RESEARCH ON NEW VACCINE DELIVERY METHODS: FOCUS ON INFLUENZA

Bruce G. Weniger, MD, MPH (Associate Editor, Vaccine)

Second WHO Consultation on Global Action Plan for Influenza Vaccines (GAP-II), 12-14 July 2011, Geneva, Switzerland

NEW DELIVERY METHODS: INFLUENZA

- Cutaneous, including Classic Intradermal (ID)
  - Improving on Dr. Mantoux’s ID Method
  - Mechanical Disruption of Stratum Corneum
  - Coated Microtines
  - Hollow Microneedles
  - Dissolving Microneedles
  - Other (Kinetic, Electromagnetic, Chemical, Sonic)
- Jet Injection
- Intranasal Spray
- Pulmonary Inhalation of Wet/Dry Aerosols
- Oral Ingestion
- Issues; Relative Pros and Cons

Cutaneous Vaccination

Putting Antigen Into or Onto the Skin

- Prepositional prefix
  - Epidermal...
  - Intradermal...
- Adjectival root
  - Cutaneous...
  - Dermal...
  - Epithelial...
- Noun
  - Antigen...
  - Delivery...

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

Suggested Nomenclature

- **Adjectives**
  - "Cutaneous" – All processes that target any part of the skin for delivery of antigen
  - Includes needle or jet passing through fat (SC) or muscle (IM)
  - "Intradermal" (a.k.a. "Classical Intradermal") – A type of cutaneous vaccination in which a bolus of liquid is deposited into the dermis to raise a visible bleb
  - Includes Mantoux needle method and new techniques of similar result

- **Nouns**
  - "Vaccination" (per Dr. Pasteur to honor Dr. Jenner) – The mechanical, 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, policies, financing, etc.

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Classical Intradermal Vaccination

The “Mantoux” Method

- Simultaneous invention in 1908
  - Felix Mendel (Germany), Charles Mantoux (France)
- Originally for TB skin testing and vaccination
- Fluid bolus below basement membrane
- Advantages
  - Uses existing, off-the-shelf vaccines
  - Enhanced immune response often permits dose-sparing
- Disadvantages
  - Requires training, skill, time, needle dangers
  - Local reactions from irritating ingredients
  - Painful

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Classical Intradermal Vaccination

Overview of Literature

- Excellent results
  - Rabies (already widely used ID in developing world)
- Good results worth pursuing
  - Polio (IPV) (~18)
- Little but promising data
  - Polysaccharide vaccines (MEN, PNU, HIB)
  - Gotschlich 1972 – MENps-A good results
  - Sanofi Pasteur 2002 (unpublished) – MENps-ACYW135 (Menomune®) good results
- Mixed to poor results
  - Hepatitis B (~90)
  - Measles (~15)

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Classical Intradermal Vaccination

Long-established Literature

- Smallpox
  - Many, primary route
- Tuberculosis (BCG)
  - Many, primary route W. Africa 1940s/50s
- Yellow Fever
  - Primary route. ~15 cases
- Rabies
  - ~117
- Hepatitis B
  - ~90
- Influenza
  - ~28
- Polio (IPV)
  - ~16
- Cholera
  - ~15
- Measles
  - ~15
- Typhoid
  - ~11
- Tetanus
  - ~6
- Hepatitis A
  - ~5
- Diphtheria-Tetanus-Pertussis
  - ~2 (Rossier 1966, Stanfield 1972)
- Tick-borne encephalitis
  - ~1 (Gottschlich 1972)
- Meningococeal A-C-Y-W135
  - ~1 (Sanofi Pasteur, 2006, unpublished)
- Typhoid
  - ~1 (Wegmann 1976)
- Tetanus-Diphtheria
  - ~1 (Karl, 1985)
- Smallpox
  - ~1 (van Gaimersbergen 1973)
- Meningococcal
  - ~1 (Budd 1967)
- Measles
  - ~1 (Meyer 1964)

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Classical Intradermal Vaccination

