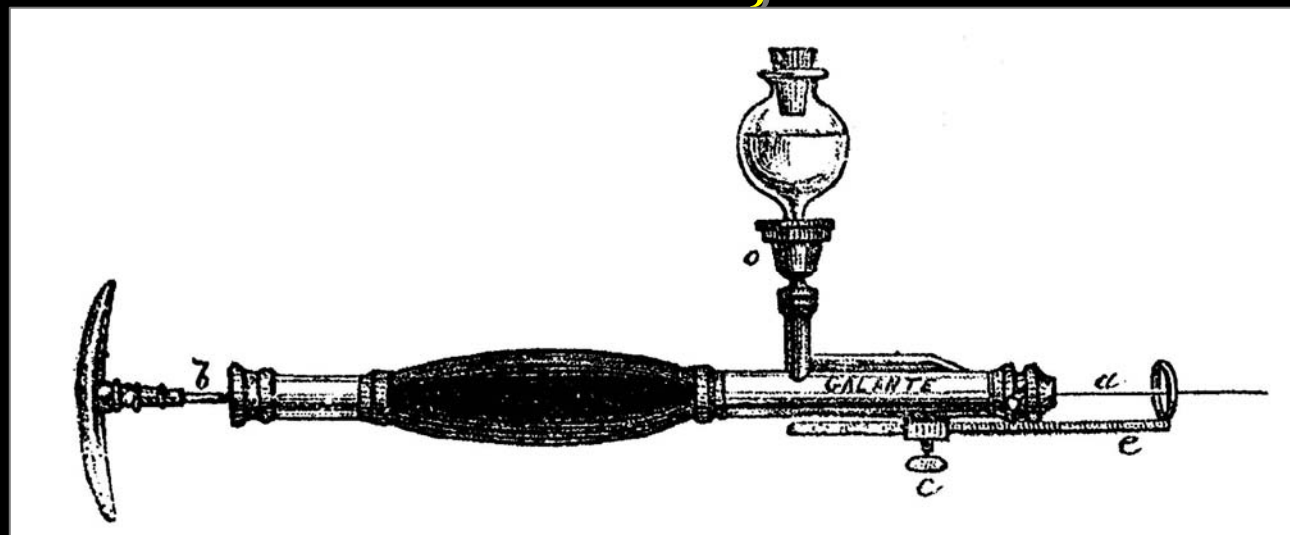


# New High-speed Jet Injectors for Mass Vaccination: Pros and Cons of Disposable-cartridge Jet Injectors (DCJIs) versus Multi-use-nozzle Jet Injectors (MUNJIs)



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National Immunization Program, Centers for Disease Control and Prevention

WHO Initiative for Vaccine Research:  
***Global Vaccine Research Forum***  
8-10 June 2004, Montreux, Switzerland

# Need for High-speed Injection Technology for Mass Vaccination Campaigns

## ● Global disease eradication

- Smallpox eradicated (1975) with MUNJIs and, later, bifurcated needles
- Polio almost eradicated with (high-speed) oral polio vaccine
- Next target for eradication: measles
  - Strategy of *National Immunization Days*, as with polio
  - Parenteral vaccine requires injections
  - Constraints of limited time and skilled manpower for needle-syringes

## ● Pandemics and regional/local epidemics

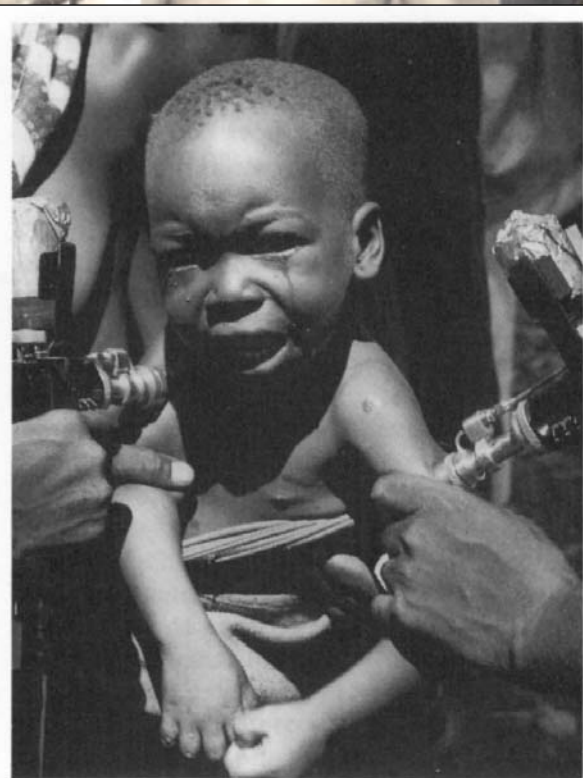
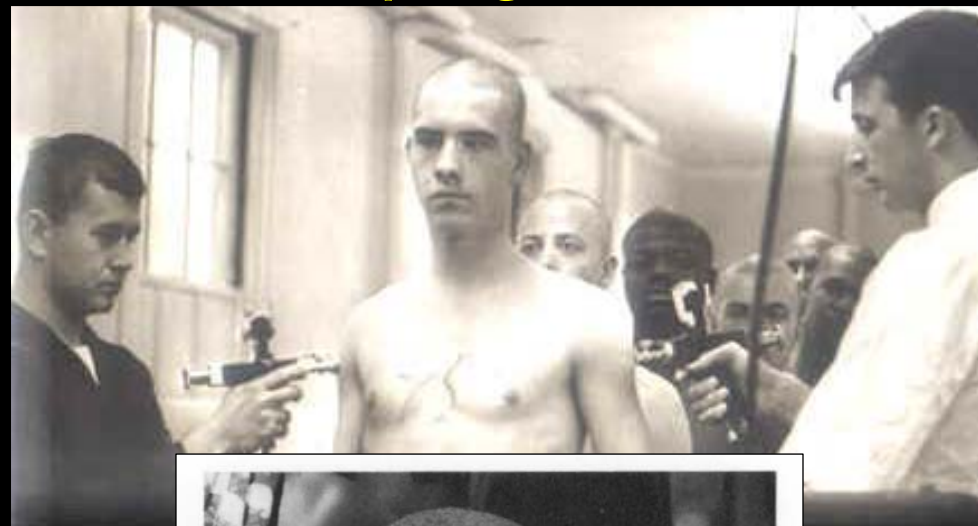
- Influenza
- Meningococcal meningitis
- Yellow fever
- SARS ? (when vaccine available)

