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**Participation in Meeting
“Jet Injectors for Immunization;
Current Practice and Safety;
Improving Designs for the Future”**

Atlanta, Georgia
October 2-4, 1996

Rebecca Fields

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ACRONYMS

BASICS	Basic Support for Institutionalizing Child Survival project
CDC	Centers for Disease Control and Prevention
EPI	Expanded Programme on Immunization
GPV	Global Programme on Vaccines and Immunization
HB	Hepatitis B
HIV	Human Immunodeficiency Virus
JI	Jet injector
PATH	Program for Appropriate Technology in Health
USAID	United States Agency for International Development
WHO	World Health Organization

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I. EXECUTIVE SUMMARY

BASICS Technical Officer Rebecca Fields participated in a meeting entitled "Jet Injectors for Immunization: Current Practice and Safety; Improving Designs for the Future." The meeting was convened by the World Health Organization and the Centers for Disease Control and Prevention and was held in Atlanta, Georgia, on October 2-3, 1996. Participants included public health experts and injection device manufacturers. The meeting provided an opportunity for these parties to interact on discussions of design features for a new generation of jet injectors that would be useful for both high and low workload situations, i.e., campaigns and routine services.

Globally, and especially in the area of immunization, there are increasing concerns about injection safety and the need for proper disposal of contaminated sharps, especially as mass measles and neonatal tetanus campaigns are being proposed in areas that are highly endemic for hepatitis B (HB) and human immunodeficiency virus (HIV). Jet injectors present a potentially very attractive alternative to needles and syringes—reusables, disposables, or autodestruct—because they do not use needles, result in a minimum of contaminated waste, and can be designed to be very easy to use. Under certain scenarios, they could also compare favorably in terms of cost. However, such appealing features must be designed actively into new jet injectors and included as part of design specifications from the outset. These issues were discussed in depth at this meeting.

Despite 40 years of jet injector (JI) use, especially in recent measles campaigns in Latin America, very few data exist on the safety of existing JIs, such as Ped-o-jet. Data suggest that it is difficult to initially contaminate the JI, but once contaminated, it does indeed have the potential to transmit disease. Because of safety concerns, in early 1996, the Expanded Programme on Immunization of WHO's Global Programme on Vaccines and Immunization (WHO/GPV/EPI) banned the use of existing jet injectors. However, a poll taken of the participants at this meeting gave a unanimous result that existing jet injectors could continue to be used under certain limited circumstances. It was clear from presentations and discussions that considerable additional safety testing, starting with the elaboration of an effective test methodology, is needed if further progress with the development and introduction of jet injectors is to take place.

A long list of desired design criteria was brainstormed by meeting participants. This will need to be reduced to a reasonable number of actionable specifications, and device manufacturers will need clear estimates of the potential market for jet injectors if they are to invest in development. At this point, there are no concrete follow-up actions for BASICS. However, BASICS should keep current with product developments and be prepared to work with WHO, CDC, USAID, PATH, and others to contribute to thinking on end-user needs, programmatic requirements, and approaches to the design, implementation, and analysis of field trials.

II. BACKGROUND

Over the past several years, concerns about the safety of injections have increased, especially as the sheer number of injections for immunization has risen in areas that are endemic for hepatitis B (HB) and human immunodeficiency virus (HIV). Although immunizations represent only about 10 percent of total injections given within the health system in the developing world, immunization programs still pose an opportunity for intervention in injection safety. As vaccinations serve preventive purposes, they are particularly vulnerable to highly visible scares to the general public about injection safety. Vaccinations are also fairly easily quantifiable and thus relatively easier to manage than injections for other purposes.

Since the mid-1980s, considerable effort and funding has gone into the development of alternatives to the standard needle and syringe for immunization or other purposes. USAID has actively promoted such alternatives for developing country use, providing funding through the HealthTech cooperative agreement with PATH for advancing the design and development of autodestruct syringes, prefilled single-use injection devices, and needleless jet injectors. The Expanded Programme on Immunization of the World Health Organization (WHO/EPI) has always been active in defining user needs and design features for injection technologies. The Centers for Disease Control and Prevention (CDC) has become involved in the development of models and methods for determining the risks of transmission through injection technologies. The National Immunization Program of CDC and WHO/GPV jointly organized the present meeting on jet injectors, primarily as a means to review experiences and develop specifications for a new generation of jet injectors.

III. SCOPE OF WORK

The author attended the two-day meeting on jet injectors (JIs), held at the Lenox Inn in Atlanta, on October 2-3, 1996, in order to both learn about new developments with JIs and to offer viewpoints on end-user and managerial concerns for developing country use of JIs within immunization programs. She did not attend the third day of the meeting, described in the meeting announcement as an optional day for informal discussions.

IV. TRIP ACTIVITIES

As stated above, the author participated in the CDC/WHO-GPV meeting, entitled "Jet Injectors for Immunization: Current Practice and Safety; Improving Designs for the Future."

In addition, she had side meetings with staff from CDC (Craig Shapiro, Susan Goldstein), WHO/GPV (Mark Kane), and the Pan American Health Organization (Peter Carrasco) to discuss the upcoming joint BASICS/CDC mission to Peru on planning for the introduction of hepatitis B vaccine into that country's EPI.

V. FINDINGS/CONCLUSIONS

The stated objectives of the meeting were as follows:

1. **Current Practice and Safety:** To review the global usage of existing devices for needleless, percutaneous administration of vaccines, to update data about transmission of bloodborne infectious diseases between jet injector vaccines, and to consider evaluation methodologies of such devices for safety.
2. **Improving Designs for the Future:** To “brainstorm” performance specifications to guide the design and development of future generations of both high-volume and low-volume vaccination devices for both developing and developed countries.

An agenda for the meeting is attached (Appendix A). Also attached (Appendix B) is a list of meeting attendees. One of the most interesting aspects of the meeting was that it brought together both public health professionals and injection device manufacturers, whose points of view were not always in agreement: device manufacturers tended to view the concerns of public health experts as overly cautious and unrealistic in terms of price and performance specifications.

Safety Concerns with Jet Injectors

The first day was spent providing an overview of public health concerns, a review of jet injector use, and development of recommendations for future use. The second day was spent largely in group discussion of desirable features of jet injectors. Given the growing levels of hepatitis B and HIV endemicity globally, there has been a great deal of concern by WHO on the need to ensure the safety of injections given by jet injectors. In terms of disease burden, hepatitis B poses a greater risk than HIV because it is far more infectious. Moreover, jet injectors carry an inherent risk of HB transmission in that the tiny lacerations that they normally produce in the process of administering vaccines in effect simulates the most common mechanism for hepatitis B transmission globally, that of horizontal transmission. With WHO planning mass campaigns for measles and neonatal tetanus, there certainly appears to be a role for JIs; however, their safety, given both theoretical and limited empirical data, must be assured before serious consideration can be given to their use.

Over the past 40 years, various types of “high workload” jet injectors have been used for campaigns, with Ped-o-jet being the type most commonly used. The U.S. Department of Defense has used Ped-o-jets to immunize some 235,000 new recruits annually for over 30 years, with no evidence of disease transmission. During mass measles campaigns in Central America in 1992-93, about 40 percent of the 10 million children immunized were vaccinated using jet injectors. In neither of these instances has there been any evidence of disease transmission. However, for an asymptomatic infection like hepatitis B, serosurveys would be required to detect transmission of the virus; in the absence of such data, it is impossible to state with any assurance that transmission has not occurred.