Influenza ID by Needle, 1930s-1970s

- Majority of reports ID immune response >= SC/IM

- Francis T, et al
- Van Gelder D, et al
  - Naval Med Bull 1947;47:197-206
- Weiler TH, et al
- Bruyn H, et al
  - J Immunol 1949;62:11
- Bruyn H, et al
  - Am J Dis Child 1949;77:149-163
- Bruyn H, et al
  - JAMA 1956;166:1134-40
- Hilleman M, et al
  - J Immunol 1958;79:393-8
- Sanger M, et al
  - Ann Allergy 1959;17:213-8
- Sanger M, et al
  - J Lab Clin Med 1964;43:273-284
- Sanger M, et al
  - J Lab Clin Med 1965:66:34-41
- Sanger M, et al
  - Can J Public Health 1968;59:401-408
- Sanger M, et al
- Sanger M, et al
  - J Infect Dis 1977;136(suppl2):s466-s471
Classical Intradermal Vaccination

Influenza ID by Needle, ‘30s-‘70s (cont.)

Minority of Reports: ID Less than SC, or Uncertain
- Boger W, et al., JAMA 1957;165:1687-1689
  - Elderly: SC 500 CCA 79% seroconv > ID 0.1 mL 39-56% (ID lower)
  - Non-naive elderly 4-fold: SC 1.0 mL 60-78% > ID 0.1 mL 77% > ID 45%, 74%, 62% (ID lower)
- Sigel M, et al., JAMA 1975;165:1860-1861
  - Mixed ages, various doses, 4-fold increase: SC 78%, 88%, 77% > ID 45%, SC > ID
  - ID 0.1 mL seroconversion: A/New Jersey/8/76 11/17, A/Victoria/3/75 22/26 (uncontrolled)

Question:
  - Adult GMTs: ID 0.1 mL > SC 1.0 mL
  - Child GMTs: ID 0.2 mL > SC 0.2 mL
  - Adults: “small doses” ID equivalent to “small doses” SC
  - Dose ranging, equal ID vs. SC: small antigen mass - ID > SC, large antigen mass - SC > ID
  - No difference in seroconversion or GMTs

Recent Reports: ID equivalent to IM
  - ID: investigational GSK, 6 μg/strain (60% sparing)
  - Using 1.5mm, 30-gauge, BD ID microneedle syringe
  - IM control: Fluzone® (Aventis), 15 μg/strain, 2001-2002
  - Adults 18-81 years, 1 dose
  - Exception: Elderly, H2N2 GMT and SC: ID < IM
  - ID: investigational GSK, 6 μg/strain (60% sparing)
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  - IM control: Fluzone® (Aventis), 15 μg/strain, 2001-2002
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Adults 18-49 years of age, 3-year-retrospective naïves
  - Equal doses of Fluzone® INF by both routes
    - ID: 3 μg, 6 μg (0.1 mL x 2), 9 μg (0.1 mL x 3)
    - IM: 3 μg, 6 μg, 9 μg
  - Immune response: ID > IM at all equivalent doses
  - Local reactions: ID > IM

Classical Intradermal Vaccination

Influenza ID by Needle, 2004-Present

- Classically ID doses were much lower, roughly 1/10-1/100 SC doses
- For convenience, assuming 5 μg/strain injected
- For 0.1 mL 3 vaccines, each 5 μg/strain
- For 0.5 mL 1 vaccine
- For 1.0 mL 3 vaccines

Classical Intradermal Vaccination

Influenza ID by Needle, 1930s-1970s

Classical Intradermal Vaccination

Influenza ID by Needle, 2004-Present

- Avian H5N1 - ID (3 or 9 μg) vs. IM (15 or 45 μg)
- ID and IM doses < 45 μg not immunogenic, even after 3rd dose at 8 months

Classical Intradermal Vaccination

Influenza ID by Needle, 2004-Present

- Seasonal 2006 ID vs. IM, one dose assessed at day 28
  - ID < IM in both naive and non-naive subjects
  - Satisfies EMEA/CHMP registration requirements

