The Unintended Consequences of Vaccine Delivery Devices Used to Eradicate Smallpox: Lessons for Future Vaccination Methods

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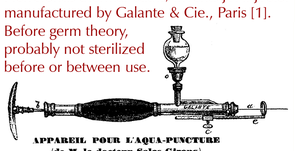
Start

1860s

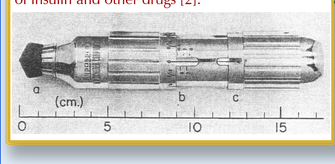
Dr. Sales-Girons, *médecin inspecteur* of the Pierrefonds thermal baths, invents jet injector manufactured by Galante & Cie., Paris [1]. Before germ theory, probably not sterilized before or between use.



APPAREIL POUR L'AQUA-PUNCTURE
(de M. le docteur Sales-Girons)

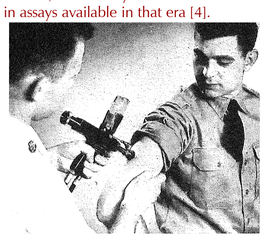
1940s

Hypospray® jet injector is introduced in USA in late 1940s for self-administration by patients of insulin and other drugs [2].



1950s

U.S. Army invents high-speed **multi-use-nozzle jet injectors** (**MUNJI**s) for fast vaccination of troops. Most common brand is the Ped-O-Jet®. Walter Reed Army Institute of Research expresses concern for blood-borne transmission of pathogens between vaccinees, but military unable to detect surrogates for viral agents in assays available in that era [4].



Multidose jet injection device developed by Medicinal Equipment Development Laboratory, Fort Totten, New York

taneous tissues. There have been no reactions suggesting intravenous infection in over 100,000 injections despite occasional bleeding indicating that the jet had traversed a blood vessel; this may well be explained by the fact that when one milliliter of material is diffused through the tissues, only insignificantly small amounts could possibly enter a vessel. Obviously, one should not inject over a major vessel.

The problem of hepatitis has been minimized. After each of five different injection sessions, with no cleansing of the nozzle between a total of 762 recipients, the nozzle was soaked in saline and then precipitin tests were set up with rabbit and horse antihuman serum. The results were negative, indicating the presence of less than 15 gammas of human serum, if any. Bacteriological tests of the vaccine ejected during the course and at the end of an injection session have consistently shown no evidence of contamination; there has been no known instance of

WHO expert committee warns of hepatitis risk by not sterilizing all parenteral injection devices between patients [3].

It is now well known that serum hepatitis is transmitted not only by transfusions and the injection of infected blood-products, but also by the accidental inoculation of traces of infected blood remaining in a hypodermic needle and syringe from the previous occasion on which it was used. It is not so generally appreciated that the disease may be transmitted by any procedure in which the skin or mucous membrane is broken by an inadequately sterilized instrument which has previously been used on another human. This risk is present in innumerable medical, surgical, clinical-

Recommendations to ensure the safety of medical procedures involving parenteral penetration

(1) Every parenteral penetration must be performed with syringes, needles, or other instruments sterilized as outlined below. Such penetrations include all kinds of injections or aspirations, the taking of specimens of capillary and venous blood, tests and vaccinations performed by scarification, as well as many other surgical and dental procedures.

Hoffman *et al* study four different **MUNJI**s for cross-contamination by ELISA assay for bovine serum albumin as a surrogate marker for blood in ejectates after injecting calves [24]. Frequencies of next-ejected quantities that would theoretically transmit HBV [17] ranged from 34% to 95%. Contamination through to the 6th post-injection specimen was found in 5% (1) of 20 calf injections by **MUNJI** "D".

Injector	Injections Sampled	Blood quantity (pL) detected in next discharge (? ≥10 pL 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%)

1962

Barrett *et al* reports safe use of the Hypospray® **MUNJI** in the Detroit schools and health dept. [5]. (No mention of any surveillance in place that would detect hepatitis.)

Hypospray injections seem to be painless in well over 90 per cent of the subjects inoculated. We have abandoned use of the needle and syringe in favor of Hypospray as a routine means of injecting immunizing material in mass inoculation programs. After having inoculated over 500,000 persons of all ages with Hypospray, there has never been a case of infectious hepatitis nor any bacteriologically confirmed cases of infection. One of the great advantages of using Hypospray equipment in mass inoculation programs is its speed efficiency.

Eli Lilly & Co. influenza vaccine product insert warns of risk of *serum* hepatitis transmission and need to resterilize **MUNJI** nozzles [6]. (No awareness of the high transmissibility of hepatitis B virus [HBV] via invisible traces of blood or serum.)