## ● Rapid response to bioterrorism

- Parenteral vaccines: anthrax, plague, glanders, tularemia, etc.
- But not smallpox (bifurcated needles simpler and just as fast)

# Jet injectors for Mass Campaigns

- ***Multi-use-nozzle jet injectors*** (MUNJIs) introduced 1950s
  - Developed under U.S. military contract for mass vaccination of recruits
  - 600-1,000 injections/hour
  - Billions of vaccine doses administered worldwide
    - **INF, MEA, MEN<sub>ps</sub>, POL<sub>IPV</sub>, SMA, YEL, *inter alia***
  - Ped-O-Jet®: earliest and most widely used MUNJI worldwide



WHO / CHEVALIER

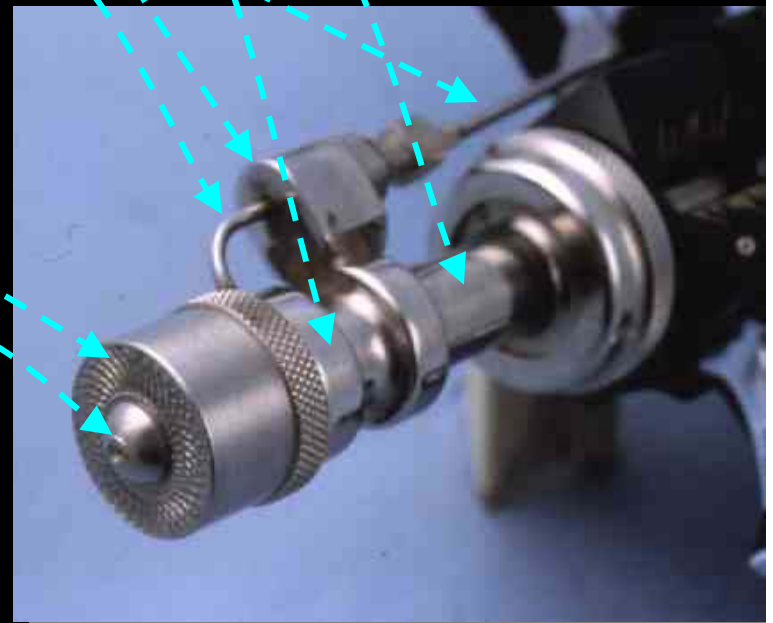
Plate 17.5. Jet injectors were used to administer

# How MUNJIs Work

- Fill from attached *multi-dose vial*
  - Spring compression for next injection pulls rearward *internal piston*
  - Vacuum created in *dose chamber*
  - Liquid enters dose chamber via *one-way valve* and *internal fluid pathways* from ...
  - Inverted and vented vial atop injector

- Trigger activated while held firmly against skin
  - Piston moves forward rapidly
  - Liquid compressed to  $>1,000$  psi (7,000 kPa)
  - Liquid ejected from the *nozzle* through its central *orifice* (diam  $\pm 0.15$  mm)
  - High pressure over small surface area penetrates epidermis

- Liquid deposited into IM, SC, or ID tissues
  - Penetration depends on skin thickness, orifice size, shape, pressure vs. time, etc.





# Types of Multi-use-nozzle Jet Injectors (MUNJIs)

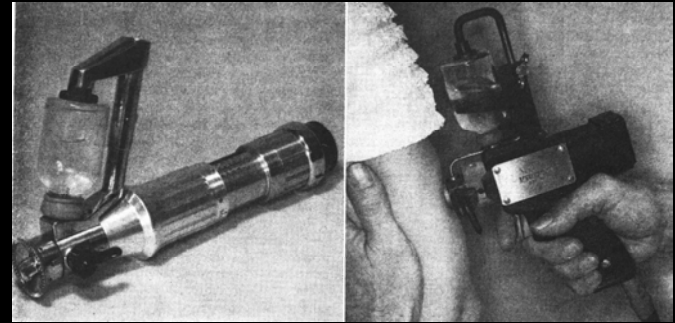
Most fill from multi-dose vial attached "on-tool"



Ped-O-Jet



Med-E-Jet



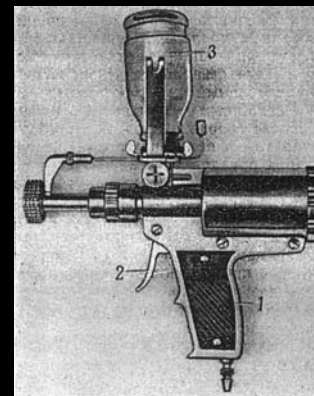
Hypospray Professional (L) & K3 (R) models