Classical Intradermal Vaccination

Influenza ID by Needle, 2004-Present

- Comparative data provided in Patel, et al. Vaccine, 2010;28:25-3029

Comparing Equal Doses by ID and IM Routes

  - Adult 18-49 years of age, 3-year-retrospective naïves
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  ▪ Oral Ingestion
  ▪ Issues; Relative Pros and Cons

Improving on Dr. Mantoux’s Method
Reinventing the Wheal

Soluvia™ Microinjection System (BD)

- 30 gauge needle
- OD = 0.305 mm, projects 1.5 mm
- Exclusive worldwide license to sanofi pasteur for commercial use
- 2009: EU approved Intanza® and IDflu® influenza vaccines
- 2011: U.S. FDA approved Fluzone Intradermal®

Sanofi Pasteur intradermal influenza vaccines
- Modest or no dose-sparing from conventional IM
  - 15 μg HA / strain / 0.5 mL volume
- EU market - Intanza® and IDflu®
  - 9 μg / strain / 0.1 mL (18-59 years) (40% sparing)
  - 15 μg / strain / 0.1 mL (>=60 years) (0% sparing)
- US market - Fluzone Intradermal®
  - 9 μg / strain / 0.1 mL (18-66 years age) (40% sparing)

Cutaneous Vaccination
Mechanical Disruption of Stratum Corneum

- Remove or reduce top layer of dead skin (stratum corneum)
  - Principal barrier to antigen entry
- Methods to abrade and strip
  - Peeling cellophane tape
  - Friction by rubbing
  - Emery, pumice
  - Uncoated microabrasives
  - Cyanoacrylate “super glue”
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Cutaneous Vaccination
Mechanical Disruption of Stratum Corneum

- Intercell AG acquired "Transcutaneous Immunization" platform from Iomai (US Army/WRAIR spinoff)
- Uses heat-labile LT toxin as adjuvant (or antigen)
- Preparation device pulls sandpaper across skin prior to applying vaccine-impregnated patch
- Travelers diarrhea vaccine
  - Randomized, placebo-controlled trials
    - Phase II (723 travelers from Europe to India)
    - Phase III (n=2036 European travelers to Mexico and Guatemala)
    - Efficacy endpoints not met
    - No reduced incidence of ETEC and/or all-cause diarrhea
  - November 2010: Suspended TD patch, but will pursue other patch-based vaccines

Cutaneous Vaccination
Mechanical Disruption of Stratum Corneum

- Iomai, US Army/WRAIR spinoff (now owned by Intercell AG)
- Patch platform using heat-labile LT toxin as adjuvant (or antigen)
  - Patch applied over injection site of conventional INF vaccination by needle

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Cutaneous Vaccination
Coated Microtines

- Vaccine or drug coated on microtine arrays elutes and diffuses upon insertion
  - Georgia Tech/Emory
    - Mice protected from influenza challenge
    - Zosano Pharma Macroflux™ patch, others
    - No human vaccine trials reported

Cutaneous Vaccination
Hollow Microneedles

- Nanopass MicronJet™
  - ~250 μm-tall array of four microneedles
  - Luer-slip interface attaches to conventional syringe
  - Van Damme et al found 3 μg or 6 μg influenza HA into skin yielded similar HAI titers as 15 μg IM
  - Vaccine 2009;27:454-459
  - Several clinical trials for influenza
    - NCT00558494, NCT01049490, NCT0104561
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Cutaneous Vaccination

Dissolving Microneedles

- Vaccine antigen or drug formulated within solid, dissolvable matrix
  - Commonly carboxymethylcellulose
- Several groups pursuing
  - Georgia Tech
    - Tines 750 μm tall before insertion; dissolve within minutes
  - Mice: good antibody and cellular responses and challenge protection

Jet Injection

What is It?

