Jet Injection of Vaccines:
Overview and Challenges for Mass Vaccination with Jet Injectors (JIs)

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Conference: ***Innovative Administration Systems for Vaccines***
Rockville, Maryland, USA, 18-19 December 2003

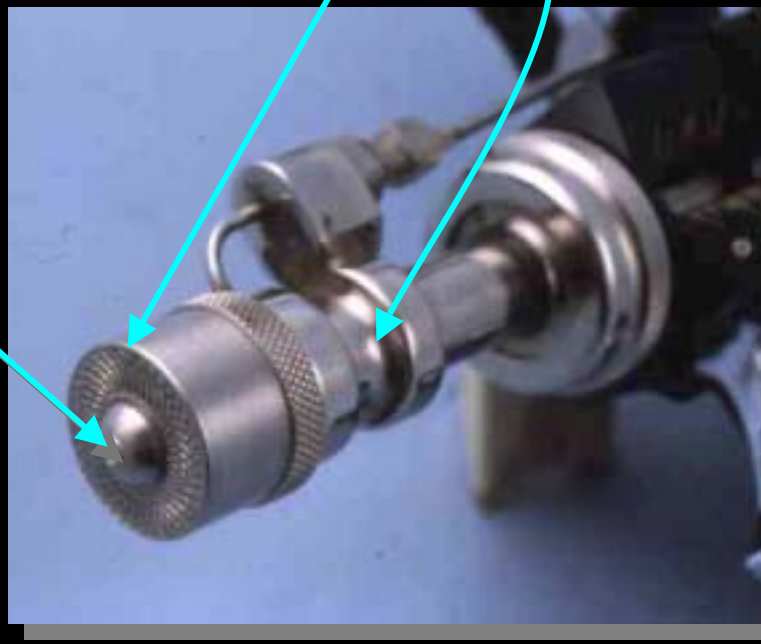
CDC

Jet Injection of Vaccines: Overview and Challenges for Mass Vaccination with Jet Injectors (JIs)

- Historical usage, efficacy and reactogenicity
- Public health need for high-speed devices for mass vaccination
- Safety concerns for *multi-use-nozzle jet injectors* (MUNJIs)
- New-generation *disposable-cartridge jet injectors* (DCJIs)
- Universal standards for DCJI cartridges

What is Jet Injection?

- Needle-free delivery of liquid through skin or mucous membrane
- Mechanism
  - Moving piston pressurizes fluid in the ***dose chamber***
    - >1,000 p.s.i. (>7,000 kPa)
    - Piston driven by release of compressed metal spring or compressed gas
    - Power sources: foot or hand pump/lever, gas cylinder, or electrical motor
  - Fluid ejected through ***orifice*** (diameter +/- 0.15 mm) in the ***nozzle***
    - High pressure over small surface area
    - Penetrates epidermis or mucous membrane
- Deposition to targeted tissues
    - Intramuscular
    - Subcutaneous
    - Intradermal
  - Penetration dependent on various factors
    - skin thickness, orifice size, pressure, speed, etc.
- Dose volumes often variable
  - Human devices: 0.1 to 1.0 mL
  - Veterinary devices: <1.0 to ≥2 mL



Further information: www.cdc.gov/nip/dev/jetinject.htm

Historical origins of jet injection - I

- Technology invented in France, 1860s
  - Various names used for technique:
    - *l'aqua-puncture*
    - *l'hydropuncture*
    - *douche filiforme* [threadlike spray]
  - H. Galante et C^ie^ device
    - Manufactured in Paris
    - Clinical studies: Dr. L. Sales-Girons, Pierrefonds-les-Bains spa
    - Treated "uncontrolled neuralgia" and other conditions
    - Injected plain water and other liquids

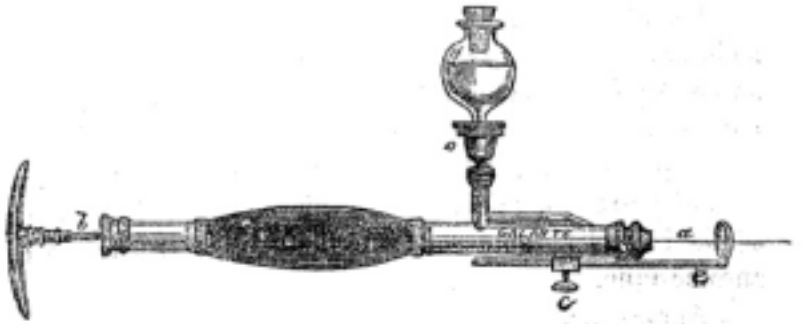
Citation:
www.cdc.gov/nip/dev/jetinject.htm#bibliography

X. M. Béclard présente à l'Académie, de la part de M. Galante, un petit instrument pour pratiquer l'hydro-puncture.

CORRESPONDANCE MANUSCRITE. 323

Un jet capillaire de liquide, lorsqu'il est projeté sur un point de la peau et avec la force de vingt-cinq atmosphères au moins, la perce, et le liquide est introduit dans les mailles des tissus organisés.

Il s'agissait de faire un petit instrument qui produisît ce jet et cette force; c'est ce qu'a fait M. le docteur Sales-Girons avec une seringue fabriquée par M. Galante.



