Historical and Clinical Background on Cutaneous Vaccination

Bruce G. Weniger, MD, MPH, Centers for Disease Control and Prevention

Meeting on Intradermal Immunization: An Alternative Route for Vaccine Administration

- Potential advantages; nomenclature
- Historical usage and methods
- Classical intradermal (ID) à la Mantoux
- Jet injectors, abandoned and resurrected
- New methods for ID vaccination
- Clinical aspects
- Research questions for ID delivery
- Promising methods for cutaneous delivery
Proven and Theoretical Advantages of Current and Future Cutaneous Vaccination - 1

- Minimal invasiveness
  - Less serious unanticipated adverse events than other routes?
    - Oral - e.g., intussusception (Rotashield®, Wyeth)
    - Intranasal - e.g., Bell’s palsy (Nasalflu®, Berna)
    - Intramuscular/Subcutaneous injection - abscess, nerve injury, hematoma
  - Local adverse reactions easier to monitor and treat?
  - Less dependent on patient cooperation to administer
    - Think children: squirming, unable to swallow capsules, actuate inhalers

- Relatively sure and certain delivery
  - Gold standard: intramuscular (IM) and subcutaneous (SC) via needle-syringe (N-S)
    - Oral delivery - spitting out or vomiting
    - Intranasal/respiratory delivery - sneezing or coughing
  - Exception: improper Mantoux method for classical intradermal (ID) injection

- Needle-free delivery
  - Reduce risks and costs of sharps in medical waste disposal stream
  - Exception: Mantoux method for classical ID

Proven and Theoretical Advantages of Current and Future Cutaneous Vaccination - 2

- Dose-sparing ability (documented for classical ID)
  - Enhanced or equivalent immune response for many antigens compared to IM and SC
  - Protect larger populations with scarce or expensive vaccines

- Large surface area for simultaneous vaccination of competing antigens

- Disadvantages
  - Difficult to perform Mantoux method of classical ID injection
  - Local reactions from irritating vaccine components? (e.g., some adjuvants)
  - High cost of newer patented technologies
### Inconsistent Nomenclature

Various terms for putting antigen into or onto the skin:

<table>
<thead>
<tr>
<th>Prepositional prefix</th>
<th>Adjectival root</th>
<th>Noun</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi…</td>
<td>…cutaneous …</td>
<td>…vaccination</td>
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<tr>
<td>Endo…</td>
<td>Cutaneous …</td>
<td>…immunization</td>
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<tr>
<td>Intra…</td>
<td>…dermal …</td>
<td>…delivery</td>
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<td>Per…</td>
<td>Dermal …</td>
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<td>Trans…</td>
<td>…epithelial</td>
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<td>Needle-free …</td>
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<td>Patch …</td>
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<td>Skin …</td>
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<td>Topical …</td>
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Latin origin (*cutis* = skin)  
Greek origin (*derma* = skin)

### Suggested Terminology

**Adjectives**

- "**Cutaneous**" – All processes that target any part of the skin for delivery of antigen
  - Excludes needles or jets passing through to deposit into fat (SC) or muscle (IM)
- "**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
  - Includes the Mantoux needle method and newer techniques that achieve a similar result

**Nouns**

- "**Vaccination**" (per Dr. Pasteur to honor Dr. Jenner) – The mechanical 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
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**Smallpox – First “Vaccine”**

- Variolation (wild variola virus)
  - Nasal insufflation, circa 1000 AD, China
  - Cutaneous inoculation, 1500s, India
    - Introduction from Asia to Europe, 1700s
    - Cutaneous route remains the standard today
- Vaccination (cross protecting cowpox/vaccinia)
  - Protection after zoonotic cowpox known in 1700s in English cattle and dairy farm communities
  - First intentional prophylactic vaccination 1774
    - Benjamin Jesty, cattle breeder
  - First scientific study and publication 1798
    - Edward Jenner, scientist, country general physician
Early Tools for Cutaneous Smallpox Vaccination