- Squirts pressurized liquid
  - Through orifice (~0.15 mm)
  - Like child’s water pistol
- 1860s: Invented in France
- 1940s: Single-user device
  - Insulin and other drugs
- 1950s: Adapted by U.S. Army for high-speed vaccination sessions
  - Multi-use-nozzle jet injectors (“MUNJIs”)

Other Mechanisms

- Kinetic deposition of propelled microparticles
  - Pfizer’s PowderMed
    - “Particle-mediated Epidermal Delivery” (PMED™) (DNA on beads)
    - “Epidermal Powder Immunization” (EPI) (protein antigens)
  - 15 μg HA via EPI induced similar seroconversion and GMT as 15 μg IM
  - Three 2006 human influenza studies at Clinical Trials.gov
    - Unpublished as of mid-2011

- Electromagnetic energy
  - Laser light ablation
    - Norwood Abbey’s LAD
  - Thermoporation to burn pores
    - Altea Therapeutics PassPort™
    - TransPharma Medical ViaDerm™
  - Iontophoresis
    - J&J Alza’s E-trans®

- Chemical enhancers
- Sound energy

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Jet Injection

MUNJI Use in Mass Campaigns

- **1950s**
  - Salk inactivated polio vaccine (IM)
- **1960s – 1970s**
  - “Swine flu” (1976)
- Many other vaccines: MPA, MEN, POL, SMA, YEL, inter alia
- Intradermal nozzle for smallpox (SMA) eradication

Jet Injection

Trial of Influenza Vaccination ID vs. SC

<table>
<thead>
<tr>
<th>Method</th>
<th>Route and dose (n=)</th>
<th>HAI titer (Fold rise)</th>
<th>Post HAI GMT (post/pre)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet Injection</td>
<td>ID 0.3 ml, 60 CCA (40)</td>
<td>37 (58%)</td>
<td>77.6 (2.3x)</td>
</tr>
<tr>
<td></td>
<td>SC 0.1 ml, 60 CCA (91)</td>
<td>29 (32%)</td>
<td>77.6 (2.3x)</td>
</tr>
<tr>
<td></td>
<td>SC 0.5 ml, 100 CCA (85)</td>
<td>50 (59%) †</td>
<td>140.4 (4.0x)</td>
</tr>
<tr>
<td>Needle-syringe</td>
<td>SC 0.3 ml, 100 CCA (77)</td>
<td>31 (40%) †</td>
<td>75.8 (2.5x)</td>
</tr>
</tbody>
</table>

† p<0.05 for jet injection vs. needle-syringe

Jet Injection

Safety Concerns for MUNJIs

- Since 1970s – Growing body of evidence for cross-contamination between vaccinees
  - Bench laboratory assays
  - Animal transmission models
  - Outbreak investigation
  - Epidemiologic studies
  - Human trials assaying “next ejectates”

- 1997 – Withdrawn from use by U.S. military
- 2000s – WHO and CDC recommend against use
- No high-speed devices remain available for mass campaigns

Jet Injection

New Generation of Disposable-syringe Jet Injectors (DSJIs) Comes to Market

- **Bioject’s ZetaJet™**
  - Pioneering DSJI manufacturer
  - 1990s: Biojector®, Vitajet™
  - www.bioject.com
  - Mid-2000s: ZetaJet™
  - CDC SBIR R&D contracts, other funding, PATH assistance
  - Low-cost for developing-country markets
  - Spring powered
  - Built-in hand crank
  - No separate cocking/reset station
  - Break-off vial adapter
  - Auto-disabling by plunger lock
  - Clinical trial HIV/DNA vaccine, Sweden
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Jet Injection
Bioject’s ID Pen Injector
- Metal-spring powered
- Manual compression
- Single-use autodisable syringes
- 0.05 or 0.1 mL intradermal volumes
- PATH-WHO agreement for R&D studies (Feb 2011)

Jet Injection
DCI’s LectraJet® M3
- Developing DSJI technology since 1990s
  - Marketed veterinary LectraVet®
  - www.dantonioconsultants.com
- CDC SBIR R&D contracts
- 510(k) clearance 0.5 mL SC/IM
  - 24 December 2009 (K090959)
- Metal-spring powered
  - Separate cocking device/storage box
- Clinical trial seasonal influenza
  - DSJI (n=30) vs. needle-syringe (n=30)
  - J. Simon, et al, Univ. Maryland, 2010
  - Seroconversion, seroprotection similar
  - HAI titer fold increases trended higher