At present, there are only limited, but important data available on the potential risks from JI use. A review of JI use over the past 40 years (presented by Lisa Lindsay of CDC, but not yet available) confirms the paucity of data. In 1985, a small outbreak of hepatitis B was found at a weight-loss camp in California and a certain brand of jet injector, no longer marketed. Med-e-Jet was identified as the mechanism of transmission. This event created the first suspicions of the possible risk of JI use. In 1987, the state of Sao Paulo, Brazil, undertook mass measles campaigns, using Ped-o-jets. A few years later, the state EPI ran some studies to investigate the risk of disease transmission with the JI. The questions asked were—

- What is the frequency of visible bleeding at the site of jet injection in the skin?
- What is the frequency of occult blood in the next vaccine dose ejected from the JI?
- Is there any correlation between visible bleeding and occult blood in the next dose?

Among a total of 2883 vaccines in three different sites, an average of 3.6 percent (range: 2.2-23.3 percent) had visible bleeding at the skin injection site. Occult blood was detected by dipstick in 1 percent of the ejectates (subsequent dose of vaccine ejected from the JI). However, there was little correlation between visible bleeding and occult blood in ejectates. Based on assumptions of HIV and HB seroprevalence in the population, plus risk of needlestick injury, it was calculated that the theoretical risk of HIV transmission through the use of Ped-o-jet was in the range of 1/238 million to 1/476 million injections; while for HB, the risk ranged from 1/100,000 to 1/840,000 injections. Appendix C contains more information on the Brazil studies.

For Brazil's mass measles campaign in 1992, the government purchased 10,000 JIs and provided extra training to vaccinators. These vaccinators provided about 70 percent of the measles vaccinations given during the campaign. However, due to growing resistance by health workers and the community (despite an investigation of an outbreak of hepatitis B that showed no association with JI use), JIs are no longer used by the government, and in recent meningitis campaigns, needles and syringes have been used instead. These Ped-o-jets were loaned to Central American countries for use in their measles campaigns in 1993-95; technical assistance in their proper use and maintenance was also provided.

Because of safety concerns, during the massive meningitis outbreak in northern Nigeria in early 1996, WHO/EPI reversed its earlier (1994) policy on injection equipment and advised against the use of jet injectors under any circumstances. This had not, however, been widely publicized and most people at the meeting were unaware of it.

Walter Bond of CDC summarized the data available thus far by suggesting that existing jet injectors, such as Ped-o-jet, are not particularly easy to contaminate, but once they are contaminated, they can indeed transmit disease. Certain design features and practices by end users affect the likelihood of transmission. In particular, the smoothness of the nozzle head surface and the practice of swabbing the head with acetone between uses can reduce the risk of transmission. But the likelihood of the latter in typical developing country situations is very low.

It was clear from meeting discussions that WHO/GPV will only accept a “zero risk” jet injector. However, “zero risk” must be defined and this is no small task, as the transmissibility of hepatitis B exceeds the limits of detection of existing test methods. A protocol for testing of cross-contamination in animals was outlined by Peter Hoffman of the Central Public Health Laboratory and it was acknowledged that this type of testing is urgently needed. Consensus was not achieved on the exact methodology to be used. Additional safety tests were also discussed, such as repeating on a larger scale the studies conducted in Brazil with Ped-o-jet, Sicim (Italy), and Medivax (Vitajet) injectors, and by examining ejectates from Ped-o-jet vaccinations given to new military recruits in the U.S. The latter would represent best-use circumstances for the jet injector.

Appropriate Circumstances for Use of Jet Injectors

Hal Margolis from CDC presented a framework for considering appropriate circumstances for the use of existing or new JIs. Especially with regard to Ped-o-jet, consideration needs to be given to—

- The age group to be injected (Is it the same population that is most likely to convert to carrier state if infected with hepatitis B?)
- The prevalence of chronic infection in that population (seroprevalence; infectivity)
- Status of the hepatitis B immunization program, if one exists
- Reasons for use of jet injector, e.g., rapid disease reduction (emergency outbreak response campaigns? or planned disease control initiatives?); reduction of medical waste; concerns about risks from existing injection methods, i.e., with needle and syringe

WHO/GPV asked that all participants be polled as to whether the use of existing JIs should be (A) banned altogether; (B) allowed under limited circumstances; or (C) used without restrictions. With the exception of some GPV staff, the response was unanimous that the use of existing JIs could be continued in certain, limited circumstances. The author gave the opinion that different situations need to be distinguished: it may be acceptable to use the Ped-o-jet in emergency situations, such as meningitis campaigns, where other options may be unavailable or undesirable and the risk of disease and death from the target disease is high; but it would not be acceptable, without first conclusively establishing safety, to use this jet injector in planned disease control initiatives, especially in geographic areas highly endemic for HIV and hepatitis B (i.e., Africa or Asia).

Design Features of Jet Injectors

A number of different injection device manufacturers described the key features of their technologies. Some distinguishing design considerations include—

- Power source (e.g., battery-operated; foot pedal with bicycle pump)
- Multiple-use versus single-use (throwaway) devices, the latter developed for self-injection by diabetics
- Design features and mechanisms to prevent cross-contamination and backsplash of blood: e.g., the use of a spacer bar, disposable head or shield, or other mechanisms
- Means of conveying the vaccine or medication from its original packaging to the injection device and across the skin
- Rate of speed with which devices can be used
- Maintenance and ergonomic considerations for end users

Although Ped-o-jets have been used for years, they are difficult to obtain (there is a sole manufacturer of this type of device) and maintain. Acceptability by health workers is generally low. Yet in emergency situations, such as the recent meningitis outbreaks in West Africa, they are frequently brought out and revived for use.

At present, one device under development that has been designed specifically for developing country immunization program use is the Medivax jet injector, developed jointly by Vitajet (Brazil) and PATH. One model of Medivax, with a reusable head, received 510(K) approval from the U.S. Food and Drug Administration in 1995. This model employs a spacer bar to avoid splashback and cross-contamination, and was intended to be reusable, so as to avoid re-supply problems. WHO/GPV has decided that any device with a reusable head or fluid path is inappropriate for use in developing countries and now has an absolute requirement for a disposable head or interface. A new Medivax with a disposable head is now under development and will require a new set of safety and clinical/field tests prior to considering it for introduction. Information on the current version of Medivax (reusable head) is included in Appendix C.

Discussions in breakout groups resulted in extensive lists of desired design features and, perhaps more important, allowed for extended exchange between device manufacturers and public health experts as to intended use of JIs. These were discussed in light of design, engineering, and manufacturing considerations. A list of clearly delineated specifications did not emerge from these discussions and CDC was planning to consolidate the lists of the working groups. A draft of potential specifications for jet injectors that was prepared by PATH just prior to this meeting is included in Appendix E.

By the end of the second day of the meeting, participants coming from the public health perspective expressed some satisfaction with the progress made, while manufacturers expressed frustration that they still lacked the clear information that they need to advance product development, i.e., clear specifications and estimates of market size. The industry representatives

did express the view, however, that the meeting had provided a useful forum for them to meet as a group, and that they would like to continue their interaction through some type of consortium.

VI. RECOMMENDATIONS/FOLLOW-UP ACTIONS

The author has been asked by PATH/HealthTech to act as a partner in Medivax development, specifically providing input on behalf of BASICS on the subject of field trial design, implementation, and analysis. At this point, however, specific plans for field trials are on hold until issues concerning safety testing are resolved. The development and implementation of safety testing may take one to two years, by which time it may be too late for BASICS to take an active role in actually carrying out field trials. The main actions for BASICS at this time are to keep apprised of developments with jet injectors and to provide input to developers and other involved parties (i.e., WHO, PATH) on field trials and on the potential applications of jet injectors, especially as major measles and neonatal tetanus campaigns are launched. The types of jet injectors currently under development have the potential to provide an extremely useful alternative to existing reusable, disposable, and autodestruct needles and syringes.

APPENDIXES

APPENDIX A
MEETING AGENDA

**JET INJECTORS FOR IMMUNIZATION:
CURRENT PRACTICE AND SAFETY; IMPROVING DESIGNS FOR THE FUTURE**

AGENDA

Wednesday, 2 October, Day One: Current Practice and Safety

Objectives:

- (1) To review the global usage of existing devices for needleless, percutaneous administration of vaccines,
- (2) to update data about transmission of bloodborne infectious diseases between jet-injector vaccinees,
- (3) to consider evaluation methodologies for safety of such devices, and
- (4) to develop recommendations regarding the safety risks vs. immunization benefits of existing jet injector devices in vaccination programs.