DermoJet



Mesoflash



BIP-4 BIP-100



Sicim

Single-dose  
"off-tool" filling:



Imo-Jet

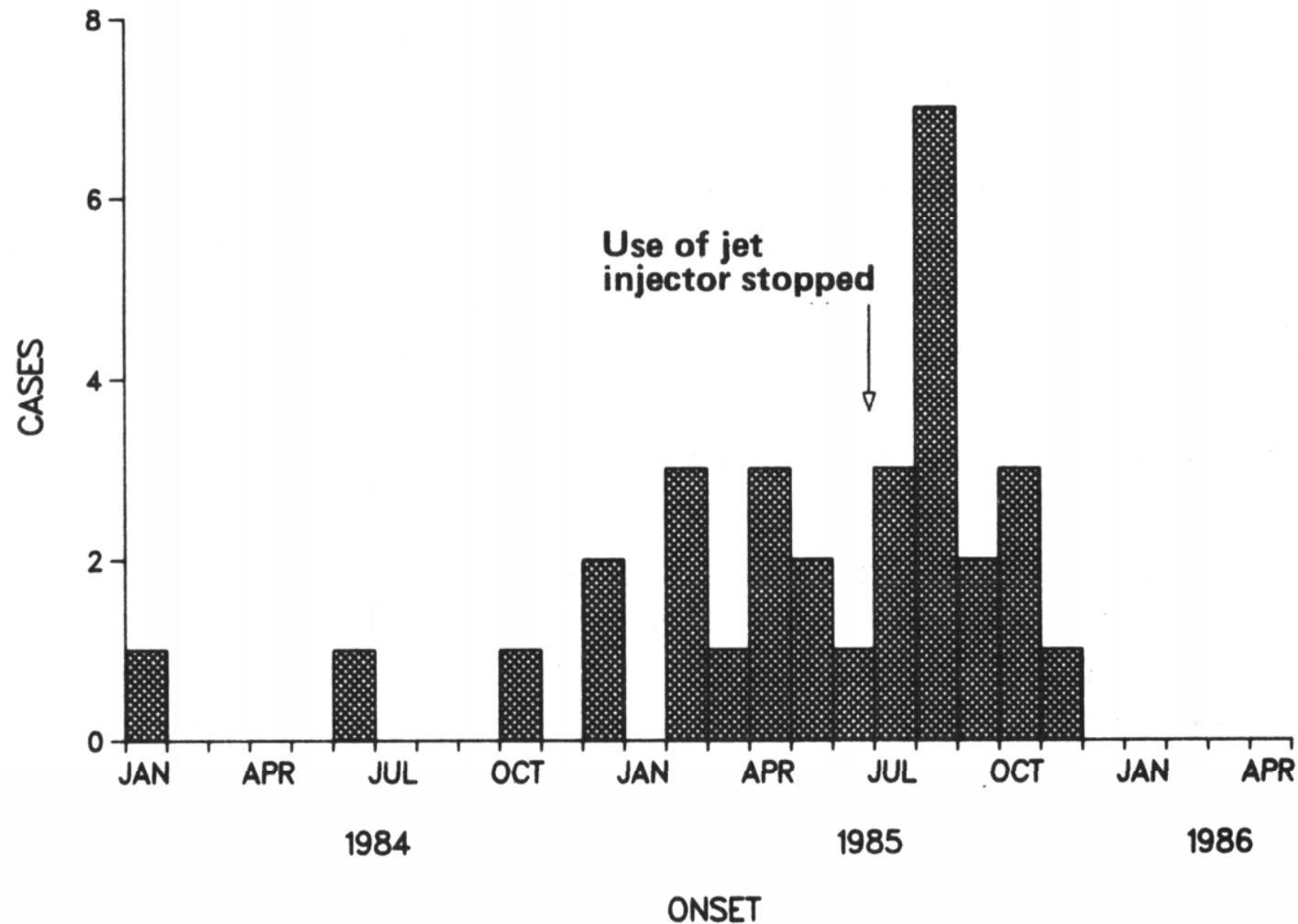


Vaccijet



AdvantaJet

**FIGURE 1. Cases of acute clinical hepatitis B in a weight-reduction clinic, by month of onset — California, 1984-1985**



Source: *MMWR* 1986; 35: 373-376



# Effect of Acetone Swabbing in Laboratory Study of HBsAg Contamination of Jet Injector Devices

**Hepatitis B surface antigen (HBsAg) positives**  
Number / total sampled (%)

**Ped-O-Jet®**

**Med-E-Jet®**

<u>Site Tested</u>	<u>No Swabbing</u>	<u>Swabbing</u>	<u>No Swabbing</u>	<u>Swabbing</u>
<b>Next ejectate</b>	19/50 (38%)	A 3/50 (6%)	40/50 (80%)	B 29/45 (64%)
<b>Nozzle exterior</b>	8/10 (80%)	A 3/10 (30%)	9/10 (90%)	B 7/9 (78%)
<b>Nozzle interior</b>	0/10 (0%)	0/10 (0%)	8/10 (80%)	B 5/9 (56%)
<b>Nozzle tip</b>	not applicable	not applicable	9/10 (90%)	B 6/9 (67%)