Special Precautions for Jet Injection—Vials supplied for use with jet-injection equipment should be used only once; any vaccine remaining in the vial at the end of the day should be discarded.

Epidermal wheals and mild bleeding may occur occasionally after jet injection. To minimize this problem, the skin should be dry before injection, the nozzle should be pressed firmly against the skin, and movement of the nozzle during injection should be avoided. If the nozzle becomes contaminated with blood or serum, it should be replaced or resterilized before further use to prevent the transmission of serum hepatitis virus or other infectious agents from one person to another.

Erythema and edema at the injection site may be somewhat more common when vaccine is administered by jet apparatus than when it is given by needle and syringe.

HOW SUPPLIED

Influenza Virus Vaccine, Polyvalent (Types A and B), is supplied as follows:
V-1304—1 cc., rubber-stoppered vial; V-1306—10 cc., rubber-stoppered vial.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

PA 1787 AMP Literature revised December 28, 1962 PRINTED IN U.S.A.

During actual mass vaccination campaigns in Brazil, Brito de Souza *et al* collect vaccine discharged from **MUNJI**s between consecutive doses administered to patients [22]. Using relatively insensitive urine dipsticks, blood is detected in average 1% of all ejectates sampled.

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

1967

Rosenthal finds blood by benzidine method on 18% of the **MUNJI** nozzles swabbed after administering tuberculin skin tests in two British schools [7].

There were 139 swabs taken of the post of the injector where it touched the skin. Forty-six, or 34 per cent, gave a positive test for benzidine (table 3). Seventy-one control swabs tested with benzidine were negative. Precipitin ring tests on eluates of the swabs were negative (8 tests of some 35 swabs).

The average diameter of the wheals for all the injections was 6.93 ± 1.875 mm. Bleeding occurred in 45 per cent of the 341 trials. The percentage of bleeding was highest when the size of the wheals were the smallest. This was also noted in School A.

There were 248 swabs made, of which 22 or 8.9 per cent gave positive benzidine tests; 103 control swabs were negative (table 3). There appeared to be less gross bleeding with this jet injector than with that used in School A.

Of 387 tests for the two schools, 68 or 17.6 per cent were positive for blood; 174 control swabs were benzidine negative (table 3).

WHO introduces **MUNJI**s for the intensified smallpox eradication programme. Over several years, Ped-O-Jets® administer hundreds of millions of smallpox vaccine doses, primarily in Brazil and western and central Africa [8].

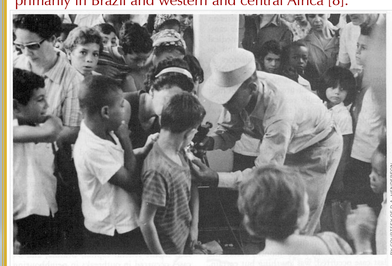


Plate 12.4. The demonstration in 1965 of the efficacy of the jet injectors provided an important stimulus to Brazil to undertake an effective national smallpox programme. This device could vaccinate as many as 1000 persons each hour.

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.

In experimental animal model to assess cross-contamination risk by **MUNJI**s, Brink, *et al* transmit lactase dehydrogenase virus (LDH) from LDH-infected to LDH-uninfected mice by consecutive injections of saline [16].

Feinman *et al* estimate the minimum volume of blood capable of transmitting HBV [17]. Titrations of human HBV-positive sera injected into a chimpanzee found 100 million chimpanzee-infectious doses per mL. This converts to 10 pL (10^{-8} mL) of HBV-infected blood transmitting infection, well below the sensitivity to detect blood by human vision, by common urine dipstick, and by non-PCR HBV assays.

Increasing evidence emerges for the risks of bloodborne pathogen transmission by **MUNJI**s [9]: **Darlow** detects human serum protein on injector nozzles after human injections, using radiolabeled antiserum assay [10]. **Horn**, *et al* detects human white blood cells on Med-E-Jet® nozzles after human injections [11]. The **CDC** Hepatitis Laboratories Division was unable to detect HBsAg by RIA (Ausria II) in subsequent ejectates after injection of HBsAg-carrier chimpanzees, but did so when nozzles were artificially contaminated (table) [12]. After injections, they observed fluid remaining on the Ped-O-Jet nozzle being sucked back into the device upon its cocking and refilling for the next injection [beyond the reach of alcohol or acetone swabbing].