8:00 - 8:30 am **Late Registrations**
Prepare One's Own Coat and Table Name Tags
Coffee - Juice - Bakeries - Fruit

8:30 - 8:35 **Welcoming Remarks - Meeting Co-chairs**
Robert Chen, CDC; Mark Kane, WHO

8:35 - 10:00 am **Overview of the Existing and Future Role of Jet Injectors**
Moderator: *John Lloyd, WHO*

8:35 Global Usage and Trends for Jet Injectors
John Lloyd, WHO; Peter Carrasco, PAHO

9:00 Recap of Content and Conclusions of Prior Jet Injector Meetings:
London, November 1995
John Lloyd, WHO

9:10 London, March 1996
John Poley, PA Consulting

9:20 Multi-Dose Jet Injector Use and Safety Aspects in Brazil
Glacus de Souza Brito, Brazil

9:30 Military Use of Jet Injectors
Col. William Bancroft, US Army Medical R&D Command

9:40 General Discussion

10:00 - 10:15 **Coffee Break**

10:15 - 11:30 **Review of Safety Considerations for Jet Injection Technology**
Moderator: *Michel Zaffran, WHO*

10:15 Views on the Comparative Risks of Injection Technologies:
Needles/Syringes vs. Jet Injectors
Mark Kane, WHO

10:25 Review of Jet Injector Safety and Field Assessment
Lisa Lindsay, CDC/Univ. North Carolina

10:35 Laboratory Assessment of Jet Injector Safety
Dan Prince, Gibraltar Labs

10:45 Animal-model Assessment of Jet Injector Safety
Peter Hoffman, Public Health Laboratory Service

10:55 Development of Low Workload Jet Injectors to Satisfy Safety Concerns
Glenn Austin, PATH

11:10 General Discussion

11:30 - 12:30 pm **Device Manufacturer's Perspective: Ensuring Safety of Multi-Dose Jet Injectors**
Moderator: *Robert Chen, CDC*

11:30 *Robert Harrington, American Jet Injector*

11:40 *Michael Roy, Auragen, Inc.*

11:50 *Sergio Landau, Vitajet*

12:00 *Terry Weston, Weston Medical, Ltd.*

12:10 General Discussion

12:30 - 1:45 pm **Lunch Break**
(For convenience due to the limited time available, the *prix fixe* buffet lunch next door at the Terrace Garden Hotel is recommended for meeting participants. \$8.75 plus \$1.25 for beverage.)

Wednesday, 2 October, Day One (continued)

1:45 - 3:30 **Roundtable Panel Discussion: Safety and Evaluation of Existing
Devices -- *Risks vs. Benefits of Existing Jet Injectors;*
Recommendations and Guidelines for their Use in
*Immunization Programs***

Moderator: *Mark Kane, WHO*

Rapporteur: *Michel Zaffran, WHO*

Panelists:

Harold Margolis, Hepatitis Branch, CDC

Walter Bond, Hospital Infections, CDC

Tim Ulatowski, US Food and Drug Administration

Discussants:

Glenn Austin, PATH

Col. William Bancroft, US Army

John Bennett, Task Force for Child Survival

Robert Harrington, American Jet Injector

*Isabelle Parent du Châtelet, Association pour l'Aide à la
Médecine Préventive*

Audience discussion and participation

3:30 - 3:45 **Coffee Break**

3:45 - 5:30 pm **Roundtable Panel Discussion (continued)**

5:30 **Day One Adjournment**

5:30 - 6:30 **Complimentary Cocktail Hour**
Lenox Inn Lounge (courtesy of the Lenox Inn)

7:00 - 9:00 **À La Carte Group Dinner**
Terrace Garden Hotel

Thursday, 3 October, Day Two: Designs for the Future

Objectives:

- (1) To consider the needs for needleless percutaneous vaccine injection technology in both the developing and developed worlds.
- (2) To "brainstorm" the performance goals for future devices by gathering experts with diverse bench and field experience in various disciplines -- public health, engineering design, academia, and industry -- to contribute their insights, ideas, and creativity.
- (3) To draft performance specifications to stimulate and guide the design and development of future generations of vaccination devices, both high-volume for mass campaigns, and low-volume for clinic use.

8:00 - 8:30 am **Coffee - Juice - Bakeries - Fruit**

8:30 - 9:50 **Challenges for Immunization Coverage; the Need and Pathways to Develop New Jet Injection Devices:**

Moderator: *Robert Chen*

8:30 Developing Countries Needs
John Lloyd, WHO

8:40 Developed Countries Needs
Bruce Weniger, CDC

8:50 Vaccine Industry Perspective: Clinical Experience in the Development of a Single-use Caps Liquid Vaccine and Jet Injector
Jean Lang, Pasteur-Mérieux Serums & Vaccins

9:05 Public Sector Perspective: Case Study of Device Development to Meet Performance Goals
Glenn Austin, PATH

9:20 Engineering-Inventor Perspective: What Does the Creative Designer Need to Guide Invention?
Sergio Landau, Vitajet, Inc.

9:35 General Discussion

Working Groups on Performance Specifications

9:50 - 10:00 am **Introduction and Procedure for Working Groups**
Bruce Weniger, CDC

Thursday, 3 October, Day Two (continued)

10:00 - 10:20

Coffee Break

(Room dividers to be closed; tables and seating to be rearranged for three working groups.)

10:20 - 12:30 pm

Working Groups on Performance Specifications

Working Group A: "Sterility and Safety"

Peachtree Room 1

Facilitator: *Mark Kane, WHO*

Rapporteur: *Lisa Lindsay, CDC/Univ. NC*

Scribe: *Ellen Wild, CDC*

Working Group B: "Vaccines"

Peachtree Room 2

Facilitator: *George Siber, WLVP*

Rapporteur: *John Lloyd, WHO*

Scribe: *Courtland Loeff*

Working Group C: "Mechanicals"

Peachtree Room 3

Facilitator: *Glenn Austin, PATH*

Rapporteur: *Bruce Weniger, CDC*

Scribe: *Kelly Dodson, Emory/CDC*

12:30 - 1:45

Lunch Break

(Over lunch, facilitators, rapporteurs, scribes, and conference chairs to share interim progress and provide feedback between working groups.)

1:45 - 3:30

Working Groups (continued)

3:30 - 3:50

Coffee Break

(Room dividers to be opened and original plenary seating layout restored.)

3:50 - 5:15

Plenary Report Summaries from Working Groups;

General Discussion

5:15 - 5:20 pm

5:20 - 5:30

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Friday, 4 October, Day Three:

8:30 - 9:00 am

09:00 - 10:25

10:20 - 10:40

10:40 - 12:00

12:00 - 12:20 pm

12:20 - 1:30

1:30

APPENDIX B
LIST OF PARTICIPANTS

Jet Injectors for Immunization:
Current Practice and Safety; Improving Designs for the Future
2-4 October 1996, Atlanta, Georgia, USA

List of Registrants - Participants

Glenn Austin
Senior Technical Officer
PATH
4 Nickerson Street
Seattle, WA 98109
Tel: (206)285-3500
Fax: (206)285-6619
email: gaustin@path.org

John V. Bennett
Task Force for Child Survival and Development
Suite 400
750 Commerce Drive
Decatur, GA 30030
Tel: (404) 371-0466
Fax: (404) 371-1087
email: 74150.2213@compuserve.com

Col. William Bancroft, Director
U.S. Army Medical Research and Development
Command
Research Areas 1 SGRD-PLA
Fort Detrick, Building 722
Frederick, MD 21701-7567
Tel(main): (301)619-8000
(direct): (301)619-7567
Fax: (301)619-2416
email:
col_william_bancroft@ftdetrck-ccmail.army.mil