<sup>A</sup> Ped-O-Jet - swab vs. no swab:  $p < 0.05$ , Fishers Exact Test

<sup>B</sup> Med-E-Jet - swab vs. no swab: not significant



# Literature on MUNJIs and Bloodborne Disease

- **1970:** Slightly increased detection of radiolabeled human serum on nozzles after injection (**Darlow, et al.** *BMJ*)
- **1978:** Med-E-Jet®: no radioactivity detected on nozzles after *in vitro* injection of isotope-labeled tissues (**Black, et al.** *BMJ*)
- **1981:** No HBsAg detected on nozzles after injection of two hepatitis B carrier patients (**Abb, et al.** *J Inf Dis*)
- **1985, 1990:** Med-E-Jet®: large outbreak of hepatitis B in weight clinic giving multiple HCG injections (**MMWR** 1985; **WER** 1985; **Canter, et al.** *Arch Int Med* 1990)
- **1985:** Med-E-Jet®: transmitted LDH virus experimentally between mice (**Brink, et al.** *J Med Microbiol*)
- **1988:** Berijet™: skin injection sites positive in 3 of 4 HBsAb+ carriers and 1/1 HIV+ patient. Device nozzles negative (**Zachoval, et al.** *Lancet*)
- **1994:** Ped-O-Jet®: occult blood by urine dipstick method in ejectate collected after routine vaccination in 1% of 2,815 military recruits and 6.6% of 30 Amazon residents (**de Souza Brito, et al.** *X Intl AIDS Conf, Yokohama*)
- **1997:** VEE virus transferred between lab animals using Russian BI-19, BI-1M, and BI-3 injectors (**Lukin, et al.** *Voенно-медицинский Журнал*)
- **2001:** Safety evaluation methodology in calf animal model - 4 MUNJI devices produced detectable blood in downstream ejectates (**Hoffman, et al.** *Vaccine*)
- **2001:** Prior yellow fever vaccination via MUNJI device in central Brazil found a multivariate risk factor for HBV infection (**Souto, et al.** *Rev. Panam. Salud Pública*)

[www.cdc.gov/nip/dev/jetinject.htm#bibliography](http://www.cdc.gov/nip/dev/jetinject.htm#bibliography)

# Jet Injectors Study, Brazil, 1989-1991

## Occult Blood By Dipstick\* In Vaccine Samples

<u>Location</u>	<u>No. of vaccinees</u>	<u>Occult blood detected</u>	<u>Percent</u>
Sao Paulo and Recife	1193	2	0.2
Amazon	30	2	6.6
Sao Paulo	1662	24	1.4
<b>TOTAL</b>	<b>2885</b>	<b>28</b>	<b>1.0</b>

\* sensitivity 0.002-0.01  $\mu$ L BLOOD/0.5 mL DOSE

# *In Vivo* MUNJI Safety Evaluation Methodology

- Animal models
  - calves, piglets, human HBsAg+ carriers
- Study locations:
  - Public Health Laboratory Serv., London
  - Univ. Florida Sch. Vet. Med., Gainesville
  - São Paulo state, Brazil
- Procedure
  - Use MUNJI to inject subject with buffered saline
  - Next ejectate(s) into specimen container
    - Represents what next vaccinee would receive
  - Repeat, to collect ~100 ejectates (fewer in human subjects)
    - Sterilize injector head between human subjects
  - Analyze ejectate for extremely small quantities of blood
    - Direct and indirect ELISA
    - Serum albumin is target antigen as surrogate for blood



# A model to assess the infection potential of jet injectors used in mass immunisation

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## Abstract

Jet injectors are needleless injectors that penetrate skin with high-pressure fluid. They have potential advantages over needles and syringes in mass immunisation programs, but concerns over their capacity to transfer blood-borne viruses have been a barrier to acceptance. Hepatitis B infection can transmit in 10 pl of blood; detection of such low volumes presents severe difficulties to such assessments. A model to assess jet injector safety was developed using injection of an inert buffer into calves and assaying the next injector discharge, representing the next dose of vaccine, for blood using a highly sensitive ELISA. Four injectors were tested: two with reusable heads and direct skin contact, one with single-use injector heads and one where the injector head discharged at a distance from the skin. All injectors tested transmitted significant (over 10 pl) volumes of blood; the volumes and frequency of contamination varied with injector. The source of the contamination was consistent with contamination by efflux of injected fluid and blood from the pressurised pocket in tissue that is formed during injection. This insight should inform the design of safe jet injectors. © 2001 Elsevier Science Ltd. All rights reserved.

# *In vivo* Model for Evaluating Safety of Mult-use-nozzle Jet Injectors

Blood quantity (pL) detected in next  
discharge (?  $\geq 10$  pL unsafe ?)

Injector	Injections Sampled	Blood quantity (pL) detected in next discharge (? $\geq 10$ pL unsafe ?)		
		0-9.9	10-49.9	$\geq 50$
"A"	114	75 (66%)	20 (18%)	19 (17%)
"B"	48	2 (4%)	5 (10%)	41 (85%)
"C"	119	69 (58%)	26 (22%)	24 (20%)

Source: Hoffman, et al. *Vaccine* 2001;19:4020-27.



# *In vivo* Model for Evaluating Safety of Multi-use-nozzle Jet Injectors

Ejectates with blood >10pL / 0.5mL

Injector	No. of Animal Injections	Pre-Inject	Post 1 <sup>st</sup>	Post 2 <sup>nd</sup>	Post 3 <sup>rd</sup>	Post 4 <sup>th</sup>	Post 5 <sup>th</sup>	Post 6 <sup>th</sup>
"D"	20 (100%)	7 (35%)	13 (65%)	8 (40%)	1 (5%)	1 (5%)	2 (10%)	1 (5%)

Source: Hoffman, et al. *Vaccine* 2001;19:4020-27.