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

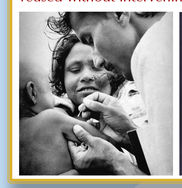
Hepatitis B surface antigen (HBsAg) positives
Number / total sampled (%)

Site Tested	Ped-O-Jet® No Swabbing	Ped-O-Jet® Swabbing	Med-E-Jet® No Swabbing	Med-E-Jet® 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

1970s

Bifurcated needles replace **MUNJI**s to administer hundreds of millions of smallpox vaccine doses in the eradication programme, primarily in east Africa and south and east Asia [8]. Although minimally-trained vaccinators were taught to flame or boil **bifurcated needles** after each use, under challenging and unsupervised field conditions they were sometimes reused without intervening sterilization [13].

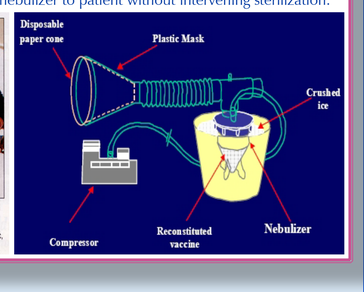


1980s

Albert Sabin and colleagues in Mexico undertake three decades of R&D for mass measles vaccination by the aerosol route, leading to the "classical Mexican device" (photo) [14,15]. For cost reasons, it re-uses tubing for vaccine pathways from nebulizer to patient without intervening sterilization.

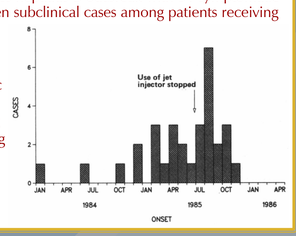
Photo courtesy of Ahmanundh Dilraj, MMedSc

Use of aerosolized measles vaccine is expected to be a boon for mass measles immunization campaigns for children older than 5 years. Here, Atmanundh Dilraj, MMedSc, demonstrates the procedure with his son.



1984-85

A **MUNJI** causes hepatitis B outbreak with 31 symptomatic and several dozen subclinical cases among patients receiving multiple injections in a California weight-loss clinic [18-20]. Attack rate 31% among patients receiving all doses by **MUNJI**; 0% by needle-syringe.



1988

After experimental intramuscular and subcutaneous injections of saline by **MUNJI** into four HBsAg carriers, nozzle surfaces are negative for HBV markers by Abbott assay. However HBV was detected from skin swabs of the injection sites of all four subjects [21].

1989-1991

Venezuelan Equine Encephalomyelitis virus is transmitted experimentally in 2.8% (15 of 534) of pairs of infected and non-infected guinea pigs, rabbits, and monkeys by various Russian **MUNJI**s [23].

1997

Due to liability concerns for pathogen transmission, the Ped-O-Jet® manufacturer ceases production and servicing. Its principal U.S. customer, the US Department of Defense (DoD), recalls them from military use [25].

DEFENSE LOGISTICS AGENCY
DEFENSE PERSONNEL SUPPORT CENTER
2800 SOUTH 20TH STREET
PHILADELPHIA, PENNSYLVANIA 19145-5099

DPSC-M December 9, 1997

MEMORANDUM FOR STAFF DIRECTOR, DEFENSE MEDICAL STANDARDIZATION BOARD

SUBJECT: Jet Hypodermic Injection Units

Ped-O-Jet, the manufacturer of the military hypodermic jet injection unit, recently sent a letter to the Office of the Assistant Secretary of Defense for Health Affairs indicating there is a potential health hazard associated with its use. Apparently, the Center for Disease Control and the World Health Organization have expressed concern that this type of device might be implicated in the spread of blood borne disease when used in the multiple dose mode. Ped-O-Jet has urged the military to discontinue use of these items until such studies are completed that would indicate they are safe to use.

It should be noted that the military designed unit has been in use for 35 years and we have no reports of any problems with the spread of blood borne disease on record. However, since the appearance of diseases such as HIV and Hepatitis C, it might be best to proceed cautiously in the present time. 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. In light of the possible serious consequences and the letter from Ped-O-Jet, this is considered the best course of action. We are also suspending issue of these items from the depot.

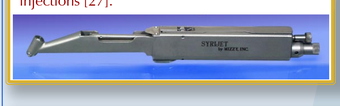
Armed Forces Epidemiological Board (AFEB) reviews **MUNJI** safety [26]. During inspection of an actual mass vaccination session at a Military Treatment Facility (MTF) of a Marine Corps training base, AFEB observes unsafe Ped-O-Jet use. Recommends to DoD the R&D of a "new generation [of safer] needleless injection technology" with "appropriate safety testing".

cleaned and sterilized daily. All services reported using the injectors routinely. Vaccines administered by jet injection included hepatitis B, influenza, MMR/MR, meningococcal, tetanus-diphtheria, and yellow fever. Some Army recruit sites did not use the jet injectors. The Navy and Marine Corps reported that they did not use jet injectors on smaller ships because there were more doses in the vaccine vials than personnel to be immunized. The Coast Guard used its jet injector only for mass influenza inoculations.