Elizabeth Bolyard
Hospital Infections
National Center for Infectious Diseases
CDC (E-68)
Executive Park Drive, Bldg 18, rm 1003
Atlanta, GA 30329
Tel: (404)639-6428

Norman W. Baylor, Ph.D.
Assoc. Dir. Regulatory Policy
Office of Vaccines, Center for Biologics, FDA
1401 Rockville Pike
Bldg. 29B, Rm 1H16 HFM-400
Rockville, MD 20852
Tel: (301)827-0655
Fax: (301)827-0448
email: baylor@al.cber.fda.gov

Walter W. Bond
Hospital Infections
National Center for Infectious Diseases
CDC (E-68)
Atlanta, GA 30333
Tel: 404-639-3901
Fax: 404-639-3822
Email: wwbl@cidhpl.em.cdc.gov

Peter Carrasco
Regional Technical Officer
Pan American Health Organization
525 23rd St. NW
Washington, DC 20037
Tel: (202)861-6667
Fax: (202)861-6089
email: carrascp@paho.org

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Robert Chen
Chief, Vaccine Safety and Development Activity
National Immunization Program
CDC (E-61)
1600 Clifton Rd NE
Atlanta, GA 30333
Tel: (404)639-8256
Fax: (404)639-8616
email: rtc1@npl.em.cdc.gov

Steve Cochi
Polio Eradication Activity
National Immunization Program
CDC (E-05)
1600 Clifton Rd NE
Atlanta, GA 30333
Tel: (404)639-8252
Fax: (404)639-8616
email: slc1@npl.em.cdc.gov

Mr. Luca Cosmai Colavecchio
SICIM spa
Via Aquileia, 94
34076 Romans d'Isonzo (GO) Italy
Tel: 39 481 90188/ 39-481 90332
Fax: 39 481 90332

Pat Criscenti
Acting Chief, GMDB
FDA/CDRH/ODE/DDIGN
9200 Corporate Blvd.
Rockville, MD 20850
Tel: (301)443-8913
Fax: (301)480-3002
email: cricentm@fdadr.cdrh.fda.gov

Linda D'Antonio
D'Antonio Consultants International
1260 Office Park Drive
Liverpool, NY 13088
Tel (main): (315)453-8946
Fax: (315)453-8949
email: dci@servtech.com

Nick D'Antonio, PE
D'Antonio Consultants International
1260 Office Park Drive
Liverpool, NY 13088
Tel (main): (315)453-8946
Fax: (315)453-8949
email: dci@servtech.com

Dr. Cato B. de Savigny
Technical Officer
Vaccine Supply & Quality Control
Southeast Asia Regional Office
World Health Organization
World Health House
I.P. Estate, M.G. Marg
New Delhi 110002 India
Tel: 91 11 3317803 to 3317823
Fax: 91 11 3318607, 91 11 3327972

Glacus de Souza Brito
Rua Caiubi, 1004
05010-000 São Paulo, SP
BRAZIL
Tel: [55] (11) 871-3194
Fax: [55] (11) 263-8298
email: glacus@sti.com.br

Mobido Dicko
Logistician
African Regional Office
World Health Organization
B.P. 6
Brazzaville, Congo
Tel: 242 407 953-922
Fax: 242 407 953-9413

Kelly Dodson
School of Public Health, Emory University
c/o NIP, CDC (E-61)
1600 Clifton Rd. NE
Atlanta, GA 30333
Tel: (404)639-8692
Fax: (404)639-8616
email: kdd9@npl.em.cdc.gov

Rebecca Fields
BASICS
1600 Wilson Blvd.
Suite 300
Arlington, VA 22209
Tel: (703) 312-6800
Fax: (703) 312-6900
email: rfields@basics.org

Richard Harland
Veterinarian
Biostar, Inc.
343-111 Research Drive
Saskatoon, Saskatchewan S7N 3R2
Canada
Tel: [1](306) 931-7500
Fax: [1](306) 242-9010

Ronald Filipski
Director of Filling, Packaging, Warehousing &
Distribution
Connaught Laboratories, Inc
P.O. Box 187
Swiftwater, PA 18370
Tel: (717)839-4326
Fax: (717)839-0955

Mr. Peter Hoffman
Laboratory of Hospital Infection
Public Health Laboratory Service
Central Public Health Laboratory
61 Colindale Ave.
London NW9 5DF United Kingdom
Tel: 44 181 200-4400 (x4274)
Fax: 44 181 200-7449

Stanley Foster
BASICS Project
Rollins School of Public Health
1518 Clifton Rd., 7th Floor, Room 712
Atlanta, GA 30322
Tel: (404)727-2446
Fax: (404)727-4590
email: sfoster@wolf.sph.emory.edu

Mitsuo Honda
AIDS Research Center
Laboratory of Immunology
National Institute of Health
1-23-1 Toyama, Shinjuku-ku
Tokyo 162 Japan
Tel: [81] (3) 5285-1111 ext. 2737
Fax: [81] (3) 5285-1150

Penina Haber
Public Health Analyst
CDC/NIP
1600 Clifton Rd., NE
Mailstop E-61
Atlanta, GA 30333
Tel: (404) 639-8256
Fax: (404) 638-8616
email: pyh0@nip1.em.cdc.gov

Mark Kane
Medical Officer
World Health Organization
20 Ave Appia
Ch-1211 Geneva 27, Switzerland
Tel: 41 22 791-2605
Fax: 41 22 791-4193
email: kanem@who.ch

Jun Kawamata
Medical Officer
World Health Organization
20 Ave Appia
Ch 1211 Geneva 27, Switzerland
Tel: 41 22 791-2631
Fax: 41 22 791-4878
email: kawamataj@who.ch

Robert Kilgore
Director, Business Development
Becton Dickinson
One Becton Drive
Franklin Lakes, NJ 07417
Tel: (201)847-5811
Fax: (201)847-4854

William R. Knepshield
President/CEO
Cutting Edge Technologies, Inc.
889 So. Matlack St.
W.Chester, PA 19382
Tel: (610)430-8746
Fax: (610)430-3954

Sergio Landau
President, Vitajet Corporation
27075 Cabot Rd. #102
Laguna Hills, CA 92653
Tel: (714) 582-0713
Fax: (714) 582-8095

Dr. Steve Landry
Children's Vaccine Program
Office of Health and Nutrition
USAID
SA-18, Suite 1200
Washington D.C. 20523
Tel: (703)875-4508
Fax: (703)875-4686
email: slandry@usaid.gov

Dr. Jean Lang
Pasteur-Mérieux Sérums et Vaccins
58, avenue Leclerc - B.P. 7046
69348 LYON
Cedex 07 FRANCE
Tel: (33) 72 73 70 36
Fax: (33) 72 73 78 13
email: lang@bdr.pasteur-merieux.fr

Todd Leonard
Vice President
Medi-Ject Corporation
1840 Berkshire Lane
Minneapolis, MN 55441-3723
Tel: (612) 551-4171, (800)-328-3077
Fax: (612) 553-1610
email: needlefree@mediject.com
tl2300@aol.com

Lisa Lindsay, MPH
University of North Carolina at Chapel Hill/CDC
1414 West Highway 54
Chapel Hill, NC 27516
Tel: (919) 933-4970
Email: llindsay@sph.unc.edu
lcl4@npl.em.cdc.gov

John Lloyd
Technical Officer
Global Programme for Vaccines and
Immunization
World Health Organization
Ave. Appia 20
1211 Geneva 27, Switzerland
Tel: 41 22 791-4375
Fax: 41 22 791-4193
email: lloyd@who.ch

Henryk Mach
Merck Research Labs
WP78-302
West Point, PA 19486
Tel: (215) 652-4689
Fax: (215) 652-5299