# *In vivo* Model for Evaluating Safety of Multi-use-nozzle Jet Injectors

## ● Summary of Results

- 5 devices, 3 mammalian models, 3 study sites
  - bovine – published
  - porcine, human – unpublished
  - All produced  $\geq 1$  “unclean” ejectate(s) following up to  $\sim 100$  *in vivo* injections
  - All had  $\geq 1$  false positives on negative controls

## ● Caveats and limitations

- Assay insufficiently rigorous (sensitivity, specificity, repeatability)
  - Differing treatment of calibration curve samples vs. unknowns
  - Loss of 2/3 of signal from freezing known dilutions
- Uncertainty of presumed minimal infectious dose (1 chimp)
- Unvalidated relevance of porcine / bovine models to humans

## ● Latest thinking: use PCR assay for HBV on carriers

# Jet Injection of Liquid Vaccines: Latest Policies on Multi-use-nozzle Jet Injectors

- US Department of Defense - 1997

- "Accordingly, we have sent a recommendation through the DoD Medical Products Quality Control System (MPQCS) that the use of these products, regardless of manufacturer, **be discontinued** until assurances of their safety are received." [Defense Logistics Agency, DPSC-M, 9 December 1997]

- WHO - 1998

- "...until safe needle-free injectors are identified through independent safety testing, **only needles and syringes should be used** for immunization, according to current WHO policy 'Safety of Injections WHO/EPI/LHIS/97.04 and 'Safety of Injections in Immunization Programmes' WHO/EPI/LHIS/96.05." [Note for the Record, 25 Mar 1998]

- CDC (ACIP) - 2002

- "...the use of existing multiple-use-nozzle JIs **should be limited** . . . [and] considered when the theoretical risk for bloodborne disease transmission is outweighed by the benefits of rapid vaccination with limited manpower in responding to serious disease threats (e.g., pandemic influenza or bioterrorism event), and by any competing risks of iatrogenic or occupational infections resulting from conventional needles and syringes." [MMWR 2002;51(RR-2):12-13]

# Re-engineering a Safer MUNJI: The BI-100™

- Felton Medical International

- Lenexa, Kansas, USA
- [www.feltonint.com](http://www.feltonint.com)
- Russian technology and PATH assistance

- Disposable "safety cap"

- Capture splashback of blood or tissue fluid onto re-used nozzle

- Advantages

- Cost-competitive with A-D needles
- Fills directly from multi-dose vials
- High speed

- Disadvantages

- Must demonstrate safety
- Explain remaining risk to public
- Prevent defeating of autodisable cap
- Nightly autoclaving of fluid pathways



# Slow-speed, Disposable Cartridge Jet Injectors (DCJIs, “dick-jees”)

Most filled by end-user from “off-tool” single- or multi-dose vial:

Biojector® 2000



Vitajet®



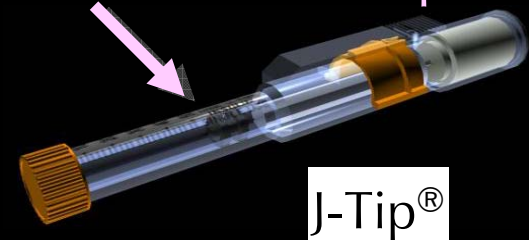
Antares Pharma



Injex®



Entire device 1-use disposable:



Some investigational devices intended for manufacturer pre-filling:

Entire device 1-use disposable (high speed?):

Mini-Imojet®



Intraject®



PenJet™





# Design Specifications of CDC for *Disposable-cartridge Jet Injector*

## ● ***Safety***

- Disposable, single-use, auto-disabling cartridges
- Clean end-user filling of cartridges
- Cartridges capable of vaccine manufacturer pre-filling
- “Fingers-free” loading and ejecting of cartridges
- All sterile components provided; no field sterilization
- No sharps waste; reduced volume of medical waste
- Prevent firing if filled cartridge not properly seated

## ● ***Speed (for Mass Campaigns)***

- $\geq 600$  injections / hour ( $\geq 10$  / minute =  $\leq 6$  seconds each)