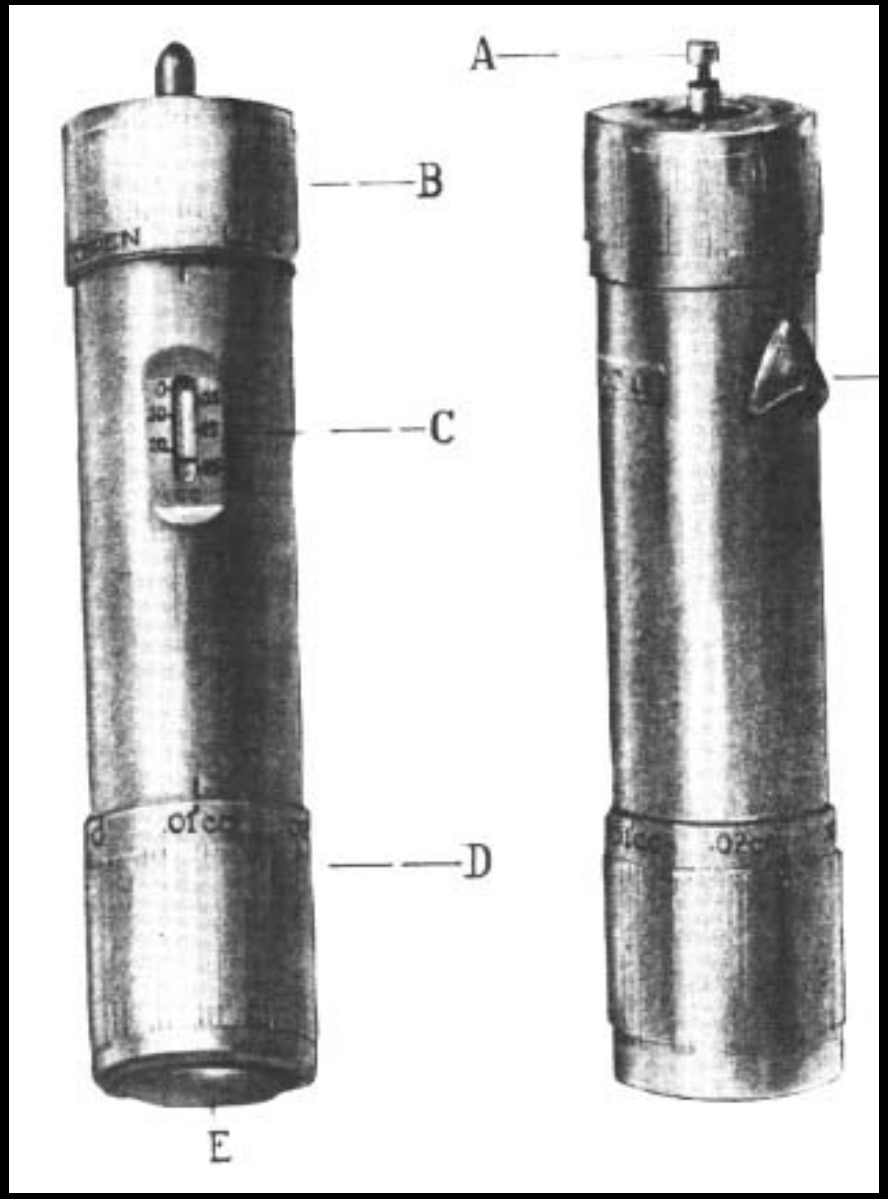
Le liquide est contenu dans une petite ampoule de verre; en tirant le piston il entre dans le corps de la pompe, dont le diamètre n'excède pas 3 millimètres de calibre; en poussant avec le simple effet de la main, il sort un filet capillaire avec la pression voulue de 25 à 30 atmosphères.

Appliqué sur le point désigné de la peau, l'opération de l'hydro-puncture se pratique avec la plus grande facilité. Ce procédé est mis à profit aujourd'hui contre les névralgies rebelles, avec de l'eau pure ou des liquides médicamenteux.

{Béclard/Galante 1866}

Historical origins of jet injection - II

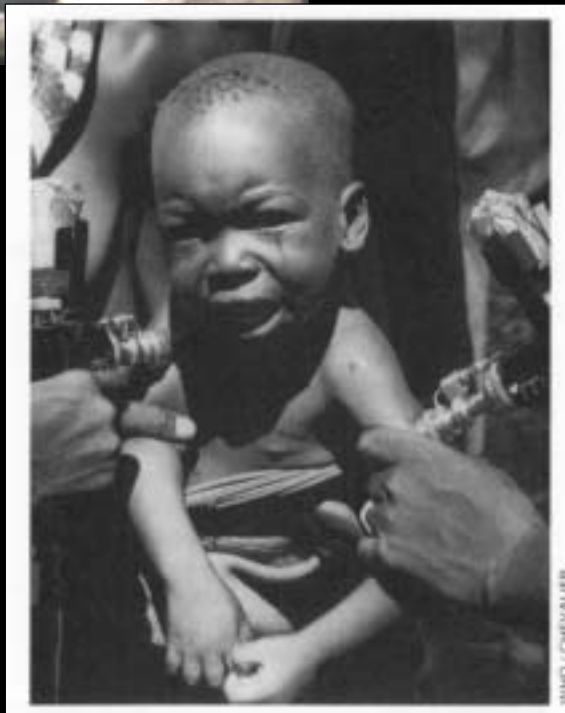
- Modern era: "rediscovered" in USA
- Clinicians noted deposition of hydraulic fluid in worker's hand from a pinpoint leak in pressurized fluid line
- First commercial device:
  - Hypospray® (R.P. Scherer Corp., Detroit)
    - Introduced late 1940s
    - Targeted to childhood diabetes to overcome needle phobia
    - Self-administration
    - Generally single-patient use



Historical origins of jet injection - III

- ***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$_{ps}$**, **POL$_{IPV}$**, **SMA**, **YEL**, *inter alia*
- Ped-O-Jet® brand: earliest and most widely used MUNJI worldwide



WHO / CHEVALIER

Plate 17.5. Jet injectors were used to administer smallpox vaccine in the left arm and measles vaccine in the right arm. Sometimes the injections were given simultaneously. Aluminium foil covers the vaccine vials to prevent the inactivation of virus by exposure to light.