Melinda Mailhot
Vaccine Technical Officer
Africa Regional Office
World Health Organization
B.P. 6
Brazzaville, Congo
Tel: 242 407 953-9226
Fax: 242 407 953-9413

Harold Margolis
Chief, Hepatitis Branch
CDC
1600 Clifton Rd. NE
Mailstop A-33
Atlanta, GA 30333
Tel: (404) 639-2339
Fax: (404) 639-1563
email: hsm1@ciddvdl1.em.cdc.gov

George Mulvaney
Product Manager
Robbins Instruments, Inc.
2 North Passaic Ave. - Box 441
Chatham, NJ 07928
Tel: (201)635-8972
Fax: (201)635-8732

Dr. Isabelle Parent du Châtelet
Association pour l'Aide à la Médecine Préventive
3 Avenue Pasteur
Boîte Postale 10
92430 Marnes-la-Coquette, FRANCE
Tel: 33 1 47 95 80 30
Fax: 33 1 47 95 80 35
email: 100442.2725@CompuServ.COM

Steve Peterson
Vice-president, R&D
Bioject, Inc.
7620 South West Bridgeport Rd.
Portland, OR 97224
Tel(main): (503)639-7221
Fax (direct): (503)624-9002

Mr. John Poley
Partner, PA Consulting Group
Melbourn
Royston, Herts SGB 6DP United Kingdom
Tel: [44] 1763 261222
Fax: [44] 1763 260023
email: john.poley@pa-consulting.com

Vitali Pool
NIP/Vaccine Safety and Development Activity
1600 Clifton Rd. NE
Mailstop E-61
Atlanta, GA 30333
Tel: (404) 639-8758
Fax: (404) 639-8616
email: vap@nip1.em.cdc.gov

Dan Prince, Ph.D.
President, Gibraltar Laboratories
122 Fairfield Road
Fairfield, NJ 07006
Tel: (201)227-6882
Fax: (201)227-0812

Stephen Redd
NIP
1600 Clifton Rd., NE
Mailstop E-61
Atlanta, GA 30333
Tel: (404) 639-8230
Fax: (404) 639-8616
email: scr1@nip1.em.cdc.gov

Zeil B. Rosenberg, MD
Assoc. Medical Director
Becton Dickinson Division
One Becton Drive, Mail Code: 250
Franklin Lakes, NJ 07417
Tel: (201)847-6683
Fax: (201)847-4845

Michael J. Roy
Director, Regulatory Affairs
Auragen, Inc.
8510 University Green
Middleton, WI
Tel: (608) 836-7300
Fax: (608) 836-5188
email: mike.roy@agracetis.com

Dr. David Sarphie
Project Manager
Oxford Bio Sciences Inc.
1450 Rollins Rd.
Burlingame, CA 94010
Tel: (415) 340-2857
Fax: (415) 340-2864
email: 100763.3411@compuserve.com

Richard R. Stout
Vice President, Clinical
Bioject, Inc.
7620 South West Bridgeport Rd.
Portland, OR 97224
Tel(main): (503)639-7221
Fax (direct): (503)624-9002
email: rrs@bioject.com

Craig N. Shapiro
Medical Epidemiologist
Hepatitis Branch, CDC
1600 Clifton Rd NE
Mailstop G-37
Atlanta, GA 30333
Tel: (404) 639-3048
Fax: (404) 639-1538
email: cns1@ciddvd1.em.cdc.gov

Roland Sutter
CDC/NIP (E-05)
1600 Clifton Rd NE
Atlanta, GA 30333
Tel: (404) 639-8252
Fax: (404) 639-8616
email: rws4@nip1.em.cdc.gov

George Siber
Wyeth-Lederle Vaccines and Pediatrics
401 N. Middleton Rd., Bldg 140, Room 401
Pearl River, NY 10965
Tel: (914)732-4249
Fax: (914)732-5517 or -3336
Email:
George_Siber@internetmail.pr.cyanamid.com

Jacques Thilly
Engineering & Development
Smithkline Beecham Biologicals
89 Rue de l'Institut
B-1330 Rixensart BELGIUM
Tel: 32 2 656 8111
Fax: 32 2 656 8034

Wilda Spalding
California

Tim Ulatowski
Director, Div. of Dental Infection Control and
General Hospital Use Devices
FDA
9200 Corporate Blvd.
Rockville, MD 20880
Tel: (301)443-8879
Fax: (301)480-3002
email: tau@fdadr.cdrh.fda.gov

Tony Stewart
Medical Epidemiologist
International Health Unit
Macfarlane Burnet Centre for Medical Research
P.O. Box 254, Fairfield 3078, Victoria, Australia
Tel (IHU): +61 3 9282 2275
Tel (direct): +61 3 9282 2282
Fax: +61 3 9482 3132
email: stewart@burnet.mbcmr.unimelb.edu.au

Mr. Regis Ungar
Soci t  AKRA - Dermo-Jet
23 bis rue Louis Barthou
Pau, FRANCE 64000
Tel: 33 59 274746
Fax: 33 59 272270

Bruce G. Weniger
Assistant Chief for Vaccine Development
Vaccine Safety and Development Activity
National Immunization Program
CDC (E-61)
1600 Clifton Rd NE
Atlanta, GA 30333
Tel: (404)639-8779
Fax: (404)639-8616
email: bgw2@nip1.em.cdc.gov

Terry E. Weston
Managing Director
Weston Medical Ltd.
New Street, Stradbroke, Eye
Suffolk, ENGLAND IP215Jg
Tel: 44 1379 384100
Fax: 44 1379 384800

Michel José Zaffran
Cold Chain and Training Coordinator
Global Programme for Vaccines and
Immunization
World Health Organization
Ave. Appia 20,
1211 Geneva 27, Switzerland
Tel: 41 22 791-4373
Fax: 41 22 791-4193
email: zaffranm@who.ch

CANCELLATIONS / INVITEES UNABLE TO ATTEND:

Dr. J. Bilous
WPRO/WHO-EPI
Manila, Philippines
Tel: [63] (2) 528-8001
Fax: [63] (2) 521-1036
Email: postmaster@who.org.ph

Joy Samuels-Reid, MD
Medical Officer
FDA
12016 Great Elm Drive
Potomac, MD 20854
Tel: (301)594-1287
Fax: (301)480-3002
e-mail: samuelsr@fdadr.ssw.dhhs.gov

Dr. Brenda Bolden
9200 Corporate Blvd. - 3rd floor
Rockville, MD 20850 HFZ-480
Tel: (301)594-1287
Fax: (301)480-3002
email: boldenb@fdadr.ssw.dhhs.gov

John Stengel
Production Manager
Syrijet/Ped-O-Jet Divisions
Keystone Industries
Cherry Hill, NJ 08002
Tel: (609) 663-4700
Fax: (609) 663-0381

Steven S. Lee
Director, Merck & Co., Inc.
Merck Manufacturing Division
P.O. Box 4, WP29M-4
West Point, PA 19486
Tel: (215) 652-9290
Fax: (215) 652-0762

END LIST

Jack Manns
Biostar, Inc.
343-111 Research Drive
Saskatoon, Saskatchewan S7N 3R2
Canada
Tel: [1](306) 931-7500
Fax: [1](306) 242-9010
email: jmanns@innovplace.saskatoon.sk.ca

Dr. Audrey Morrison
FDA Office of Surveillance and Biometrics
1350 Piccard Dr.
Rockville, MD 20850
Tel: (301)594-2884
Fax: (301)594-1967

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APPENDIX C

“MULTI-DOSE JET INJECTORS AND SAFETY ASPECTS IN BRAZIL”

Multi Dose Jet Injectors and Safety Aspects in Brazil

Glacus de Souza Brito()*

Communication Paper

Atlanta October 2-3, 1996

CDC & WHO Meeting on Jet Injectors

Background

Jet injectors have been widely used in Brazil since the beginning of smallpox eradication program and after then for yellow fever control in Amazon area and border and also for diphtheria and tetanus vaccination program for urban and rural workers and students. In 1977 and 78 jet injectors were essential for meningococcal A and C epidemics control.