## ● ***Low cost***

- Competitive to auto-disable syringes

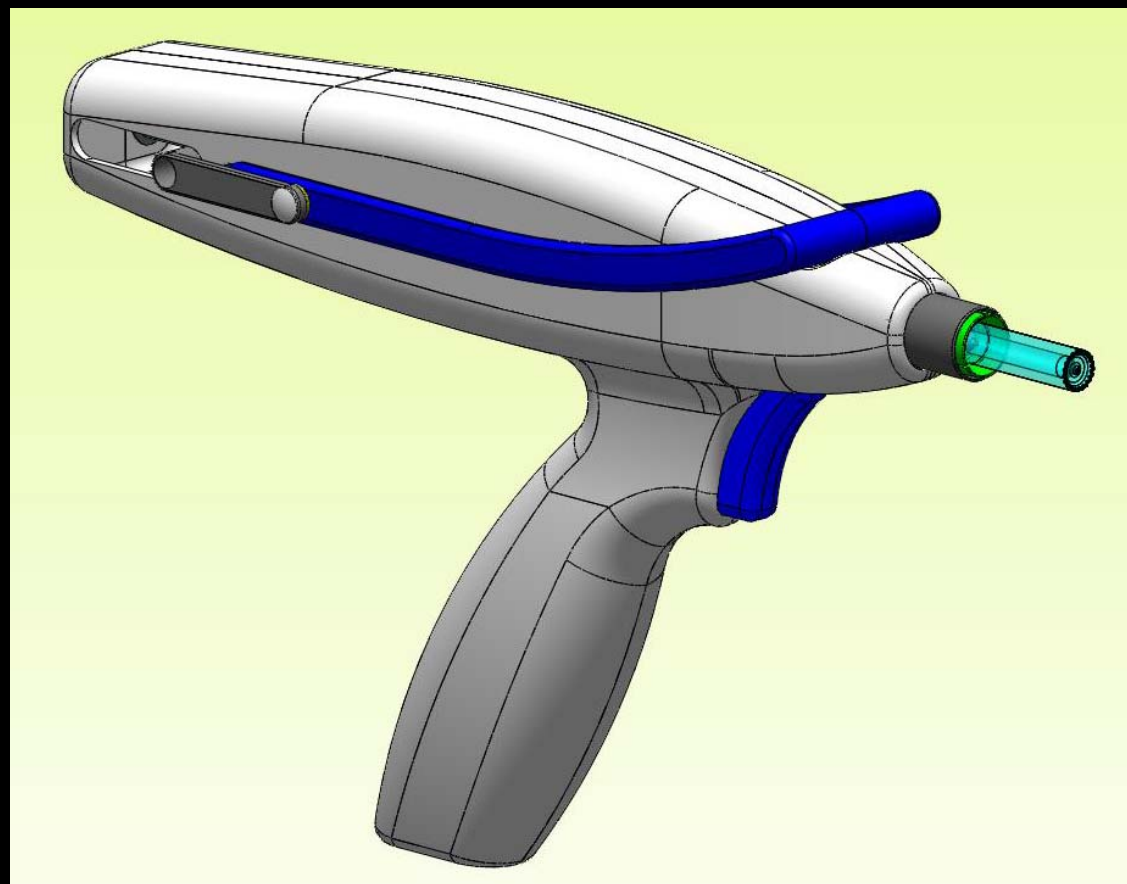
# LectraJet® – Motorized Model

- DCI, Inc., East Syracuse, NY
  - [www.dantonioconsultants.com](http://www.dantonioconsultants.com)
- Spring compressed by internal motor
- Rechargeable, replaceable battery pack
- >3,000 injections per charge
- Battery-charging – AC mains, vehicle battery, solar, etc.
- Backup manual spring compression possible
- Electronic injection counters
  - Non-resettable lifetime, resettable session



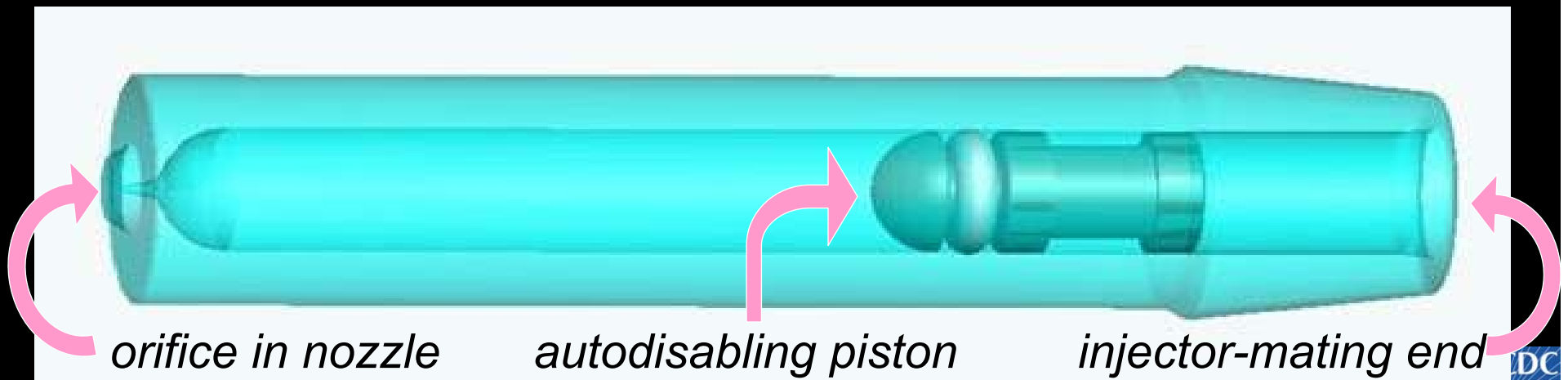
# LectraJet® – Manual Model

- Spring compressed by cocking hand lever
- Suitable for either
  - Routine clinic use
  - High-speed mass campaigns without electricity ( $\geq 600/\text{hr}$ )



# LectraJet® Cartridges

- Filling options
  - Onsite by end user
  - Prefilled by vaccine manufacturer
- Material
  - Polycarbonate “plastic” for field filling
  - Cyclic olefin copolymer (COC, Topas®) “plastic” for pre-fills
- Autodisable piston to ensure single-use-only
- Low cost at high volumes (~U.S. \$0.06 each)



# LectraJet® Magazine

- Holds and manages 30 cartridges to minimize handling
- Foil seals and folding flanges covering nozzles maintain cleanliness during filling and use
- Allows filling and use of individual cartridges without wastage of remainder in magazine
- Furnished wrapped and sterilized for end-user filling
- Disposable