Medicaments Delivered by Jet Injectors

- Anesthetics, local and systemic, sedation
  - e.g., lidocaine, morphine, midazolam
- Antibiotics
  - e.g., penicillin, streptomycin
- Corticosteroids
- Heparin
- Hormones
  - e.g., insulin, erythropoetin, chorionic gonadotropin, growth hormone
- Immunostimulating drugs
  - e.g., interferon
- Tuberculin
- Vaccines
- Vitamins

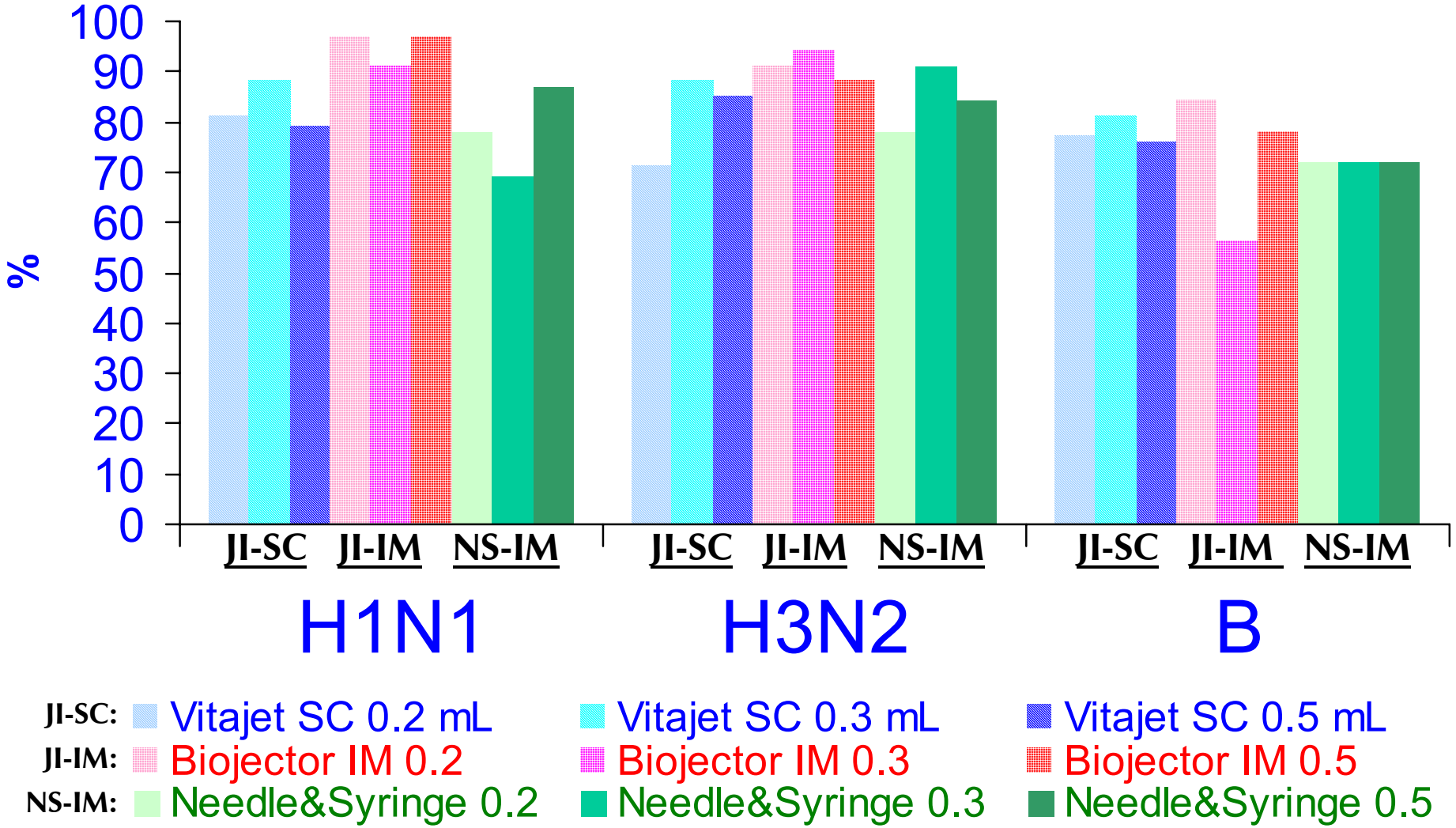
Immunogenicity of Jet-injected Vaccines

- Generally equivalent to or better than needle/syringe
  - Effect of antigen-presenting dendritic (langerhans) cells in skin ?

- Live vaccines
  - Bacille Calmette-Guérin
  - Measles
  - Mumps
  - Measles-Mumps-Rubella
  - Measles-Smallpox (vaccinia)
  - Rubella
  - Smallpox (vaccinia)
  - Yellow fever

- Inactivated vaccines
  - Botulism
  - Cholera
  - Diphtheria - tetanus - pertussis
  - Hepatitis A
  - Hepatitis B
  - Influenza
  - Meningococcus A, C
  - Plague
  - Polio
  - Tetanus
  - Tularemia - Typhoid

Needle-free Influenza Vaccination: Percent subjects with >=4-fold rise in HAI titer by day 28



Source: Jackson, et al. *Vaccine* 19:4703-4709, 2001.

Local Adverse Effects of Jet-injected Vaccines

- Slightly more reactogenic than needle-syringe (N-S)
  - Immediate local reactions
    - erythema
    - hematoma
  - Delayed local reactions
    - soreness
    - erythema
    - induration/edema
    - ecchymosis
  - Inactivated vaccines usually more reactogenic than live vaccines
- Pain generally less than or similar to N-S
  - Results vary by study
  - Patients report “no pain”, “less pain”, and “equal pain to N/S”
- Other local adverse events
  - Bleeding at injection site more common than with N-S
  - Laceration if movement occurs during injection
  - Traumatic injury (e.g., neuropathy) reported

Advantages and Disadvantages of Jet Injection

- Advantages
  - Administers existing, off-the-shelf vaccines
  - Long history of efficacious use with many vaccine types
  - Avoids need and delay in reformulating and licensing new vaccines intended for other needle-free methods
  - Both end-user filling ***and*** manufacturer prefilling possible
  - Eliminates needlestick dangers and sharps-waste burden
  - Potential high rates of vaccination (>600 patients / hour)
- Disadvantages
  - Increased pain for irritating medications
    - e.g., adjuvanted vaccine
  - Potential laceration injury from improper technique
  - Potential blood cross-contamination via MUNJI devices
  - Requires reconstitution of dried vaccine into liquid