Measles Campaign 1987 - State of Sao Paulo

In 1987, the State of Sao Paulo has started its Measles Control Program with an indiscriminate Mass Campaign vaccination. A total of 8.7 million children from nine months to fourteen years old should be vaccinated against measles within a time interval of a month as a first step of this strategy. However, raised up the results of Hepatitis B outbreak investigation in California where the low weight Med-E-Jet injector was identified as the cause of this event. In addition there was an article of experimental LDH virus transmission through Med-E-Jet among mice in Netherlands. We could turned around this situation using the following arguments.

1. Equipments are not comparable, Med-E-Jet is a low weight jet injector quite different of those ones that will be used during measles campaign the Ped-O-Jet that is foot pedal pressure, high pressure,
2. Different using conditions, at the clinic where those Med-E-Jet jet injectors were used every day for the same people group, and during immunization campaign it does not happen.
3. There was unappropriated cleaning and sterilization conditions of those injectors at the clinic
4. The animal assay results can not be applicable for human being skin.
5. Ped-O-Jet has being used for 30 years and more and there is no report of infectious diseases transmission during vaccination procedures.

According this arguments there was a total acceptance from health workers.

Complementary safety device

In order to assure a safety procedure with Ped-O-Jet we attempt to develop a device like a tube ring to be attached at the standart nozzle.

The intention was to maintain a certain distance between orifice of jet exit at the nozzle and the vaccinee skin. Studies in cadaver using methilen blue assured comparable jet distribution in the tissues of these two different nozzle models. The standart Ped-O-Jet eject the vaccine dose up to the muscle fasciios spreading in the subcutaneous fat tissue.

An study was designed to compare these two different nozzles during military routine vaccination. All recruits in Brazil, are previously screened for HIV, HBV, syphilis and chagas. This study aimed to answer these questions.

1. What is the frequency of visible bleeding at the site of jet injection in the skin?
2. What is the frequency of occult blood in the next vaccine shot dose?
3. Is there any correlation between visible bleeding and occult blood of the next dose?

We included two additional procedures during military routine vaccination:

First, we visually examine the injection site immediately after removal of the nozzle for obvious bleeding.

Second, after have vaccinated a person we collect the next dose in a test tube instead of adminestering it to

(*) Brito, Glacus S. & Cols - Centro de Vigilancia Epidemiologica "Prof Alexandre Vranjac"
Secretaria de Estado de Sao Paulo - Brasil - Fax 55-11-263-8298 e-mail glacus@st.com.br

another person

We then test the vaccine in the tube qualitatively for the presence of blood, which sensitivity is 0.002 to 0.1 microliters of blood per 0.5 vaccine dose vaccine.

The results were disappointed, the table 1 shows that while the standart nozzle has not had any positive sample for blood, the device attached induced 11.8 per cent positive blood samples.

TABLE 1

Vaccinator	Type of Nozzle					
	Standart Nozzle			New Device attached		
	Occult blood			Occult Blood		
	#	+	%	#	+	%
Vaccinator A	32	0	0.0	29	5	17.2
Vaccinator B	31	0	0.0	30	2	6.7
TOTAL	63	0	0.0	59	7	11.9

These results encourage the team to continuous studying the standard, or better the old Ped-O-Jet, according to the same methodology in different settings under controlled conditions among military, and hard field conditions like Amazon Rivers.

The Table 2 summarizes the results of three studies on visible bleeding. We see that frequency of immediate bleeding varies from two point two (2.2) to twenty three point three percent(23.3%), being much higher in the Amazon study. On average, bleeding occurred in three point six percent(3.6%) of vaccinees.

Table 2

Study Location	# of Vaccinees	Visible Beeding at Skin Injection Site	
		#	%
S Paulo/Recife(Military)	1193	60	5.0
Amazon	30	7	23.3
Sao Paulo (Military)	1662	37	2.2
TOTAL	2885	104	3.6

(*) Brito, Glacus S. & Cols - Centro de Vigilancia Epidemiologica "Prof Alexandre Vranjac"
Secretaria de Estado de Sao Paulo - Brasil - Fax 55-11-263-8298 e-mail glacus@sti.com.br

The Table 3 shows how often occult blood was detected by a dispstick method, varying from zero point two(0.2) to six point six percent(6.6%), also being much higher in the Amazon. On average, occult blood was detected in one percent (1.0%) of successive vaccine shot samples.

TABLE 3

Study Location	# of Vaccinees	Occult Blood Detect by a Dispstick in the Next Dose	
		#	%
S Paulo/Recife(Military)	1193	2	0.2
Amazon	30	2	6.6
Sao Paulo (Military)	1662	24	1.4
TOTAL	2885	28	1.0

In our studies Table 4, there was little to no correlation between visible bleeding and detection of occult blood in the successive vaccine doses. Only one person had both.

TABLE 4

Study Location	# of Vaccinees	Visible Bleeding Only	Occult Blood Only	BOTH
Spaulo/Recife (Military)	1193	60	2	0
Amazon	30	07	2	1
Sao Paulo (Military)	1662	30	24	0

HIV transmission - Estimate Risk

Base up on these results, the Technical Advisory Committee of National Immunization Program has tried to quantify the risk of HIV transmission for the 1992 Measles Mass Campaign.

Taking into account

- The rate of blood contamination in successive vaccine shot samples, estimated 1.0 %
- The HIV prevalence in Brazilian children belong to campaign age group, estimated to be between 7-14 cases per hundred thousand people.
- The rate of HIV transmission by needle-sticks in health care workers estimated to be 0.03 %.

Using these data, we estimate the theoretical risk of HIV transmission through the use of Ped-O-Jet injector to be in the range between 1/238 to 1/476 million injections.

HBV transmission - Estimate Risk

Similar calculations were done regarding Hepatitis B for Amazon, that has the highest prevalence in Brazil. It shows that the risk could be range from on per hundred to eight hundred forty(840) thousand injections.

(*) Brito, Glacus S. & Cols - Centro de Vigilancia Epidemiologica "Prof Alexandre Vranjac"
Secretaria de Estado de Sao Paulo - Brasil - Fax 55-11-263-8298 e-mail glacus@sti.com.br

- The rate of blood contamination in successive vaccine shot samples, estimated 1.0 %
 - The HIV prevalence in Amazon area to between 2 - 15 % of population.
 - The rate of HIV transmission by needle-sticks in health care workers estimated to be 0.108 %.
- Using these data, we estimate the theoretical risk of HBV transmission through the use of Ped-O-Jet injector to be in the range between 1/101 to 1/840 thousand injections.

Measles Campaign in Brazil

In 1992, Brasil has started its measles control program with a large Mass Campaign for children from 9 months to fourteen years old. We had to vaccinate about 50 million people during one month time interval. Ten thousand Ped-O-Jet were purchased by the government.

So, we develop a communication strategy for training to keep using Ped-O-Jet, once we decided to use them for children over two years old, which avoid newborn HIV carriers. We presented the research data and discuss theoretical risk of HBV and HIV transmission through jet injectors vaccination. Training for field maintenance and repairs were emphasized.

During training we have received many complains of jet injectors such as:

- Expensive equipment
- Heavy, need strong vaccinators
- Unappropriated to children under one year old
- It is necessary to pump 2 or 3 times to get enough pressure
- Different levels of trainees
- Bleeding may happen, so the risk of blood contamination also
- Existing data on theoretical risk of HIV contamination

Despite of these complains, we have got high acceptance, with a 96% percent of coverage, being 70 percent vaccinated by jet injectors.

families, about 200 landless from the south of country. In December, 1991 a cluster of icteric cases was identified, and 80 % of 22 samples collect in January were positive for HBV markers.