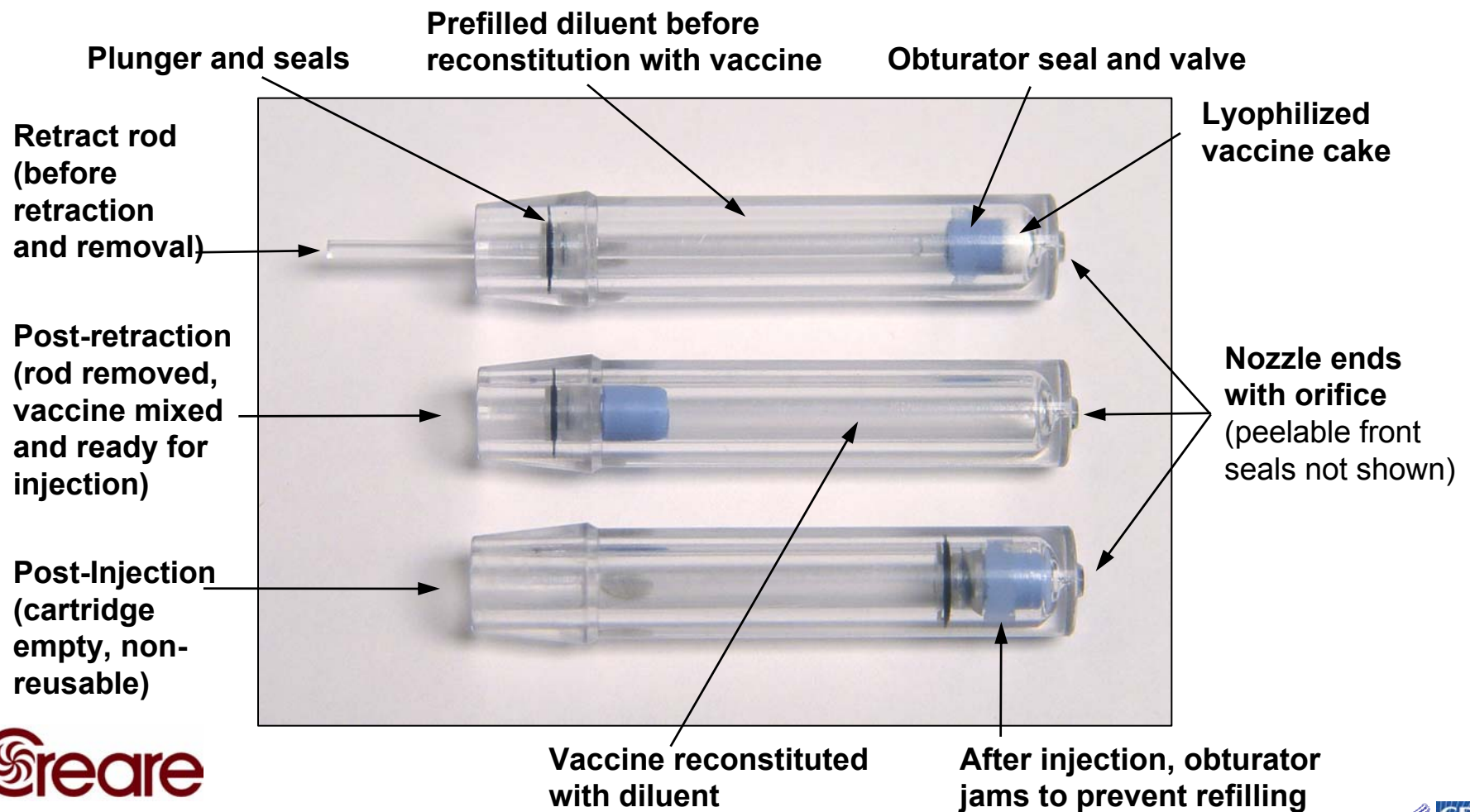
# Demonstration of LectraJet® Jet Injector, High-speed Model



Manual model with hand-cocking lever just as fast, but more tiring to health worker.

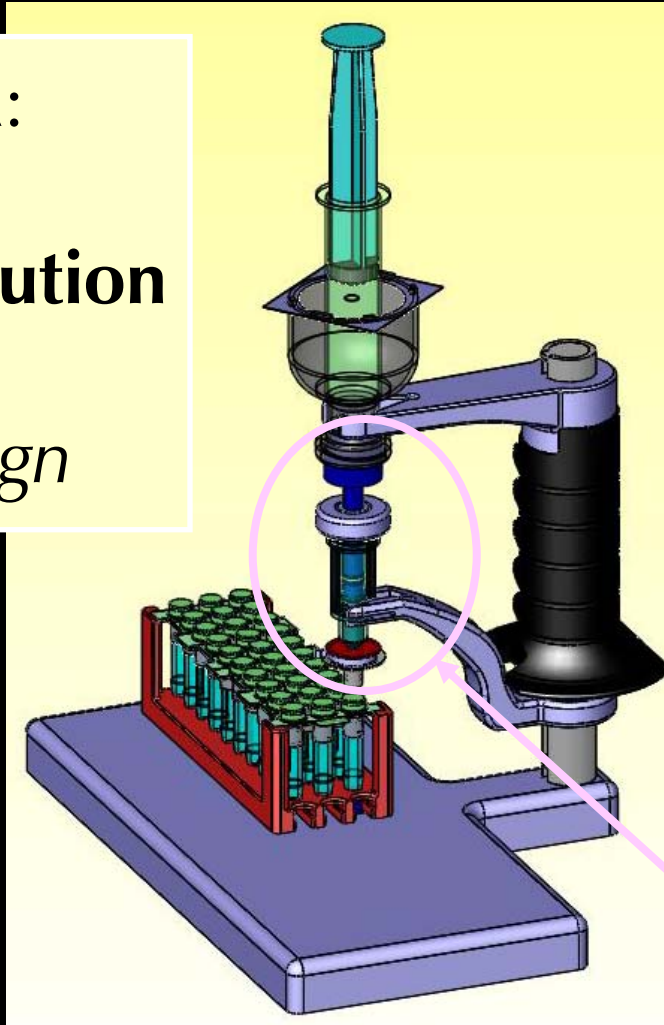
# Prototype Manufacturer-prefilled Auto-reconstitution Disposable Cartridges for Jet Injection