Of note is that the AFEB made a site visit to the MTF at Parris Island and directly observed high volume recruit immunization using jet injectors. It was noted that jet injector nozzle's were frequently contaminated with blood, yet sterilization practices were frequently inadequate or not followed.

1998

The Syrijet **MUNJI** commonly used for dental anesthesia is found by *in vitro* bench assay using fluorescein and bacterial markers to transfer material from prior to subsequent injections [27].

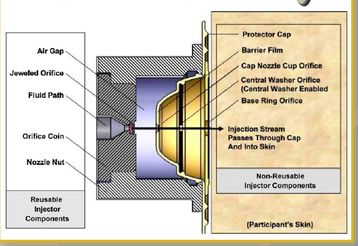


HBsAg-carrier volunteers in Brazil receive 234 injections with saline by sterilized Ped-O-Jets. After each, the subsequent three ejectates from the **MUNJI** -- representing what the next vaccinees in a mass vaccination campaign would receive -- are assayed by ELISA for human serum albumin as a marker for blood [28]. Without alcohol swabbing of the nozzle after human injection, 13 (11%) of 117 subsequent first ejectates contained calculated blood volumes of >10 pL, considered positive for HBV infectivity [17]. Swabbing reduced the blood-positives to 8% (9/117). Second discharges after injection were positive 3% of the time with or without swabbing. All third ejectates after human injection were negative for blood.

PATH evaluates **MUNJI** safety in HBsAg-carriers [39] according to suggestions from the 2002 and 2004 CDC and WHO consultations [31,32].

Attempting to prevent splashback of infectious blood and tissue fluid onto the reusable nozzle, the Felton HSI-500 **MUNJI** (photo) features a disposable "safety cap" with three axially-aligned, 1 mm-diameter holes on three parallel polyethylene planes through which the jet stream passes to the patient.

Nevertheless, 8% (17 of 208) of post-injection samples discharged from the device were positive for HBV by PCR assay.



2001

In a town in the Amazon basin of Brazil, Souto *et al* surveyed 754 randomly-selected inhabitants, of whom 31% (232) had serologic evidence of prior HBV exposure and 3% (19) were HBsAg carriers [30]. History of prior yellow fever vaccination by **MUNJI** was associated with past or current HBV infection on univariate analysis (p=0.0001) and among those <30 years of age in multivariate model (p<0.005).

WHO warns against the use of **MUNJI**s [29].

1.5 Needle-free injectors

Needle-free injectors designed for use with multi-dose vials and with a multiple-use fluid path should not be used for immunization. These injectors have an inherent risk of bloodborne disease transmission[1]. Needle-free injectors designed for use with mono-dose pre-filled cartridges[3], or mono-dose cartridges for filling at the point of use, with a disposable fluid path may be used for immunization. These injectors do not share the same risk of contamination and disease transmission as the multi-dose injectors.

WHO recommendations for vaccination equipment [29] would preclude **bifurcated needles** as used in smallpox eradication because they are not *autodisabling*, and because their sterilization was without proper supervision and lacked sterilization indicators.

1.4 Sterilizable Syringes

Sterilizable syringes can be used for routine immunization sessions where compliance with cleaning and sterilization procedures between each use can be assured, as verified by supervisory visits and by routine use of 'time, steam & temperature' (TST) control spots. Sterilizable syringes are neither practical nor

2002-2004

CDC reiterates a fundamental principle of hospital infection prevention in developed countries: One must sterilize or replace all aerosol tubing pathways and drug reservoirs between use by consecutive patients to prevent respiratory pathogen transmission [33].