A. Vaccinostyle
B. Rotary lancet
C. Surgical needle


Smallpox mass campaign, New York City, April 1947

- 12 cases (2 fatal) of smallpox
- >5.265 million persons vaccinated in 2 weeks (6.35m total)
- “1,000s” of MDs, RNs
Later Methods for Cutaneous Smallpox Vaccination

- **Multi-use nozzle jet injectors (“MUNJJs”)**
  - Invented in 1950s by U.S. military
  - High-speed devices - 600-1,000 doses/hour
  - Used in mass campaigns 1950s-1990s
    - polio, meningitis, yellow fever, measles, influenza vaccines
  - Used in first half of smallpox eradication program
    - Special intradermal nozzles
    - Mid-1960s – early 1970s
    - Latin America, West Africa
    - Tens of millions of doses of smallpox vaccine
    - Billions of doses administered worldwide

- **Bifurcated needle**
  - Invented 1967 by Benjamin Ruben (Wyeth)
    - Waived royalties for WHO smallpox program
    - Replaced MUNJJs for latter half of eradication
    - Required higher-titer formulation
      - Tines hold 0.0025 mL; most not delivered

Largest Cutaneous Vaccination Campaign in History – Smallpox Eradication

- **Early:** Ped-O-Jet® MUNJJs - South America, West Africa
- **Later:** Bifurcated needles – Asia, Africa, elsewhere
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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
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Jet Injectors for Immunization

• Pressurized liquid via tiny orifice (~0.15mm) squirts path 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 (MUNJIs)
  ■ Many manufacturers

Aquapuncture device
Galante et Cie.

Hypospray® single patient device, R.P. Scherer Corp.

Hypospray® MUNJI
Types of Multi-use-nozzle Jet Injectors (MUNJIs)

Most fill from multi-dose vial attached “on-tool”

- Ped-O-Jet
- Med-E-Jet
- DermoJet
- Imo-Jet
- Sicim
- Vaccejet
- BIP-4
- BIP-100
- AdvantaJet

Single-dose “off-tool” filling:

- Hypospray Professional (L) & K3 (R) models

Ped-O-Jet® MUNJI Intradermal 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
- Spacer on IM nozzle also works
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Three Decades of Safety Concerns over Multi-use-nozzle Jet Injectors (MUNJIs)
- 1970s onwards – growing body of evidence for cross-contamination between vaccinees
  - Bench laboratory, animal transmission models, epidemiologic surveys
- 1985 - large hepatitis B outbreak
  - Weight loss clinic, Long Beach, CA
  - Implicated Med-E-Jet® as mode of spread
  - CDC studies revealed contamination
    - Both Med-E-Jet® and Ped-O-Jet®
- 1990s - Brazil vaccination campaigns
  - Blood detected in average 1% of ejectates
- 2000s – International consultations at CDC and WHO
  - Cannot specify safety evaluation method
  - WHO and CDC recommend against use
- 2007 – Reengineered HSI-500® MUNJI with safety cap
  - Disposable cap to prevent splashback of blood/liquid to nozzle
  - Study in China of HBV carriers (Vaccine 2008;26:1344-1352)
  - Found HBV by PCR in 8% of next ejectate

Disposable-cartridge Jet Injectors (DCJIs)
Filled by end-user from vial, with adaptor, transfer device, or needle:
- Biojector® 2000
- Vitajet®
- Antares Pharma
- Entire device 1-use disposable:
  - The Medi-Jector Choice™
  - Injex®
  - PharmaJet™
  - J-Tip®
  - Others

Some investigational devices intended for manufacturer pre-filling:
- Entire device 1-use disposable
  - Mini-Imojet®
  - Intraject®
  - PenJet™
Investigational Intradermal Spacer on Bioject® 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, influenza, lymphoma, malaria, polio