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Public Health Need for High-speed Devices for Mass Vaccination

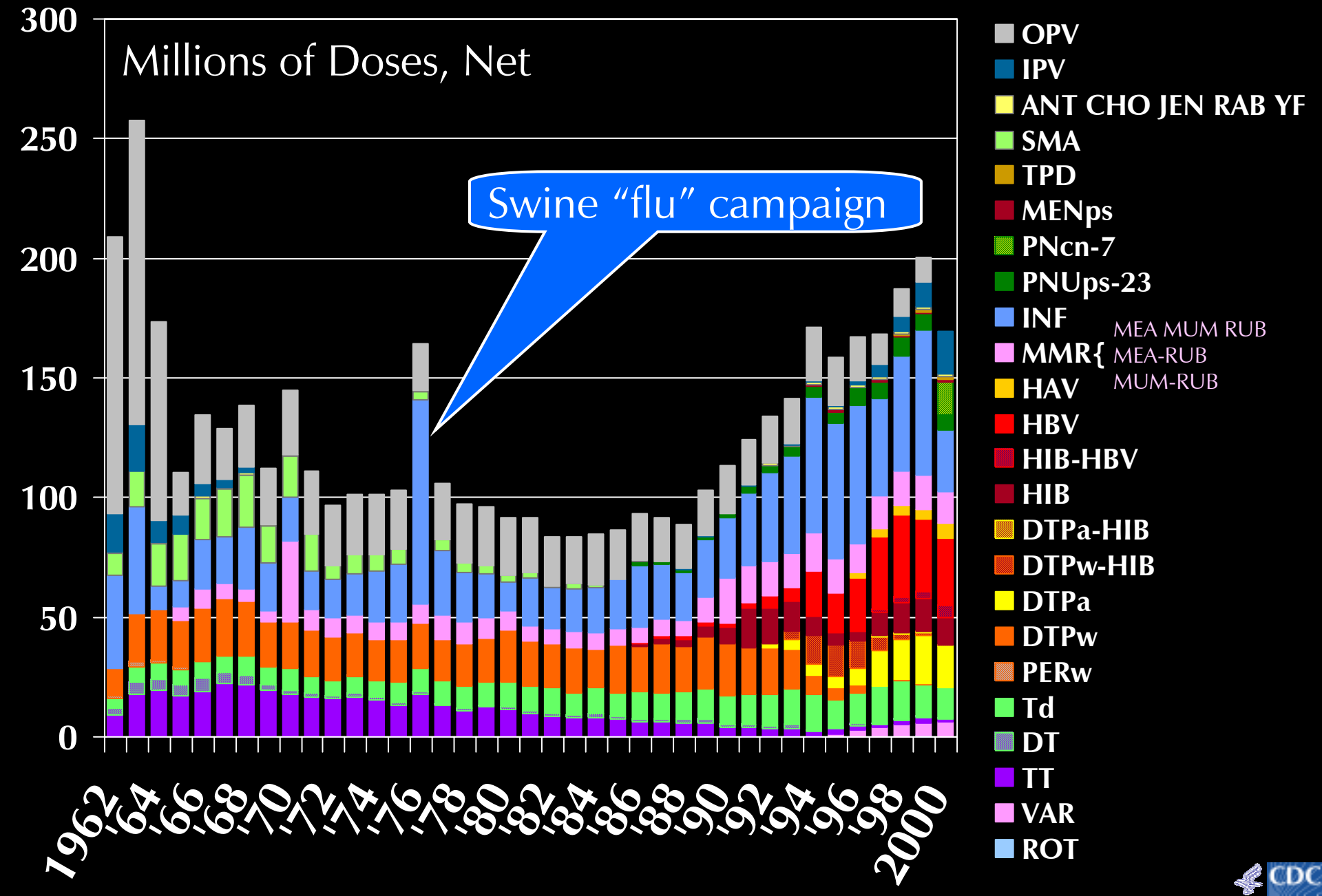
- Global disease eradication
  - Smallpox eradicated (1975) with MUNJIs and bifurcated needles
  - Polio almost eradicated with (high-speed) oral polio vaccine
  - Next target for eradication: measles
    - Will use strategy of *National Immunization Days*, as with polio
    - Parenteral vaccine requires injections
    - Constraints of limited time and skilled manpower for using needle-syringes
- Pandemics and regional/local epidemics
  - Influenza
  - Meningococcal meningitis
  - Yellow fever
- Rapid response to bioterrorism
  - Parenteral vaccines: anthrax, plague, glanders, tularemia, etc.
  - But not smallpox (bifurcated needles simpler and just as fast)