This migrant group has received Yellow Fever vaccine by jet injectors in two different places and dates according to this graphic, and a small number has received by needle and syringes in the south of the country.

For this investigation 567 questionnaires were applied in order to assess possible risks of HBV transmission and blood samples were collected from 557 people. Four lab tests were performed. Anti-HBc-IgM, Anti-HBc-IgG, Anti-HBs-IgG, HBsAg.

The conclusion of this investigation was

- The HBV markers prevalence where much higher in the previous residents than the new migrants.
- There was no correlation between place of vaccination and HBV markers, also between vaccination by needles and syringes and Jet injectors and HBV markers.
- This results reinforce the previous estimation of HBV transmission for the Amazon area.

Technical Advisory Committee of National Immunization Recommendation.

The current recommendation for Jet Injectors issued by Technical Advisory Committee of National Immunization Program is:

- No longer used J.I. in high HBV prevalence areas.
- Operational conditions and Epidemiological situation of disease, age group and geographic area should be considered for Jet Injectors Vaccination.

Anyway nowadays we are facing the following situation

Increasing Resistance to use Jet Injectors

The State of Sao Paulo has no longer using Jet injectors

For the last two Meningococcal C outbreaks in 1991 and 1995, needles and syringes were used instead of injectors.

The development of Safety devices is essential to continuously use jet injectors.

To conclude this presentation I want to show you this graphic that shows the impact of measles vaccination strategy in Brasil, and the State of Sao Paulo with ten years of follow up with very low measles cases incidence and no death since 1990. Without use Jet Injectors it could not be reached in Brasil.

APPENDIX D
INFORMATION ON MEDIVAX JET INJECTOR

MEDiVAX™ Jet Injector Quick Profile

MEDiVAX™ was designed to deliver safe, comfortable, and efficient injections of vaccines and other intramuscular or subcutaneous medicaments in clinics and small campaign settings. It is the first jet injector in over 30 years to operate on a completely new principle. Eleven patent pending design innovations are distinct from any other jet injector and offer unique benefits of safety, ease-of-use, and cost-effectiveness:

- A safety guard shield keeps the nozzle away from the skin, drastically reducing the risk of cross infection of blood-borne diseases. This shield can be sterilizable and reusable or disposable (and replaceable for continuing resale potential) depending on the application.
- The nozzle is made of durable one-piece stainless steel and has been engineered to provide a comfortable injection at a distance from the skin. It is the first nozzle to follow CDC design guidelines for cleanability.
- An easy-in-easy-out stainless steel injection head is self-rinsing and can be cleaned and steam sterilized without disassembly.
- Simple low-pressure air power improves durability dramatically while virtually eliminating maintenance. MEDiVAX™ can use any air source with an 80 psi capacity from a foot pump to an electric compressor.
- Fully adjustable power will permit the user to adjust the injection power for maximum comfort if desired. A version of MEDiVAX™ with a single all-purpose power setting is also available.
- Innovative use of molded components reduces cost of manufacture by up to 60 percent over other jet injectors, reduces the weight by at least 50 percent, and improves ergonomics and user appeal.
- Vial holders are compatible with any multidose vial and can be changed instantly to allow a variety of medicaments to be used without wastage or awkward time-consuming individual filling.
- Key components of MEDiVAX™ can be made of materials that can be sterilized thousands of times. This eliminates the medical waste created with syringe and needle use.
- MEDiVAX™ is extremely easy to use and fits all hand sizes.
- Like most jet injectors, MEDiVAX™ virtually eliminates the danger of infection from needle-stick injury. It also provides a significant barrier to infection from reuse.

Status

PATH and Vitajet Corporation jointly developed MEDiVAX™ over a period of four years. This development was funded by the Program for Health Technologies, USAID. US Patent application was filed in 1993 and subsequently foreign filings were initiated. A final design was successfully tested for clinical efficacy and safety in 1994. A study of 500 volunteers showed zero blood contamination in subsequent shots. This compares to 1 to 6 percent rates for other reusable injectors. An application for FDA approval has been submitted.

MEDiVAX™ is ready for production scale up and large scale field testing. There are currently a handful of fully functional prototypes for demonstration and evaluation. The World Health Organization (WHO) has requested that units be submitted for laboratory and field evaluation. Upon successful evaluation, WHO will recommend use of jet injectors in their immunization programs. These injectors will be purchased by UNICEF for distribution. UNICEF now supplies needles, syringes, mass campaign injectors, steam sterilizers, and other equipment for vaccination programs.

The development team at PATH is continuing discussions with CDC, WHO, and regional health organizations to insure compatibility with immunization needs and effective evaluation. PATH is also seeking funds for additional research into nozzle optimization and pediatric use. Vitajet is seeking investors for scale-up activities and for jointly adapting the innovative core technology for commercial sales.

MEDiVAX™ Vaccine Jet Injector

Using funds from sources other than HealthTech, significant progress has been made in preparation of the MEDiVAX™ vaccine jet injector for distribution as approved by WHO. During this time period, PATH MEDiVAX™ team members met with the WHO consultant who has been writing a field trial protocol for use of the injector in the Philippines and reviewed an outline of the planned protocol.

In August, the FDA granted 510K status to PATH's commercial partner, Vitajet, Inc., California, to permit sale and distribution of MEDiVAX™ in the United States. This status will improve acceptance of MEDiVAX™ in a number of developing countries that consider FDA approval important for their own use of medical products. It also should improve the probability that Vitajet can raise the additional capital required for scale-up of MEDiVAX™.

On the technical side, Vitajet produced their first full set of MEDiVAX™ sub-components to PATH-defined specifications. These parts have been incorporated into the current prototypes that will be provided on request to WHO for field trials.

In October, WHO/EPI invited a PATH representative to a meeting in London to rewrite safety standards for all jet injectors. CDC and WHO experts on device safety, vaccine safety, and laboratory testing were also in attendance. During the meeting, CDC discussed an updated draft of their field trial protocol that focuses on safety. The outcome of the meeting was a decision to raise safety standards for injectors to a "zero tolerance" level—no contamination should be detectable on any reusable surface of the device that

comes into direct or indirect contact with the patient's skin.

WHO has assigned the London Public Health Laboratory Service to oversee the design and implementation of a new laboratory safety test to evaluate all injectors against this new standard. WHO recently updated its timeline for field trials to include this preliminary laboratory screen of injectors before they will be considered for WHO-sponsored trials. PATH supplied the WHO-designated test laboratory with information on PATH's past research in animal and laboratory test development. This information includes literature sources as well as summaries of PATH's tests with simulated models, primates, rabbits, baby pigs, and human test subjects.

WHO is encouraging PATH to update the MEDiVAX™ device to incorporate a disposable skin-contact component. Development of this component is planned for early 1996 under HealthTech III and will occur simultaneously with the test development activity at the London laboratory.

APPENDIX E

LOW-WORKLOAD JET INJECTORS FOR VACCINE DELIVERY, 1987-1996

Low-workload Jet Injectors For Vaccine Delivery 1987 - 1996

Background

Jet Injectors have been used for immunization in developing countries for several decades. WHO sponsored testing of commercially available mass campaign injectors as early as 1977.

In July 1987 WHO met with representatives of CDC and other experts in immunization technologies to evaluate new designs of syringes equipped with features to assure single use and eliminate or reduce needle stick injury. Also under consideration were both mass campaign jet injectors (high workload) and a new class of jet injector, low-workload. In 1988 a detailed draft specification was sent out from WHO authored by R. Bisch and JA Henderson. Peter Evans and John Lloyd have clarified specifications in succeeding years.