Investigational 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 GSK vaccine (6μg/strain) – good responses
    - Control vaccine: full dose IM of Aventis Fluzone®
  - Exclusive worldwide license to sanofi pasteur for many vaccine indications

Photos courtesy BD
BD Investigational Prefilled Intradermal Syringe

- 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

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### Literature on Intradermal Vaccination

- Smallpox (many, primary route)
- Tuberculosis (BCG) (many, primary route)
- Yellow Fever (primary route, W. Africa 1940s/50s)
- Rabies (117)
- Hepatitis B (≥90)
- Influenza (≥24)
- Polio (IPV) (16)
- Cholera (15)
- Measles (15)
- Typhoid (11)
- Tetanus (6)
- Hepatitis A (5)
- Diphtheria-Tetanus-Pertussis (2: Rossier 1968, Stanfield 1972)
- Tick-borne encephalitis (2: Zoulek 1984, 1986)
- Meningococcal A (1: Gotschlich 1972)
- Tetanus-Diphtheria (1: Wegmann 1976)
- Rift Valley Fever (1: Kark 1985)
- Smallpox-BCG (1: Vaughan 1973)
- Smallpox-Measles (1: Budd 1967)
- Smallpox-Measles-Yellow Fever (1: Meyer 1964)

### 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) (~16)
- **Poor to mixed results**
  - Hepatitis B (~90)
  - Measles (~15)
- **No data**
  - Polysaccharide vaccines (MEN, PNU, HIB)
  - Exception: Gotschlich 1972 – good results for \(\text{MEN}_{ps-A}\)
**POL<sub>IPV</sub> Intradermal Vaccination**

- First studied by Salk in 1953
  - Route abandoned in favor of oil-in-water emulsion SC for adjuvant effect

<table>
<thead>
<tr>
<th>Source</th>
<th>Subjects</th>
<th>Dose / Tissue / Method</th>
<th>Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salk, <em>Pediatrics</em> 1953;12:471-482</td>
<td>Children n=443</td>
<td>Aqueous 0.1 mL x 2 doses 6 w apart ID NS</td>
<td>Type 1: not effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 2: 100% ≥4-fold rise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 3: not effective</td>
</tr>
<tr>
<td>Salk, <em>JAMA</em> 1953;151:1081-98</td>
<td>Children and adults n=25</td>
<td>Aqueous 0.1 mL x 3 doses 1 w apart ID NS</td>
<td>Type 1: 100% (25/25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 2: 84% (21/25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 3: 96% (24/25)</td>
</tr>
</tbody>
</table>

**POL<sub>IPV</sub> Intradermal Vaccination**

- Denmark - ID was standard route mid-1950s
  - 2.3 million persons vaccinated ID 1955-1957
  - 1956 survey
    - 91% of population 9 months – 40 years
    - “Most of them” with 2 doses
  - Von Magnus (1957, 1967): good immune responses in naïves
POL$_{elPV}$ Intradermal Vaccination

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<td>Nirmal 1998</td>
<td>Immune-naïve infants 6-8w No maternal Ab $\dagger$</td>
<td>0.1 mL @0,2 m ID NS</td>
<td>1: 100% 2: 100% 3: 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 mL @0,1,2 m ID NS</td>
<td>1: 100% 2: 100% 3: 100% *</td>
</tr>
<tr>
<td></td>
<td>Immune-naïve infants 6-8w + maternal Ab $\dagger$</td>
<td>0.1 mL @0,2 m ID NS</td>
<td>1: 87% 2: 68% 3: 96% **</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 mL @0,1,2 m ID NS</td>
<td>1: 89% 2: 74% 3: 96% **</td>
</tr>
</tbody>
</table>

* ns: p>0.05  ** ns: p>0.05  † ns: p>0.1

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

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Key Research Questions To Address for Intradermal Delivery - 1