*Developed under CDC SBIR contract p.o. 65819 by  
Create, Inc., Hanover, NH, USA ([www.create.com](http://www.create.com))*

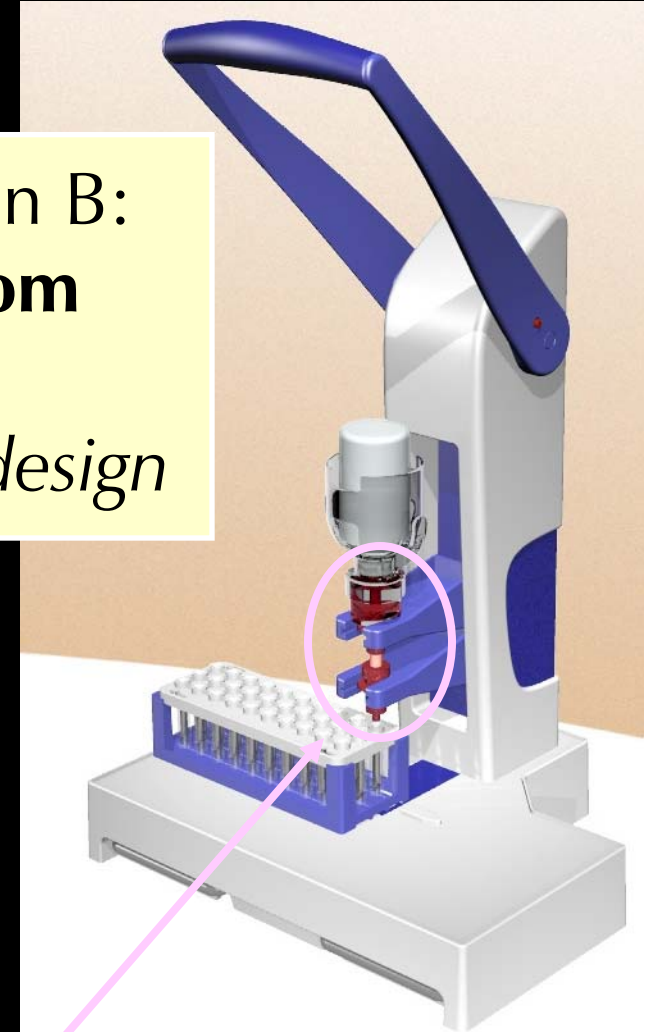


# LectraJet<sup>®</sup> Filling Station Models

Option A:  
**fill from  
reconstitution  
syringe,**  
*early design*



Option B:  
**fill from  
vial,**  
*later design*



- No finger contact with sterile surfaces
- Minimal wastage in disposable **fluid pathway interface/pump**
- Next cartridge quickly indexes into position after prior one filled

# LectraJet® DCJI System

- Advantages

- Cartridges cost-competitive with A-D needle-syringes
- Avoids safety concerns for cross-contamination
- Electrical and manual-cocking models similarly high-speed
- Multiple filling options
- Proven depth and deposition from piglet studies

- Disadvantages

- Injectors not yet field tested for ruggedness and reliability
- Field filling systems not yet assessed for cleanliness and reliability
- Prefilled cartridges dependent on convincing vaccine manufacturers and major procurers to adopt them

# Benefits of standardization in photographic industry



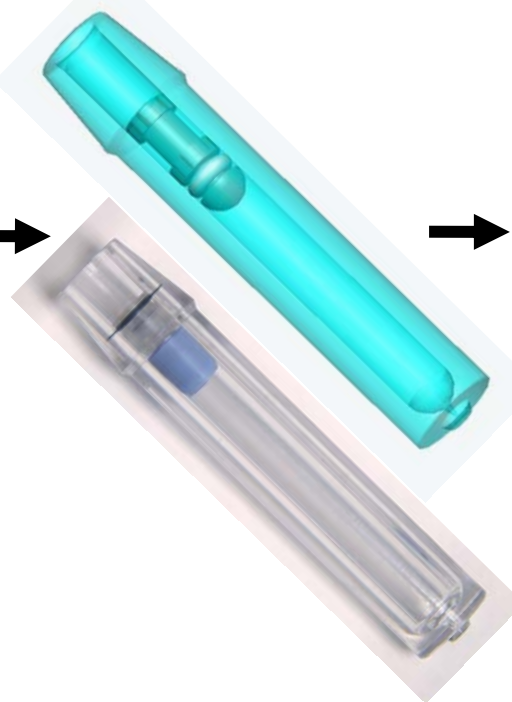
35 mm camera and film cartridge developed 1913-1924 by Oscar Barnack at E. Leitz company, Wetzlar, Germany,







*Vision of  
standardized  
cartridges in  
jet injector  
industry*



*WHO and CDC initiative*





# DCJIs vs. MUNJIs