Jet Injection
DCI’s LectraJet® HS
- High-Speed device for mass campaigns
  - Same 600-1000/hour as Ped-O-Jet
  - Novel fingers-free, rapid loading and unloading
  - Same cartridges as for manual M3 model
- Metal spring compressed by internal motor
- Rechargeable, replaceable battery pack
  - >3,000 injections per charge
- Battery-charging – AC mains, vehicle, solar
- Backup manual spring compression possible
- Electronic injection counters
- Investigational
  - U.S. military expressing interest

Jet Injection
PharmaJet®
- www.pharmajet.com
- Rapid R&D-to-market pace
  - 510(k) clearance 0.5 mL SC/IM
    - 26 Feb. 2009 (K081532)
  - Brazil ANVISA clearance
    - Nov. 2009 (80102519021)
  - EU (CE mark) January 2010
- Modest but growing US sales 2009; overseas sales 2010
- Coincided with pandemic influenza campaign of 2009

IPV Polio Vaccination by DSJI
- Polio eradication switch from cheap OPV to expensive IPV (10x cost)
  - Pre-eradication: overcome decreased immune responses to OPV in remaining hot zones
  - Post-eradication: avoid reversion to virulence from live sites in OPV
- Deliver ID by licensed, needle-free jet injectors
  - Avoid difficult Mantoux method for ID route
  - Avoid dangers and drawbacks of needle-syringes
- WHO trials of IPV by dose-sparing ID route
  - 80% dose reduction: 0.5 mL to 0.1 mL
  - Roland Sutter, WHO point person

PharmaJet® 2000 with
Investigational ID spacer
Bijector® 2000 with
Investigational ID spacer
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Jet Injection
PharmaJet Intradermal Program
- CDC SBIR R&D contracts since 2009
- FDA “510(k)” clearance in 2011
- Dengue vaccine (DEN)
  - Primate study completed
  - Human trial begun 2010
- Other clinical trials
  - Rabies (RAB) ID (India)
  - Polio (IPV) ID (Oman, India, Netherlands)
  - Eradication requires switch from OPV
  - HPV vaccine (Hong Kong)

Intranasal Spray
BD’s Accuspray™ Nasal Spray System
- Becton Dickinson’s syringe for prefilled packaging
- Produces large droplets for nasal deposition
  - MedImmune’s FluMist® live attenuated influenza vaccine (LAIV)
  - Successful and widespread market use since 2003

Intranasal Spray
OptiNose™ Nasal Delivery Device
- Bi-directional deposition to nose only
- Dry powder or liquid aerosol delivery

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OptiNose™ Nasal Delivery Device
- After 2 doses OptiNose™...
  - ...titers equivalent with nasal drops
  - ...better than simple nasal or nasal sprays
  - All methods similar on HA1 seroprotection
  - a.k.a. OptiMist™

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<th>n</th>
<th>Postimmunization</th>
<th>Predose</th>
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Table 1: Percentage of subjects with HAI titers ≥ 40 (seroprotection)

Video demonstration (http://www.optinose.no)
Intranasal Drops
Simple Instillation

- TIV (7.5 μg HA/strain) + 3/10/30 μg LTK63 adjuvant + "Biovector" lip nanoparticle carrier
- Controlled 12 μg volumes + 240 μl adhesive pad
- 2 doses, 1-week apart
- Delivery: simple instillation from dropper
- Moderate antibody responses; partial CHMP criteria
- Peak seroconversion rate at 6 weeks
  - H3N2: 27% (IM=67%)
  - B: 67% (IM=80%)
- Peak seroprotection rates at 6 weeks
  - H3N2: 27% (IM=73%)
  - B: 73% (IM=87%)
- Peak fold-rise at 6 weeks
  - H3N2: 2.2 (IM=6.4)
  - B: 5.8 (IM=20)

