Jet Injection for Influenza

A randomized controlled clinical trial to demonstrate non-inferiority of jet injection vs. needle and syringe for administration of TIV influenza vaccine

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Author Disclosure

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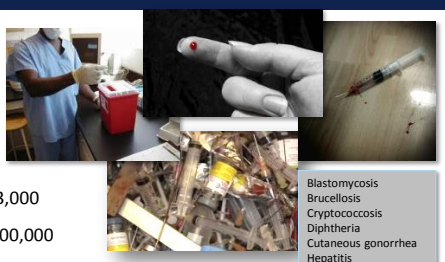
Cobb is employed by ***Medical Center of the Rockies***, Loveland, CO

Talk Outline

- Why is needle-free injection important?
- Jet injection history & technology
- Efficacy of needle free vaccine delivery
  - Published evidence
  - PharmaJet pilot study results
  - Preliminary results from PharmaJet – CSL JIFI study

The Problem with Needles

- Needlestick injuries
  - 800,000 annually in the US
  - 3.5 million annually worldwide
  - $2 Billion burden in US alone
  - Cost of needlestick testing/counseling = $3,000
  - Cost of needlestick treatment = $3,000-$100,000
- Needlesticks can transmit many blood-borne diseases:
- 40-70% of needles are reused in the developing world
- Needle disposal is expensive: adds $0.50-1.00 to each injection
- Many patients fear needles

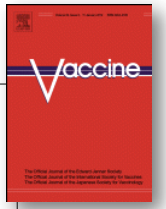


Blastomycosis
Brucellosis
Cryptococcosis
Diphtheria
Cutaneous gonorrhea
Hepatitis
Herpes
HIV
Malaria
Mycobacteriosis
Mycoplasma caviae
Sporotrichosis
Syphilis
Rocky Mountain spotted fever
Streptococcus pyogenes
Staphylococcus aureus
Toxoplasmosis
Tuberculosis

No needle = eliminate/reduce above AND improve patient experience

References:
- International Health Care Worker Safety Center
- Needlestick and Sharps Injury Prevention Act
- American Journal of Industrial Medicine

Needles Contribute to Immunization Non-compliance



Survey of the prevalence of immunization non-compliance due to needle fears in children and adults.

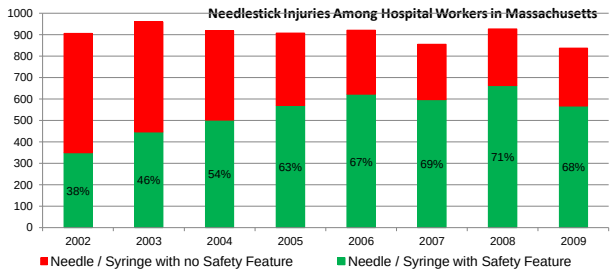
Taddio, A *et al*
Vaccine, Vol 30:32, July 2012; 4807-4812

- **"Needle fears are a barrier to immunization in children and adults."**
- **Surveyed: 1907 children and parents**
  - **24% of adults and 63% of children report a fear of needles.**
  - **1/12 of all candidates are non-compliant due to needles.**

Limited Impact of Safety Needles

- Injection Safety
  - "Safety syringes" are recommended in U.S. healthcare facilities to protect against risk of needlestick injury
  - Reported needlestick injuries stay level
    - despite "safety" needle/syringes being implemented
    - overall modest decline in all sharps injuries: 2002-3400; 2010-2947

Massachusetts Sharps Injury Surveillance System: www.mass.gov/dph/ohsp, "Needlesticks and Other Sharps Injuries" and "Data and Statistics" for hypodermic needle injuries.

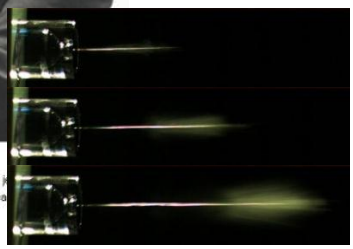


MUNJIs: Multiple Use Needle-free Jet Injectors

Used by US Govt. for Pandemic Influenza Vaccine Delivery

15 Sep 1976, Washington, DC—
Betty Reilly (left), a swine flu staff member, receives an immunization from Dr. Basil G. Delta, with a j
capable of immunizing 800 persons an hour. The jet injector is being distributed to state and local hea
and the Red Cross to help with swine flu shots this fall.