4 MMWR

III. Prevention of Transmission of Microorganisms
A. Sterilization or Disinfection and Maintenance of Equipment and Devices
1. General measures
a. Thoroughly clean all equipment and devices to be sterilized or disinfected (IA) (*23,24*).
b. Whenever possible, use steam sterilization (by autoclaving) or high-level disinfection by wet heat pasteurization at >158 F (>70°C) for 30 minutes for reprocessing semicritical equipment or devices (i.e., items that come into direct or indirect contact with mucous membranes of the lower respiratory tract) that are not sensitive to heat and moisture (Box). Use low-temperature sterilization methods (as

BOX. Example of semicritical items* used on the respiratory tract

Anesthesia device or equipment including:
- face mask or tracheal tube
  - inspiratory and expiratory tubing
  - Y-piece
  - reservoir bag
  - humidifier
- Breathing circuits of mechanical ventilators
- Bronchoscopes and their accessories, except for biopsy forceps and specimen brush[†]
- Endotracheal and endobronchial tubes
- Laryngoscope blades
- Mouthpieces and tubing of pulmonary-function testing equipment
- Nebulizers and their reservoirs
- Oral and nasal airways
- Probes of CO_2 analyzers, air-pressure monitors
- Resuscitation bags
- Stylets
- Suction catheters
- Temperature sensors

* Items that directly or indirectly contact mucous membranes of the respiratory tract should be sterilized or subjected to high-level disinfection before reuse.
† Considered critical items and should be sterilized before reuse.

Unpublished consultations on the evaluation of **MUNJI** safety hosted by CDC and WHO in 2002 and 2004 question the relevance of prior animal model studies and the sensitivity and specificity of albumin assays to detect cross-contamination [31,32]. They suggest only human trials of HBsAg carriers injected with **MUNJI**s, followed by the most sensitive PCR assays for HBV in subsequent discharges from the injector.

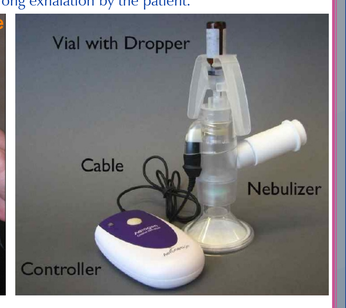
WHO, CDC, and the American Red Cross begin the Measles Aerosol Project in 2002, with eventual funding from the Gates Foundation. The aim is to develop and license at least one device and vaccine for respiratory delivery of currently-licensed measles vaccines for the developing world [15,34-37].

A phase I trial of a delivery device which claimed -- without evidence -- to have "avoided risk of contamination" was completed in India in 2008. A phase II/III "pivotal" study began in 2009 in 2,000 Indian children from 9 to 11.9 months of age.

For cost reasons, the Aerogen delivery device (photo) reuses the aerosol pathways between the vaccine reservoir and nebulizer mechanism and the patient without intervening sterilization, changing only the disposable facemask.

Despite more than 17 published papers on the immunogenicity and "safety" of aerosol measles vaccination since the 1960s [15,35], there have been no publications -- or descriptions of unpublished ones -- of bench, animal model, or clinical studies for definitive assessment of the risk for transmission of respiratory pathogen between consecutive vaccinees.

Claims that disposable "one-way valves" prevent retrograde entry of pathogens into the aerosol stream in reusable pathways of the device have not been proven, particularly under situations of coughing, crying, sneezing, spitting, or other strong exhalation by the patient.



Hepatitis B virus infection rates by country groups are estimated to model the global burden of disease and impact of vaccination [38]. Among women of childbearing age as a sentinel group, HBsAg carriage is around 12% for Africa and certain countries in east and southeast Asia, 4% in countries on the Indian subcontinent, and 2% in Brazil and some neighboring states.

2005

2006

Conclusions

- An unintended legacy of smallpox eradication is that iatrogenic transmission of hepatitis B is likely to have occurred as a result of the inherently unsafe design of multi-use-nozzle jet injectors (**MUNJI**s) such as the Ped-O-Jet®, as well as the unsterile reuse of **bifurcated needles** in involved countries with moderate-to-high prevalence of infection.
- Nevertheless, the benefits of smallpox eradication are overwhelmingly positive and lasting. Errors in past public health programs should not be critiqued on the basis of knowledge accumulated and policies developed in later eras.
- Modern emphasis on safety regarding the administration of vaccines requires higher standards than in the past, particularly for technologies for the developing world for which the intended method of use in mass campaigns would likely not be licensable by regulatory authorities in developed countries.
- This unfortunate lesson from smallpox eradication should teach caution to avoid similar outcomes for novel vaccine delivery systems such as aerosol vaccination by the respiratory route. Its reuse of the aerosol pathways that are in direct contact with the exhaled respiration of patients is potentially unsafe. It does not satisfy developed-country standards for infection control. Human trials with such reusable components should be conducted only after rigorous, independent studies definitively demonstrate that features claimed to prevent infectious cross-contamination with pathogenic respiratory viruses and bacteria do indeed work. Safer options may include delivery from disposable pouches which are disconnected from the aerosol generator before patient contact.

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