Reported Measles Cases, Brazil, 1990-1996*

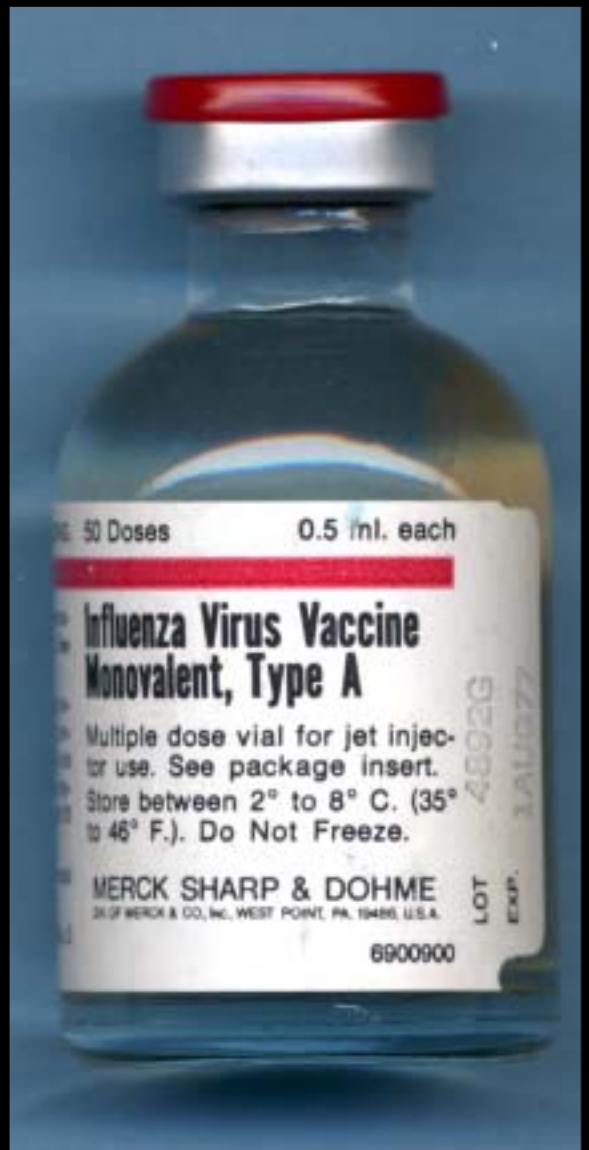
Data courtesy: Glacus de Souza Brito, Ministério da Saúde, São Paulo

CDC

Vaccine Doses Distributed in the U.S., 1962-2000



"Swine" Influenza Vaccine (A/New Jersey/8/76 - Hsw1Nsw1) 1976-1977 Mass Campaigns with Multi-use-nozzle Jet Injectors (MUNJIs)



Published Russian Studies of Potential Biowarfare Agent Vaccination with High-speed Jet Injectors

- ANTHRAX vaccine
  - Saltykov 1971, Burgasov 1973, Cherkasski 1973, Pilipenko 1974 (+ plague, tularemia), Burgasov 1976, Loktev 1980 (+ plague, tularemia)
- BOTULISM vaccine
  - Agafonov 1974 (+ typhoid, tetanus)
- PLAGUE vaccine
  - Agafonov 1972, Pilipenko 1974 (+ anthrax, tularemia), Agafonov 1978 (oral plague + JI typhoid, oral smallpox), Lebedinskii 1979, Loktev 1980 (+ anthrax, tularemia), Gapochko 1981 (+ smallpox), Gapochko 1992 (+ typhus, smallpox)
- SMALLPOX vaccine
  - Agafonov 1969, Lev 1972, Marennikova 1972, Agafonov 1973 (+ tularemia), Balabaniuk 1974, Agafonov 1977, Agafonov 1978 (oral smallpox + typhoid, oral plague), Gapochko 1981 (+ plague), Gapochko 1992 (+ plague, typhus)
- TYPHUS vaccine
  - Gapochko 1992 (+ plague, smallpox)

Прививка оспенной вакцины с помощью безыгольного инъектора.

- TULAREMIA vaccine
  - Agafonov 1973 (+ smallpox), Pilipenko 1974 (+ anthrax, plague), Uglovoi 1975, Loktev 1980 (+ anthrax, plague)
- VENEZUELAN EQUINE ENCEPHALITIS vaccine
  - Lukin 1977

www.cdc.gov/nip/dev/jetinject.htm#bibliography

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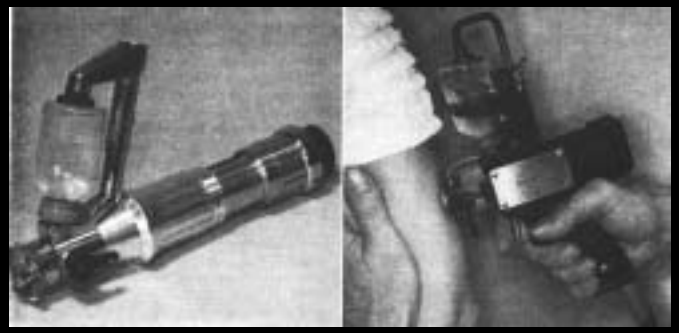
Types of Multi-use-nozzle Jet Injectors (MUNJIs)

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

CENTERS FOR DISEASE CONTROL

June 13, 1986 / Vol. 35 / No. 23

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Hepatitis B Associated with Jet Gun Injection — California

In March 1985, during routine investigation of hepatitis B (HB) case reports, an epidemiologist at the Long Beach (California) Department of Public Health noted that three HB patients had each received injections at the same weight-reduction clinic (clinic A) before disease onset. When review of previous case records and questioning of newly reported HB patients identified five additional HB cases among clinic attendees, the California Department of Health Services joined in the investigation of the clinic on July 1, 1985.

Clinic A belonged to a chain of 29 weight-reduction clinics located throughout southern California. Attendees at the clinics typically received a series of daily parenteral injections of human chorionic gonadotropin (HCG). Injections were usually given by jet injectors (Med-E-Jet Corp, Cleveland, Ohio), although some attendees received injections with single-use disposable needles and syringes. A standard regimen consisted of 30 injections; however, individuals varied considerably in duration of treatment and number of injections received.