Jet Injection has moved from MUNJIs to Disposable Syringe Jet Injectors (DSJI)



Jet Injection - Clinical Efficacy and Safety

60 Years of Published Evidence

- ***Delivery by jet injection is equal to or better than needle & syringe as evaluated by immune response***
- ***Increased local site reactions with jet injection; well tolerated***

Inactivated Vaccines:
- Botulism
- Cholera
- DTP
- Hepatitis A
- Hepatitis B
- **Influenza**
- Japanese encephalitis
- Meningococcal A, C
- Polio
- Tetanus
- Typhoid
- Novel: DNA, Peptide

Vaccines, 5th ed. Philadelphia, PA: Saunders (Elsevier); 2008;1357-1392 [ISBN 978 1 4160 3611 1]. Weniger BG, Papania MJ. Alternative Vaccine Delivery Methods [Chapter 61]. In: Plotkin SA, Orenstein WA, Offit PA, eds.

Live Vaccines:
- BCG
- Measles
- Mumps
- MMR
- Measles-Smallpox
- Rubella
- Smallpox
- Yellow Fever

Practice Recommendations for Needle-free Jet Injectors

- ANA & OSHA recommend needle-free option
  - OSHA: Federal Register, Vol. 66, No. 12January 18, 2001**Department of LaborOccupational Safety and Health Administration29 CFR Part 1910Occupational Exposure to Bloodborne Pathogens; Needlesticks and Other Sharps Injuries; Final RulePage 5319**
  - **ANA:** American Nurses Association Needlestick Prevention Guide 200 2Page 13 Hierarchy of ControlsMost Effective:"Jet injectors may substitute for syringes and needles."
- CDC–Centers for Disease Control & Prevention
  - **General Recommendations on Immunizations- Jan 2011**http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.html

Recommendations and Reports January 28, 2011 / 60(RR02);1-60

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Jet Injectors specifically mentioned and discussed under Needle and Syringe safety:

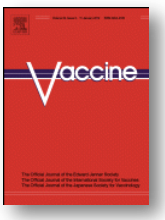
"Safety-engineered needles and syringes or needle-free injection devices are preferred and should be encouraged to reduce risk for injury. "

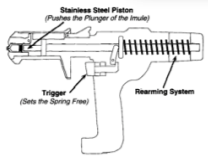
….and …

"Jet injectors prevent needle-stick injuries to health-care providers (86) and can overcome improper, unsterile reuse and other drawbacks of needles and syringes in developing countries (87,103--104). Immune responses generated by jet injectors against both attenuated and inactivated viral and bacterial antigens are usually equivalent to, and occasionally greater than, immune responses induced by needle injection. However, local reactions or injuries are sometimes more frequent on delivery of vaccine by jet injectors compared with needle injection, depending on the inherent irritability of the vaccine and operator technique (102)."

3 Small Randomized Controlled Trials on Delivery of Influenza Vaccine
Demonstrate Efficacy of Jet Injection vs Needle & Syringe

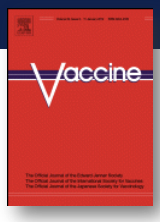
DSJIs vs Needle & Syringe for delivery of Fluzone



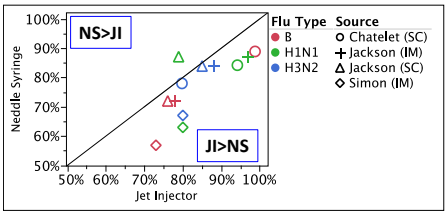


- Simon et al, 2011
  - DCI device vs NS in 60 subjects (30/30)
  - Fluzone TIV delivered IM
- Jackson et al, 2001
  - Biojject devices vs NS in 304 subjects (33 per group)
  - Fluzone TIV delivered IM & SC
  - Only full dose considered further herein
- Parent du Chatelet et al, 1997
  - Imule device vs NS in 213 subjects (~ 1/1)
  - Pasteur-Merieux TIV vaccine delivered SC
- Measures of influenza vaccine efficacy
  - Influenza type-specific hemagluttination inhibition (HI) antibodies on day 21 or 28
    - GMT, seroconversion rate, seroprotection rate
  - By all metrics of immunogenicity each device is effective for influenza vaccination
- Safety parameters – Local & systemic
  - Local site reactogenicity is greater with DSJI but tolerated
  - Systemic Sx tend to be greater with NS (Simon *et al*)