- Reactogenicity
  - “Alum”: irritating aluminum salts (hydroxide, phosphate)
  - Currently in killed and subunit vaccines $\text{DTP}_a$, $\text{DTP}_w$, $\text{DT}$, $\text{HAV}$, $\text{HBV}$, $\text{MEN}_{cn-\text{ACYW135}}$, $\text{PNU}_{cn-7}$ and $\text{Td}$ vaccines
  - Alum being added to H5N1 $\text{INF}$ vaccines for dose-sparing booster effect
  - Many early studies do not meet current standards for assessing safety
    - $\Rightarrow$ Will local skin reactions to existing and future adjuvants be tolerable?
    - $\Rightarrow$ Will these two major dose-sparing strategies – ID route and adjuvantanation – be synergistic or antagonistic?
    - $\Rightarrow$ How tolerable in the skin will be Novartis’ MF-59 and GSK’s “AS” adjuvant family ($\text{RTS}, \text{S}$, AS02A, etc.)?

Key Research Questions To Address for Intradermal Delivery - 2

- Immunogenicity
  - Current vaccine formulations differ from antigens previously studied; must repeat studies using current trial standards
    - $\Rightarrow$ How will current formulations fare when used in targeted populations?

- Polysaccharide vaccines
  - Expensive, urgently-needed products in the developing world:
    - $\text{HIB}$
    - $\text{PNU}_{cn-7} -11 -13$ etc.
    - $\text{MEN}_{cn-A}$
    - $\text{MEN}_{cn-\text{ACYW135}}$
    - $\Rightarrow$ Can any be delivered ID in economical reduced doses?
Key Research Questions To Address for Intradermal Delivery - 3

- Study design
  - Many ID studies lack a reduced-dose IM or SC control arm, in addition to the full-dose control
  - Must establish that the ID route, not a flat dose-response curve, made the difference
    - Is the intradermal route really dose sparing?
    - Would a reduced dose into the traditional IM or SC compartment work as well as ID?

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Passive diffusion with or without enhancers
- Mechanical disruption of stratum corneum
- Coated microtines
- Hollow and dissolving microneedle arrays
- Electromagnetic energy
- Sound energy
- Gas-mediated kinetic deposition

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)
  - Cholera toxin
- Other chemicals
  - Acetone rubbing
  - Protein and colloidal carriers
    - Bacterial flagellin
    - Colloidal carriers

"Transcutaneous Immunization (TCI)"
Frech et al (Iomai)
Vaccine 2005;23:946-950
Activated Langerhans cells in Epidermis 48 Hours after Cutaneous Vaccination with E. coli LT

Microphotograph courtesy: IOMAI, Inc.

Promising Methods for Cutaneous Delivery

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

OnVax™ “microenhancer array” (MEA)
Becton, Dickinson
Promising Methods for Cutaneous Delivery

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

- Others

Promising Methods for Cutaneous Delivery

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

- Dissolving microneedle arrays
  - Georgia Tech
  - Therajekt
  - Many others

McAllister et al.
PNAS 2003;100:13755-60

Fig 2. Hollow microneedles fabricated out of silicon, metal, and glass, imaged by optical and scanning electron microscopy. (a) Straight-sided metal microneedle from a 100-needle array fabricated by lithography onto a polymethyl (200 μm tall). (b) Tip of a tapered, beveled, glass microneedle made by conventional micropipette pulling (300 μm, length shown). (c) Tapered, metal microneedles (300 μm tall) from a 37-needle array made by electrophoretic deposition onto a polymeric mold. (d) Array of tapered metal microneedles (300 μm height) shown next to the tip of a 26-gauge hypodermic needle.
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Promising Methods for Cutaneous Delivery

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

- Laser Assisted Drug Delivery
  - Nonwood Abbey

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

- E-Trans®
- Alza
- ViaDerm™
- TransPharma Medical
- PassPort™ Patch
- Altea Therapeutics

Promising Methods for Cutaneous Delivery
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