Low-workload injectors are meant to serve populations that can't effectively use mass campaign injectors due to cost or maintenance limitations. Low-workload injectors may be used in health centers giving more than 20 shots per day, outreach programs, or immunization day "mini-campaigns of fewer than 800 shots per session. A key difference compared to mass campaign injectors is that low-workload injectors must allow rapid change among vaccines while minimizing wastage and assuring no contamination of the new vaccine with the previously used vaccine. Ideally these injectors will provide 25,000 shots or 5 years of maintenance-free service. They should be relatively easy to learn to use for immunization personnel who have been trained to use syringe and needle.

The below specifications and performance goals for low-workload jet injectors for vaccine delivery have been gleaned from various communications with WHO, CDC, and through observations of tests during use of commercially available injectors. These specifications are sometimes contradictory and remain open for evaluation and refinement by qualified experts. However, they have been used to guide development and public sector investment over the past decade and reflect a number of critical tradeoffs in light of current core technologies, manufacturing practices, and prevailing wisdom regarding affordability, scenarios of use, durability, and other practical issues.

Specifications

- Type: • Low-workload 0.5 ml Vaccine Jet Injector ¹
- Capacity: • Multiple (sequential) 0.5 ml doses ¹
- Accuracy: • +/- 0.0025 ml per dose ¹ (+/- 0.5%)
(Device should guarantee full dose filling in field setting)
- Delivery: • Intramuscular or subcutaneous in adults and children ¹
Note: no specific standard has been set for infants
• Manufacturer must provide evidence of acceptable injection ¹
Note: Uniform standards for efficacy have not been determined

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- Safety:**
- Risk of cross infection must be zero. 9 (Note: this standard represents a direct trade off for cost and supply/disposal logistics requirements)
 - Risk of cross infection must be minimal ¹
 - Manufacturer must provide evidence that there shall be no reflux of external fluid into the fluid path way after repeated injections ¹ ("suck-back")
 - Reduce or eliminate skin cuts due to movement during injection ²
 - Safety switch or status indicator to reduce hazardous firing ^{2,6}
 - Remains relatively safe if not used correctly ⁶
- Bleeding Rate:**
- 5% or less within 30 seconds ⁷ 5% or less within 2 seconds ⁸
- Cleaning:**
- Manufacturer shall demonstrate that (all parts, including) nozzle surface is easily cleaned ¹ (if reusable)
- Sterilization:**
- Can be sterilized with existing sterilization equipment ³ (if reusable)
- Comfort:**
- No specifications have been promulgated as of 9/4/96
- Nozzle:**
- Surfaces in contact with the skin must not become contaminated during use or must be autodestruct disposable. ⁹
 - Surfaces in contact with the skin must contain no gaps or occluded areas ¹
 - Any disposable components must be required for use and not be reusable ¹
 - Reusable components must withstand pressure sterilization at +126°C in hard water ¹
 - The fluid path (head) must allow for easy removal and replacement ¹
- Complete Unit:**
- The unit should be self contained and portable ¹
Note: no current standards for replacement or disposal of disposable items
- Ease of Use:**
- Easy to use with minimum steps and force ¹
 - Routine maintenance should be easy for user ¹
 - Easy to identify and correct nozzle blockage ²
Note: Instructions and training standards have not been established.
- Durability:**
- Units should not require trained technician maintenance before 25,000 injections ¹
 - Should resist breakage or accelerated wear even when misused ⁶ (eg. "dry fire resistance")
- Vaccine:**
- Compatible with standard multiple dose vaccine vials ¹
 - Easy to change vaccines ¹
 - Minimum vaccine wastage ¹ or
 - No vaccine wastage when changing vaccines ⁶
 - Allows maximum vaccine protection during use (temperature, light, contamination) ¹
 - Protect vaccine from damage w/ cleaning/swabbing alcohol ³

- Cost:**
- US \$250 initial ¹
 - (Note: this specification was promulgated before zero-tolerance safety standards were established)
 - Use rate of 25,000 over two to five years ¹
 - Fully amortized "pay off" in first year of use ⁴
 - \$0.05 per use (includes sterilization, disposables, spare parts, maintenance, amortization) ¹
 - Competitive with current price of autodestruct syringes. ⁹
- Validation:**
- Manufacturers will be required to devise their own test programs to prove compliance ¹
 - Submissions will be reviewed by an expert committee convened by WHO ¹
 - Submissions will be lab-tested for safety by a laboratory designated by WHO ⁹
 - Submissions will be field tested by a WHO recognized independent party. ⁷

Specification Documents

1. Criteria for Low-workload Jet Injectors; May 11, 1989, J. Bish UNICEF and R.H. Henderson, WHO/EPI.
2. WHO/EPI, Task Force on Child Survival, June 2,3, 1987, John Lloyd.
3. WHO Email ID IPM-141-910313-053010296, Jet Injector, March 13, 1991, Peter Evans
4. WHO Email ID IPM-141-910719-086221272, from Peter Evans, July 19, 1991, Terrance Hill, UNICEF
5. WHO/EPI meetings with Peter Evans and John Lloyd, April 4,5, and 6, 1993.
6. PATH TIP update, February 11, 1992, Glenn Austin.
7. WHO/EPI draft field trial protocol; 1992, Peter Evans.
8. Observations of US Navy influenza campaign with PetoJet injectors, Bremerton Naval Base, November 1992, C. McCann.
9. Determined at joint CDC/WHO meeting, November 1995, London.

Performance Standards For Low-workload Jet Injectors

Performance standards differ from specifications and criteria. Performance standards provide quantifiable means of comparing actual performance. The following standards are derived from jet injector criteria provided by UNICEF and WHO as well as from laboratory tests and field pretest results. These sources are listed below within the Specifications section. Protocols for described test methods are attached.

Laboratory Standards

- Accuracy:** Deliver 0.5 ml +/- .0025 ml per injection at any time during it's useful life (5 years or 25,000 injections)
- Test Method:** Weigh each shot for 20 shots in succession with deionized water 1 gm = 1 cc
- Injection Force:** Peak force and overall force curve over time must not vary more than 5% from one injection to another AND

Peak force should be between 0.35 and 1.1 Newtons and occur by 175 milliseconds from start AND
Entire shot should be complete within 360 milliseconds

- Test Method: Measure force by shooting saline solution at force gauge
Plot results over time
Note: Injection Force can correlate to shot depth, dispersion, comfort, and possibly bleeding rates.
- Penetration Hole: Penetration hole (in patients skin) shall not have tears beyond 20% of its diameter AND
Shall not exceed 0.22 mm(0.009") in average diameter
- Test Method: Measure shot through 0.1 mm (0.004") plastic film (average of 5 shots)
- Durability: Withstand 50,000 use cycles (representing 25,000 shots plus rinses
Reusable parts with fluid path contact must withstand 500 steam sterilization cycles (1 per 100 use cycles on average)
Withstand 100 dry-fire cycles (use without liquid- as in learning)
Alternatively may prevent dry fire.

Field Standards

- Bleeding Rate: Immediate bleeding at the injection site should not occur in more than 5% of cases
- Test Method: Observation of a minimum of 200 injections given by trained vaccinators
- Clogging Rate: Device should not clog in more than 1% of cases
- Test Method: Observation of a minimum of 200 injections given by trained vaccinators
- Ease of Use: Mistakes in filling or administering the dose should not occur more than 0.5% of cases
- Test Method: Observation of a minimum of 200 injections given by trained vaccinators

Specification and Test Issues for further discussion

Safety standards and cost are direct tradeoffs as currently defined. What are the actual cost limitations? How will the capital cost of the device be covered if self-destruct disposables are employed?

Is 0.5% accuracy really required? This may be difficult to achieve with disposable nozzle assemblies.

Should explicit standards be developed for use of jet injectors with very young infants (as in first measles shot or DPT, etc.)

What are the human subjects approval issues (particularly regarding informed consent) for infant subjects of a field trial?

Could laboratory standards be developed to uniformly assess durability or clogging in field simulated conditions?

Could a ballistic test (such as the PATH ballistic gel test) be included to assess safety or performance issues?

Other Issues?