Intranasal Sprays
Dry Powder Measles Vaccine Inhalers

- Grand Challenge in Global Health #3
  - "Needle-free Delivery"
    - Needle-free Delivery of Stable Respirable Powder Vaccine
  - Objective 2: Design and fabricate one or two inexpensive, single-dose devices to deliver microparticles to the respiratory tract
- Antigen: freeze/spray-dried with sugar stabilizers
  - E.g., measles antigen by Aktiv-Dry LLC
- Two Inhalation delivery devices
  - Aktiv-Dry’s PuffHaler™
  - BD’s Solovent™
- Both devices protected rhesus macaques with Aktiv-Dry’s spray-dried live measles virus vaccine

Pulmonary Inhalation
Aktiv-Dry PuffHaler™

- Only internal dose capsule need require cold-chain storage
- Detachable reservoir avoids cross-contamination from aerosolizer system

NEW DELIVERY METHODS: INFLUENZA

- Cutaneous, including Classic Intradermal (ID)
  - Improving on Dr. Mantoux’s ID Method
- Mechanical Disruption of Stratum Corneum
- Coated Microtines
- Hollow Microneedles
- Dissolving Microneedles
- Other (Kinetic, Electromagnetic, Chemical, Sonic)
- Jet Injection
- Intranasal Spray
  - Pulmonary Inhalation of Wet/Dry Aerosols
  - Oral Ingestion
  - Issues; Relative Pros and Cons

Pulmonary Inhalation
BD Solovent™ Dry Powder Delivery

- Powder capsule only component needing cold-chain storage
- Luer-lock fits onto regular syringe
- Good IgG, IgA, influenza HAI responses in rats compared to IM delivery
- Particle sizings can be increased (>50 μm) to target nose, not lung

Video demonstration
http://www.aktiv-dry.com/puffhaler.html
**Pulmonary Inhalation**

**Influenza Study Mice - Univ. Gröningen**

- Whole inactivated influenza A/HIR virus in wet and dry aerosols
  - Freeze- and spray-dried with inulin cryoprotectant
  - IM controls: A/PR/8 split virus
- Delivery by model DP-4 Dry Powder Insufflator™ to intubated BALB/c mice
  - Two doses of 5 μg HA to lungs at 2-week intervals
  - Controls: 5 μg IM once
- Similar to IM controls:
  - Antibody (IgA higher with powder – not shown)
  - Virus grams per lung tissue upon A/PR/8 challenge

**DP-4 Dry Powder Insufflator™ for murine studies**

**Pulmonary Inhalation**

**Inhaler for Human Use - Univ. Gröningen**

- Twincer® powder inhaler for human applications
  - 23%-37% particle sizes <5 μm
  - No human trials yet reported

**Pulmonary Inhalation**

**Wet Aerosol Measles Vaccine Inhaler**

- Method Pioneered by Sabin
  - Requires electrical nebulizer
- Measles Aerosol Project
  - Since 2002: WHO, CDC, American Red Cross
  - Gates Foundation funding
  - Goal: Develop and license at least one device for a currently-licensed measles vaccine for the developing world
  - Caveat: Cross-contamination with respiratory pathogens?

**NEW DELIVERY METHODS: INFLUENZA**

✔ Cutaneous, including Classic Intradermal (ID)
  ✔ Improving on Dr. Mantoux’s ID Method
  ✔ Mechanical Disruption of Stratum Corneum
  ✔ Coated Microneedles
  ✔ Hollow Microneedles
  ✔ Dissolving Microneedles
  ✔ Other (Kinetic, Electromagnetic, Chemical, Sonic)
  ✔ Jet Injection
  ✔ Intranasal Spray
  ✔ Pulmonary Inhalation of Wet/Dry Aerosols
  ✔ Oral Ingestion