DSJIs Yield Comparable or Higher Seroconversion Rates to TIV



- Scatter plot of all seroconversion rates: 3 antigens/4 devices



For all antigens DSJI yielded the same or better seroconversion rates (except Bioject SC device for H1N1, although not statistically different from NS)

- Analysis of pooled (359) data points- seroconversion rates

For all three antigens NS-JI is negative indicating higher serconversion rates with JI

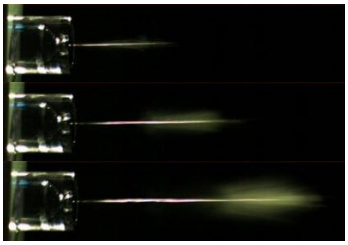
For Influenza types B and A H1N1, DSJI is superior to NS*

For Influenza type A H3N2, DSJI is not statistically different from NS, but tends toward superiority

Flu Type	NS N = 163	JI N = 196	NS-JI	p-value (H_a: JI > NS)
B	79.8 %	87.8 %	-8	0.0276 *
H1N1	81.0 %	89.8 %	-8.8	0.0130 *
H3N2	77.3 %	82.1 %	-4.8	0.1566

PharmaJet *Stratis®* Needle-free Jet Injector

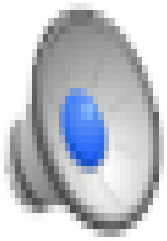
- 0.5mL Needle-free Injections



- Intramuscular (IM) & Subcutaneous (SC) injections
- Launched and available for worldwide use
- Regulatory Clearances:
  - FDA 510(k)
  - CE
  - WHO PQS

Stratis® - Needle-free Jet Injector

- 0.5mL Needle-free IM/SC Injections



Measles vaccinations on 5-9 year-old children.

Note the children smiling before, during and after injections.

Pilot Influenza Study - January 2012

Population:

79 adults, 18-64 years old, students @ Veterinary School

Vaccine:

Fluzone® (2011-2012 vaccine), full dose IM

Delivery device:

Randomized (unblinded) to delivery of vaccine by

- Jet Injection (JI)
- Needle & Syringe (NS)

Serology:

Blood draw before vaccination and 28 days after

Safety:

- Diary cards and AE/SAE reporting
- Increased local site reactogenicity, but short lived (per 7 day Diary Card)

Site: Bel Rea Veterinary School, Denver, CO; PI: Dr. Dan Perlman, Infectious Disease specialist

Pilot Study Seroconversion Results: JI vs. NS

No significant difference in SCR based on delivery method

- NS - Needle syringe
- JI - Jet injector

Strain	NS	JI	P-value*
A1	85% (71 – 93)	79.5% (64 – 89)	0.5679
A2	85% (71 – 93)	89.7% (76 – 96)	0.7370
B	65% (49 – 78)	59% (43 – 73)	0.6466

**do not reject H0: pNS = pPJ so we conclude there is no evidence to suggest a difference in SCR due to injector type.*

Pilot Study GMT Results:

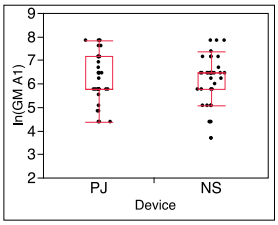
No Difference between JI and NS

Influenza A H1N1

- GMT ratio

NS/PJ = 0.94

- 95%CI: (0.60, 1.49)
- Confidence interval <1.5 meets criteria for non-inferiority



Influenza B

- GMT ratio of

NS/PJ = 1.0,

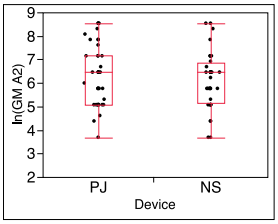
- 95%CI: (0.63, 1.59)
- Upper limit just beyond 1.5

