterial flagellin
  • Colloidal carriers

Promising Methods for Cutaneous Delivery

• Mechanical disruption of stratum corneum
  Stripping and Abrading
  • Cellophane tape
  • Friction by rubbing
  • Emery, pumice
  • Uncoated microabrasives

Promising Methods for Cutaneous Delivery

• Coated macrotines
  Longstanding BCG device
• Coated microtines
  • Macroflux® platform (Zosano Pharma)

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Promising Methods for Cutaneous Delivery

PROMISING METHODS FOR CUTANEOUS DELIVERY

Hollow microneedle arrays
- Microneedles (Georgia Tech)
- Easy Vax™ DNA Vaccination System (Cytopulse Sciences)
- Norwood Abbey/MIT
- Corium (ex P&G)
- Many others

Dissolving microneedle arrays
- Georgia Tech
  • Carboxymethyl cellulose
  • 75µm tall before insertion
  • Theraject
  • Many others

http://www.zosano.com
http://www.corium.com
http://www.cytopulse.com
http://www.pellion.com
Promising Methods for Cutaneous Delivery

- Electromagnetic energy
  - Light
  - Laser ablation
  - Electricity
  - Thermoporation
  - Induced current zaps holes in stratum corneum
  - Electroporation
  - Electric current promotes antigen uptake (abstr. S9)
  - Electro-osmosis
  - Solvent flows carry non-charged molecules
  - Iontophoresis
  - Field carries charged molecules
  - RF waves / heat
  - Sound energy
  - Ultrasound

Laser Assisted Drug Delivery
Norwood Abbey
ViaDerm™ TransPharma Medical
PassPort™ Patch
Altea Therapeutics

Promising Methods for Cutaneous Delivery

- Gas-mediated kinetic deposition
  - Helium gas blows antigen carriers into skin
  - PowderMed (Pfizer)
    - RNA/DNA-coated gold beads (Patent-Mediated Epidermal Delivery)
    - Antigens reformulated to suitable size and density (Epidermal Powder Immunization)
  - Microcision
    - “Sandblast” coated aluminum oxide microcrystals
    - Harvard-MIT

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Thank you.

Disclaimers
- Commercial products and prototypes are named and illustrated for information only. No endorsement or recommendation by the CDC or DHHS is implied or should be inferred.
- The findings and conclusions in this presentation are those of the author. They do not necessarily represent the views of the CDC, have not been formally disseminated by CDC, and should not be construed to represent any agency determination or policy.

Skin Cross-section (1.6 - 3 mm thick)

Activated Langerhans cells in Epidermis 48 Hours after Cutaneous Vaccination with E. coli LT

Microphotograph courtesy: IOMAI, Inc.
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Literature on Classical Intradermal Vaccination
- Smallpox
  - Many, primary route
- Tuberculosis (BCG)
  - Many, primary route
- Yellow Fever
  - Primary route W. Africa 1940s/50s
- Rabies
  - 2/17
- Hepatitis B
  - 20
- Influenza
  - 2/3
- Polio (IPV)
  - 16
- Cholera
  - 15
- Measles
  - 15
- Typhoid
  - 11
- Tetanus
  - 6
- Hepatitis A
  - 5
- Diphtheria-Tetanus-Pertussis
  - 2 (Rossier 1968, Stantonfield 1972)
- Tick-borne encephalitis
  - 2 (Zdaudek 1984, 1986)
- Measles-Typhoid
  - 1 (Wegmann 1976)
- Rota-Virus
  - 1 (Koek 1985)
- Smallpox-BCG
  - 1 (Vaughn 1973)
- Smallpox-Measles
  - 1 (Budd 1967)
- Smallpox-Measles-Yellow Fever
  - 1 (Meyer 1964)
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  - 1 (Budd 1967)
- Smallpox-Measles-Yellow Fever
  - 1 (Meyer 1964)

Older, Alternative Cutaneous Methods
- Primarily for BCG vaccine
- Scarification
- “Multiple Puncture” method
- Rosenthal: straight needles
- Multi-tined devices
  - “Kuchiki needle”
- “Percutanous” (PC) method
  - Still used in Japan and few other markets
- Mono-test™, Mono-Vacc™
  - Discouraged for both BCG and tuberculin skin testing

Classical Intradermal (ID) Injection
- Intradermal nozzles or spacers on jet injectors
  - Multi-use-nozzle jet injectors (MUNJs)
  - Disposable-cartridge jet injectors (DCJIs)

Early Tools for Cutaneous Smallpox Vaccination
- A. Vaccinostyle
- B. Rotary lancet
- C. Surgical needle

Jet Injectors for Immunization
- Squirts pressurized liquid via tiny orifice (~0.15mm) into tissues
- 1860s: Technology invented in France
- 1940s: Single-use devices for insulin and other drugs
- 1950s: adapted for high-speed vaccination mass campaigns
  - Multi-use-nozzle jet injectors (MUNJs)
  - Many manufacturers

Using Multi-use-nozzle Jet Injectors (MUNJs)
Demonstration of Motorized LectraJet® Jet Injector


- Subjects: Healthy 26-to-<24 month old children
- Design:
  1. Experimental: N=150 (50 per study arm)
  2. Control: N=150 (50 per study arm)

- Size: Total N=450 (150 per study arm)
  - Phase 1: n=48 (16 per arm)
  - Phase 2: n=402 (134 per arm)

- Soluvia™ Micro-delivery System
  - Animal model version
  - 34 gauge needle (shown on 1¢ coin)
  - OD=0.178 mm
  - Sized for animal model studies - mice, rabbits, Cynomolgus monkeys
  - Good responses: anthrax, influenza, Japanese encephalitis vaccines

- Promising Methods for Cutaneous Delivery
  - Mechanical disruption of stratum corneum (continued)
  - Sharped human abdominal skin, then 30 toothbrush strokes, applied liquid vaccine and occlusive patch

- Immune responses
  - Skin: modest to good immune responses at highest doses
  - Intranasal: best

- Local reactions
  - Skin: mild erythema, rash, itching
  - Nose: mild irritation

Key Research Questions for ID to Address

- Reactogenicity to alum and other adjuvants?
  - Will local skin reactions to existing and future adjuvants be tolerable?
  - Will these two major dose-sparing strategies – ID route and adjuvantation – be synergistic or antagonistic?

- Immunogenicity?
  - How will current formulations fare when used in targeted populations?

- Polysaccharide vaccines?
  - Can any be delivered ID in economical reduced doses?

- Study design to prove dose sparing?
  - Would a reduced dose into the traditional IM or SC compartment work as well as ID?