**Relative Pros and Cons; Issues to Consider**

**Oral Ingestion**

**Few Human Studies for Influenza**

- Generally poor results
- 2 – 10 doses, split or whole vaccines, 24, 140, 150 μg HA/strain
  - No detectable IgG
  - Secretory IgA up, then down after further doses (F tolerance)
- Spray of conventional A/H1N1/New Caledonia/20/99 (Chiron Behring)
- As control arm for Optinose™/OptiMist™ intranasal spray device
- Sprayed into mouth with conventional device
- Good proportions with HAI seroprotection (≥40) in serum
- Diminished virus-specific IgA antibodies detected in nasal secretions and saliva compared to nasal routes (OptiMist™, spray, drops)

**NEW DELIVERY METHODS: INFLUENZA**

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  ✔ Oral Ingestion

**Issues; Relative Pros and Cons**
Needle-free delivery methods more desirable for developing countries

- Avoid dangers / drawbacks of conventional needle-syringe:
  - Inadvertent or intentional reuse of unsterile equipment
  - Unsafe disposal of medical sharps posing threat to community
- Some end-user-fillable methods that can use existing, off-the-shelf vaccines advantageous for lower cost, sooner availability
  - E.g., jet injection, some hollow microneedles
  - BD invented end-user-fillable Soluvia™ – useful for economical ID rabies filled from multi-dose vials

EMEA/FDA criteria may not be relevant for novel non-parenteral routes/antigens

- Hemagglutination inhibition (HAI) assay primarily validated on basis of inactivated antigen delivered by needle into fat or muscle
- Newer antigens delivered to other tissues may induce cellular or other mechanisms for protection not predicted by HAI titer
- Potentially effective vaccines may be falsely rejected (type II $\beta$ error ?) using HAI performance alone
- Phase III field efficacy trials may be required to tease out and validate new immunologic correlates of protection for new routes

Cutaneous Advantages

- Minimal invasiveness
  - Easier to monitor and treat local adverse reactions ?
  - Visualizable
  - Amenable to local, topical treatments
  - Fewer unanticipated serious adverse events than other routes ?
  - Oral - e.g., intussusception (Rotashield®, Wyeth)
  - Intranasal - e.g., Bell's palsy (Nasalflu®, Berna)
  - Pulmonary – allergic reaction ?
  - IM/SC injection - e.g., abscess, nerve injury, hematoma

- Dose-sparing ability (in many, but not all cases)
  - 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 but separate vaccination of competing antigens
  - In contrast to oral & intranasal & respiratory routes
  - Separate vaccines may compete at same delivery site or draining lymph node

Cutaneous Advantages - 2

- Less dependent on patient cooperation
  - Think: squirming, uncooperative children, unable to swallow capsules or actuate inhalers
- Relatively sure and certain delivery
  - Next to gold standard: needle IM or SC
- The ideal delivery method a “patch”
  - (“Band-Aid®”, “plaster”)
  - Painless upon delivery to epidermis
  - Containing dissolving micro needles or coated microtines
  - Extremely space-efficient for cold chain volume demand
  - Inexpensive disposal as non-hazardous waste
  - No complex delivery device to buy, transport, maintain, break, lose

Cutaneous Advantages - 3

- Conventional Mantoux ID injection tedious and difficult to perform consistently
- Some adjuvants may be too irritating to tolerate in the skin
- Live antigens requiring growth may not do so well in skin
- Technologies (patches, kinetic devices) not using existing off-the-shelf vaccines will require extensive and expensive formulation efforts
Issues; Relative Pros and Cons
Intranasal Spray Advantages
- Needle-free
- Relatively quick delivery
- Proven method for administering LAIV
- Wide patient acceptance

Issues; Relative Pros and Cons
Intranasal Spray Disadvantages
- Less certainty of delivery/antigenicity in some situations
  - Sneezing after administration
  - Mucoid or purulent rhinitis ("11 sign")
  - Pivotal FluMist LAIV trials limited to “healthy children”
  - Was chronic/acute rhinitis excluded?
  - Is LAIV effective in such conditions common in developing world?