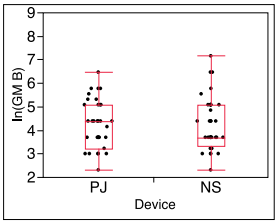
Influenza A H3N2

- GMT ratio of

NS/PJ = 0.84,

- 95%CI: (0.49, 1.45)
- Confidence interval <1.5 meets criteria for non-inferiority





JIFI Study - *Jet Injection for Influenza*

bioCSL™

afluria® INFLUENZA VIRUS VACCINE

PharmaJet®

- Purpose: To demonstrate non-inferiority of the immune response when flu vaccine is administered with a jet injector vs. needle/syringe
- CSL *afluria®* TIV flu vaccine (2012-2013 NA formulation)
- PharmaJet *Stratis®* Needle-free Jet Injector vs. standard needle and syringe
  - Randomized, unblinded comparator controlled
  - Target enrollment: 1400
  - Blood draw for serologic testing before vaccination and 28 days later
  - 2012 – 2013 US flu season - during Employee Health Influenza Campaign at Medical Center of the Rockies

JIFI Study

- **Primary objective:** To demonstrate the non-inferiority of Jet injection vs. needle/syringe for the delivery of standard depth and dose ***afluria®*** influenza vaccine. (2012-13 NA formulation)
  - **Six Co-Primary endpoints:**
    - **GMT ratios (<= 1.5) - for each of the three strains**
      - [GMT(NS)] / [GMT(JI)]
      - The upper bound of the 95% C.I. should not exceed 1.5
    - **SCR differences (<= 10%) - for each of the three strains**
      - SCR(NS) – SCR(JI)
      - The upper bound of the 95% C.I. should not exceed 10%
- **Safety/Secondary objectives:**
  - **Immediate reactions** in 30 minute observation period
  - **Solicited local and systemic AE's** Diary Cards
  - **Unsolicited AE's & SAE's** Up to and including 28 days after vaccination
  - **Seroprotection**
  - **GMFR**
  - **Subgroup analyses: BMI, Age, Sex**

JIFI Study Conduct

Opened enrollment Oct 15th 2012 … Closed January 16th 2013

- Enrolled 1,250 subjects:
  - 623 assigned to the NS group
  - 627 assigned to the JI group
  - 70.6% females
  - 96% white
  - Mean age is 41 years old
    - 18 - 49 years old: 835 subjects
      - 417 assigned to the NS group
      - 418 assigned to the JI group
    - ≥ 50 years old: 415 subjects
      - 206 assigned to the NS group
      - 209 assigned to the JI group
- Good subject follow-up:
  - 98% completed study
  - Over 1,100 evaluable subjects in the Immunogenicity Population
- **SAFETY:**
  - Very few (26) missing Diary Cards

JIFI Study Preliminary Results: Efficacy

- **For the three influenza virus strains**
  - Geometric Mean Titer (GMT)
    - The postvaccination GMT ratios (NS/JI) ranged from
      - 0.94 – 1.08
    - The highest upper bound of the 95% confidence interval (CI) is
      - 1.21
    - Influenza Guidance criterion: upper bound 95% CI < 1.5
  - Seroconversion Rate (SCR)
    - NS – PJ, where SCR is the per cent with > 4-fold rise in postvaccination titer, or when prevaccination titer is <10, the per cent for whom postvaccination titer is ≥ 40.
    - The SCR differences ranged from
      - 0.8% - 1.3%
    - The highest upper bound of the 95% confidence interval (CI) is
      - 7.1%
    - Influenza Guidance criterion: upper bound 95% CI < 10%

JIFI Study Preliminary Results: Safety

- Three subjects experienced 6 SAEs during the Study
  - all unrelated to study
- Diary Cards
  - Local:
    - pain, tenderness, tenderness, redness, swelling, and bruising greater in Jet injection group, but mild in intensity (only few subject reported moderate intensity)
  - Systemic:
    - Myalgia most common; same frequency in both groups
- JI had a clinically acceptable safety and tolerability profile

Acknowledgements

- JIFI subjects: Healthcare workers and their families
- JIFI site: Medical Center of the Rockies
- JIFI PI: Dr. Cobb
- JIFI vaccine partner: CSL
- FDA
- BARDA
- PATH

Thank you for your attention

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