The investigation focused on a cohort of 341 persons who attended clinic A during the first 6 months of 1985. Clinical history, review of risk factors for acquiring hepatitis B virus

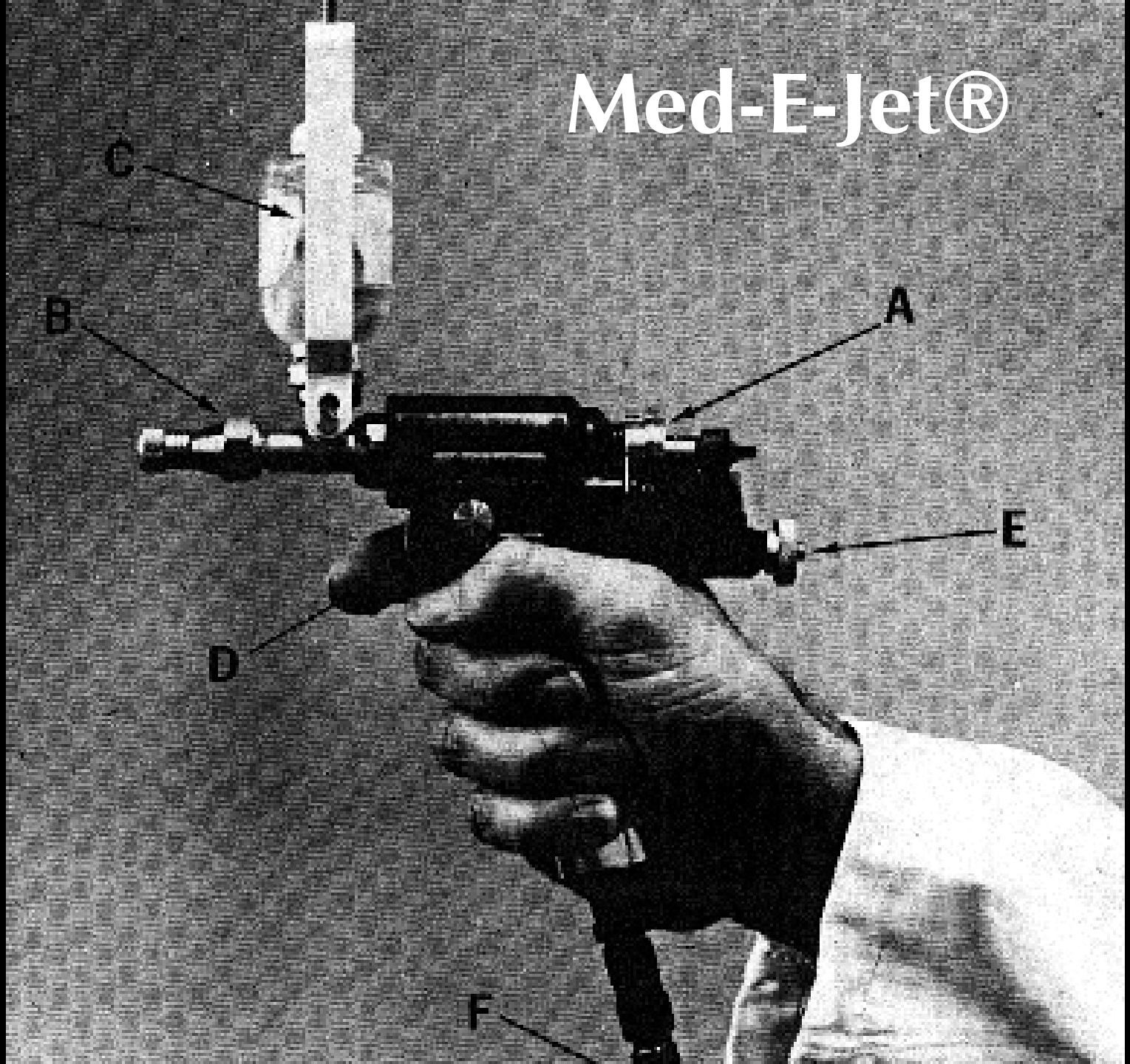
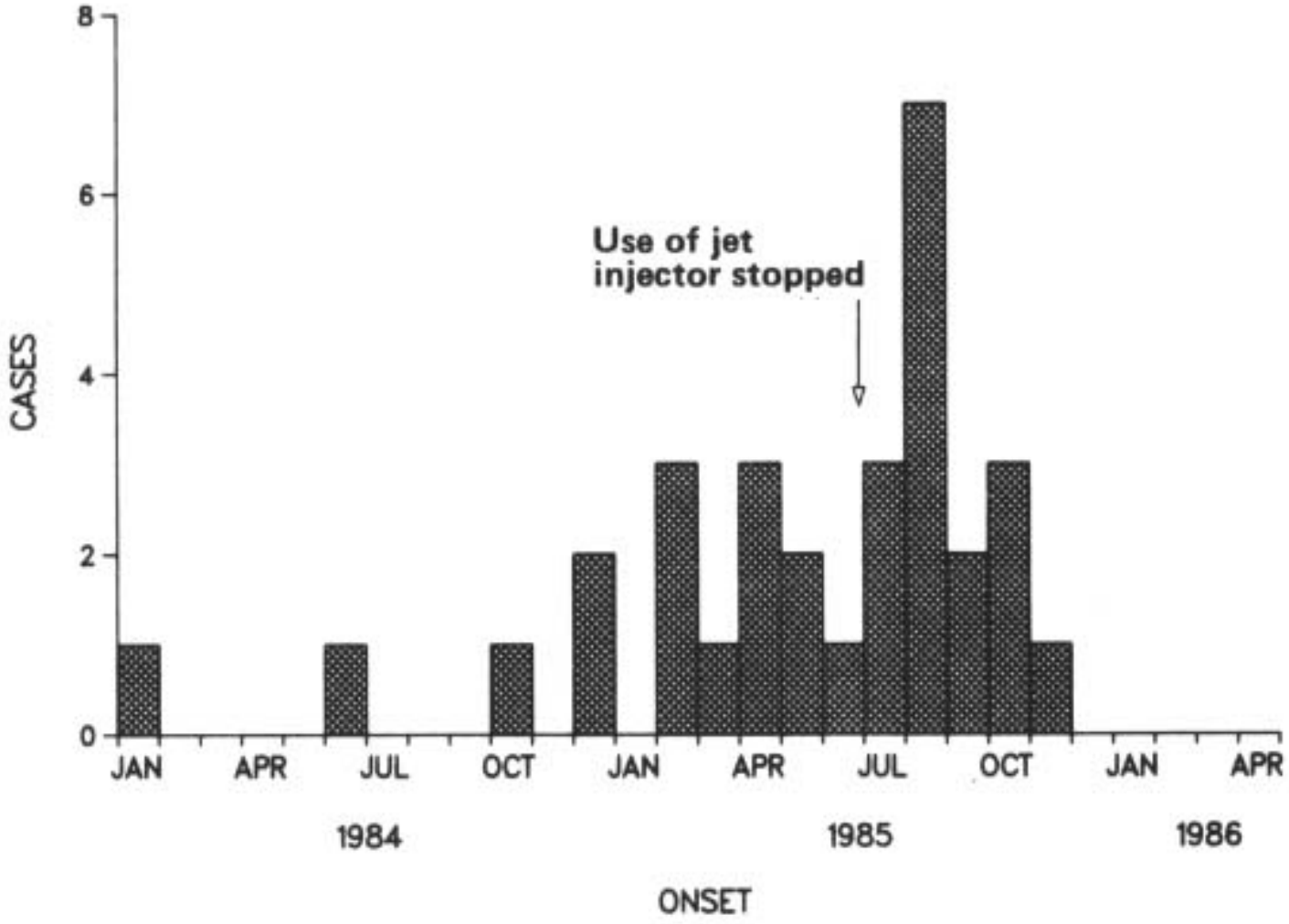