Issues; Relative Pros and Cons
Pulmonary Inhalation Advantages
- Needle-free
- May takes advantage of immune system cells ideally located for antigen sampling
- May induces both systemic and mucosal immune responses

Issues; Relative Pros and Cons
Pulmonary Inhalation Disadvantages
- Highly invasive - targets organ essential for survival
- Disposable tubing and masks (auto-disabling?) may increase per-dose costs
  - Respiratory pathogens may cross-contaminate if dose pathways reused
- May require patient cooperation (? Infants, children)
- Different anatomies an obstacle in development and predictable and consistent dosing
  - Animal models to humans
  - Human-to-human variation
- Health workers constantly exposed to stray antigen
- Some methods tedious (30 seconds per dose)

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✔ Issues; Relative Pros and Cons

Thank you
**Classical Intradermal Vaccination**

- **Influenza ID by Needle, ‘30s-’70s (cont.)**
  - Majority of reports ID immune response > SC/IM
      - Outbreak attack rates: ID 40 CCA = 10% (v.e. 75%)
      - SC 200 CCA = 10% (v.e. 75%)
      - unimmunized = 33% (referee)
      - Adult 4-fold rise: ID 20 CCA 41% = SC 200 CCA 43%
      - Non-race elderly 4-fold: ID 0.1 ml = SC 1.0 or 0.5 ml > SC 0.25 ml
      - ID 0.1 ml x2 = SC 1.0 ml x2
      - Adult ID 160 CCA 88%, Children SC 400 CCA 86%
      - 0.1 ml ID equivalent antibody titers to 0.5 ml IM
  - Local reactions
    - Immune responses
    - Skin: mild erythema, rash, itching
  - Routes
    - ID: 0.1 ml
    - SC: 0.5 ml

**Cutaneous Vaccination**

- **Mechanical Disruption of Stratum Corneum**
    - Shaved human abdominal skin, then 30 toothbrush strokes, applied liquid vaccine and occlusive patch
    - Adenovirus vector expressing hemagglutinin of influenza strain A/PR/8/34 (H1N1) (uncontrolled)
  - Immune responses
    - Skin: similar to good immune responses at highest doses
    - Intradermal: bad
  - Local reactions
    - Skin: mild erythema, rash, itching
    - Nose: mild irritation

**Jet Injection**

- **Clinical Evidence**
  - Generally equivalent to or better than needle-syringe
    - Antigen-presenting dendritic/Langerhans cells in skin
  - Routes
    - ID, SC (MUBs), one DCB
    - SC (DCBs, investigational)
  - Often more local reactions than needle-syringe (alum?)
    - Other vaccines: HIV, DNA, cancer, etc.
RESEARCH ON NEW VACCINE DELIVERY METHODS: FOCUS ON INFLUENZA
Bruce G. Weniger, MD, MPH (Associate Editor, Vaccine)
Second WHO Consultation on Global Action Plan for Influenza Vaccines (GAP-II), 12-14 July 2011, Geneva, Switzerland

Jet Injection
PharmaJet® SC and IM “DSJI” Injectors
- Metal-spring powered
- Separate cocking station
- Color coded
  - Blue
    - Thicker-skinned adults
  - Green and Violet (not shown)
  - Thinner-skinned children and elderly

Jet Injection
PharmaJet® Collaborations
- R&D
  - CDC for intradermal system
  - PATH for technical, bench, regulatory, country-access
  - U.S. Army for investigational smallpox vaccine
- Netherlands Vaccine Institute for IPV
- Clinical trials of SC/IM injectors
  - PATH and/or WHO and local institutions
    - Measles-Mumps-Rubella (MMR) vaccine SC (Brazil)
    - 582 Brazilian infants aged 12 - 18 months
    - Yellow fever vaccine (YEL) trial (Brazil)
    - DTP-HIB or DTP-HIB-HBV vaccines (Brazil)

Intranasal Drops
Simple Instillation
- MEM71-reassortant inactivated split-virus antigen.
- Nasal instillation of drops
  - 0.01, 0.1, 1.0, or 10 μg virus + 10 μg ISCOMATRIX™ adjuvant
  - No IM/SC controls
  - Challenged with 10^4.5 pfu infectious MEM71 virus
  - Caveat: some antigen swallowed? Only Ag reaching lower respiratory tract successful