Med-E-Jet®
C
B
A
E
D
F

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

[A] Ped-O-Jet - swab vs. no swab: $p<0.05$, Fishers Exact Test
[B] Med-E-Jet - swab vs. no swab: not significant

Canter *et al* 1990; unpublished data, CDC, 1986-1987, courtesy Walter W. Bond

Jet Injectors Study, Brazil, 1989-1991

Occult Blood By Dipstick* In Vaccine Samples

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

* sensitivity 0.002-0.01 uL BLOOD/0.5 mL DOSE

de Souza Brito, et al. Int'l Conf AIDS, Yokohama, 1996 abst. PC0132

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]

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
    - Plus HBsAg+ in human study

ELSEVIER

Vaccine 19 (2001) 4020–4027

www.elsevier.com/locate/vaccine

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

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[b] *Division of Life Sciences, King's College London, University of London, London SE1 8WA, UK*
[c] *PHLS Statistics Unit, 61 Colindale Avenue, London NW9 5EQ, UK*
[d] *Enteric and Respiratory Virus Laboratory, Central Public Health Laboratory, London NW9 5HT, UK*
[e] *GPV, WHO, 1211 Geneva 27, Switzerland*

Received 16 October 2000; received in revised form 8 March 2001; accepted 13 March 2001

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.

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

Injector	Injections Sampled	Blood quantity (pL) detected in next discharge (? ≥10 unsafe ?)		
		0-9.9	10-49.9	≥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

Injector	No. of Animal Injections	Ejectates with blood >10pL / 0.5mL						
		Pre-Inject	Post 1st	Post 2nd	Post 3rd	Post 4th	Post 5th	Post 6th
"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

- Results
  - 5 devices, 3 models, 3 sites
    - bovine – published
    - porcine, human – unpublished
  - All produced ≥1 "unclean" ejectate(s) following up to ~100 *in vivo* injections
- Caveats and limitations
  - To be discussed in later presentation from WHO

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Slow-speed, Disposable Cartridge Jet Injectors (DCJIs, *"dick-jees"*)

Most filled by end-user from *"off-tool"* single- or multi-dose vial:

Biojector® 2000

Antares Pharma

Injex®

Entire device 1-use disposable:

Some investigational devices intended for manufacturer pre-filling:

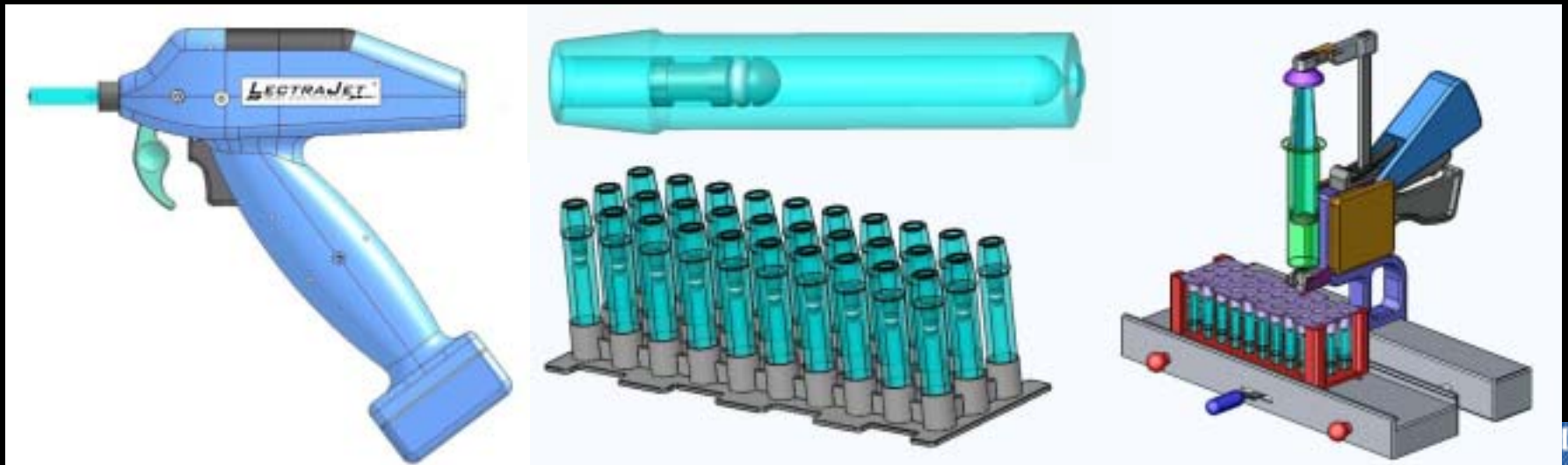
Entire device 1-use disposable (high speed?):

CDC

High-speed, Disposable Cartridge Jet Injectors (DCJIs)

Early MEDiVAX™ prototype by PATH filled from multi-dose vial *"on tool"*:

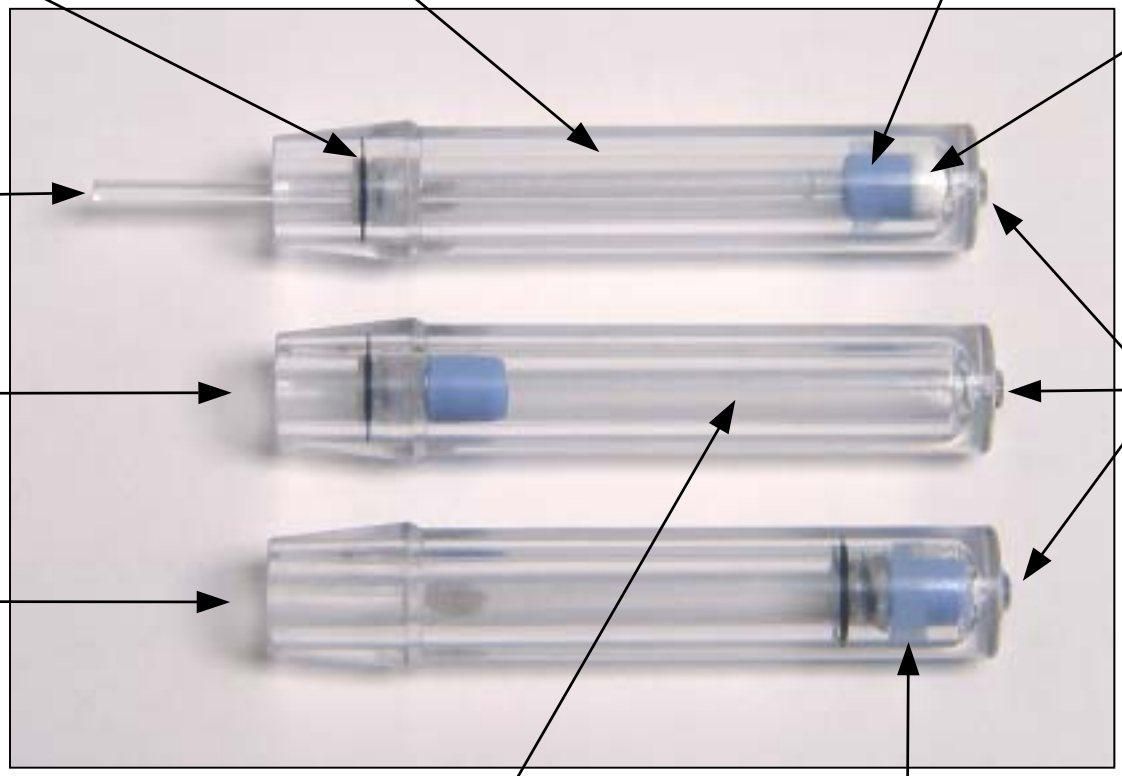
Investigational LectraJet® by DCI, Inc. filled from multi-dose vial *"off tool"*:



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

Developed under CDC SBIR contract p.o. 65819 by

Creare, Inc., Hanover, NH, USA (www.creare.com)



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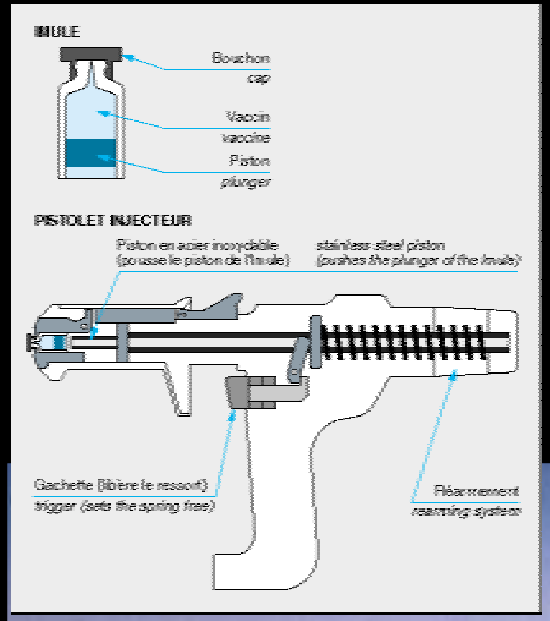


Charles Mérieux

1907 - 2001

Manufacturer-pre-filled *Imule*™ cartridges/vials for *Mini-Imojet*™ jet injector

(Institut Mérieux, later Pasteur Mérieux Connaught, now Aventis Pasteur)

Imule™ cartridge/vial for use with Mini-Imojet™ injector

(Institut Mérieux, now Aventis Pasteur)

Benefits of standardization in photographic industry

AGFA

FUJIFILM

Kodak

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

Leica

Fisher-Price

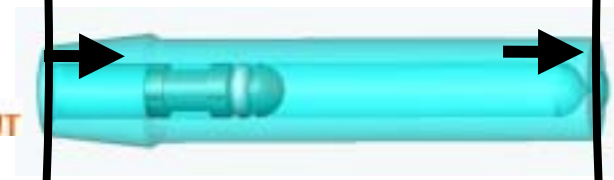
Canon

MINOLTA

Nikon

RICOH

Vision of standardized cartridges in jet injector industry



Acambis

Aventis

Aventis Pasteur

GREEN CROSS

LG Chem

Baxter

MERCK

BERNA PRODUCTS

STATENS SERUM INSTITUT

Wyeth

CSL

gsk GlaxoSmithKline

POWDERJECT

Chiron

EVANS VACCINES

SBL Vaccin

Shire

+ Others

ACTIVA

BIOJECT

CHEMICAL AUTOMATICS DESIGN BUREAU

J-TIP

ELECTRONICS IN MOTION

Equidyne

Felton INTERNATIONAL

MADA Medical
MADA Equipment
MADA International

Medi-Jet

NMP

PENJET INC.

SYRIJET

weston medical

+ Others

CDC

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CDC