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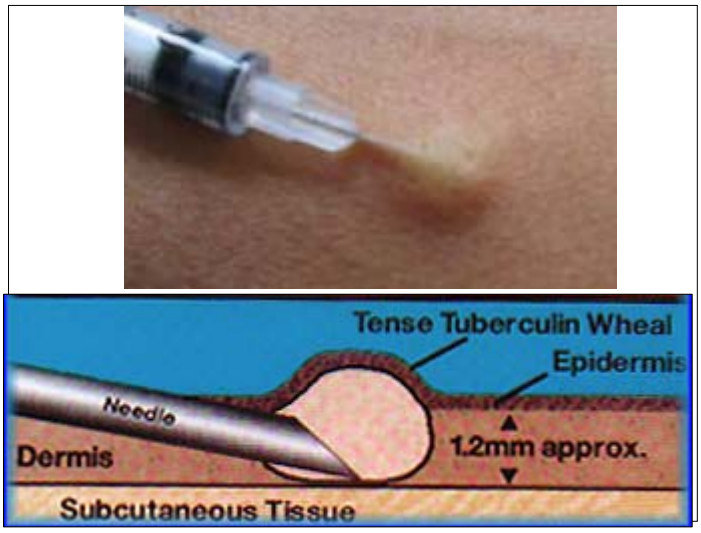
9. Introduction and Background

9.1 Pandemic Preparedness – Utility of Intradermal Jet Injection

Were a pandemic of high-mortality influenza to occur, developing countries will be challenged in protecting their most vulnerable populations with the limited amounts of vaccine that would likely be available or affordable. Administering reduced doses of various antigens via the intradermal (ID) route have often found immune responses to be equivalent to full doses administered into conventional intramuscular (IM) or subcutaneous (SC) target tissues (e.g., for rabies,[Briggs2000, Wilde2005] hepatitis B,[Wahl1987, Bryan1992] and influenza,[Halperin1979] among other vaccines). One hypothesis explains this phenomenon by the skin's rich endowment with antigen-presenting dendritic (Langerhans) cells, which upon activation migrate to deeper lymphoid tissues for the next steps in the immune response.[Goldsby2003]

Such dose-sparing with ID-administered influenza vaccine (**INF**) may be a useful strategy to protect greater proportions of susceptible populations with scarce antigen.[Avison1973] For example, reduction of the standard dose of **INF** from 0.25 mL (for young children) and from 0.5 mL (for adults) to the usual intradermal volume of 0.1 mL can extend the protection of vaccine to 2½ and 5 times as many people, respectively, who would otherwise remain vulnerable to influenza morbidity and mortality.

Figure 2. Intradermal (ID) injection by Mantoux method with needle-syringe



INF vaccination in the face of a pandemic threat will likely require mass campaigns in which a limited number of trained health workers would need rapidly to vaccinate large populations in limited periods of time. ID vaccination with needle-syringe (N-S) by the traditional Mantoux method (see Figure 2), as used for PPD tuberculin application, would severely constrain mass campaigns because of the difficulty and tediousness of this technique, which requires practiced health workers and time. Needle-free jet injectors, however, have a history of rapidly and easily administering tens of millions of doses of ID vaccines, primarily for smallpox (see Figure 3), but also BCG, using specialized intradermal nozzles. Use of jet injectors for vaccination reduces the dangers and drawbacks of needle-syringe injection (see section 9.2), including intentional or inadvertent unsterile reuse, needle-stick injuries to health workers, and the unsafe disposal of sharps waste.

Figure 3. Intradermal smallpox vaccination by jet injection, simultaneous with subcutaneous measles vaccination

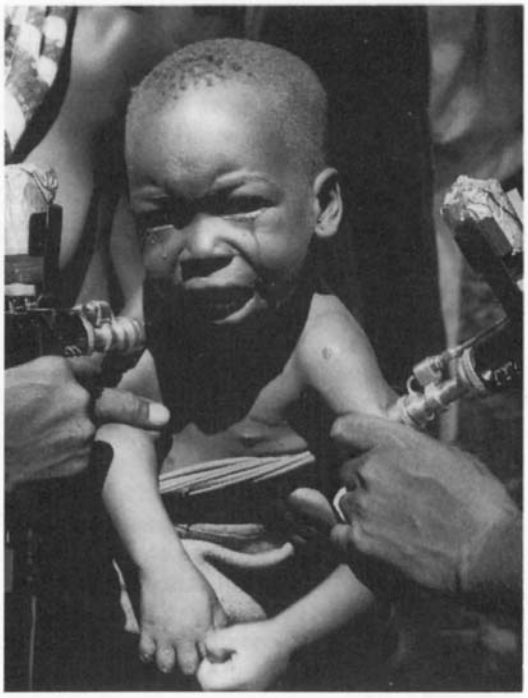


Plate 17.5. Jet injectors were used to administer smallpox vaccine in the left arm and measles vaccine in the right arm. Sometimes the injections were given simultaneously. Aluminium foil covers the vaccine vials to prevent the inactivation of virus by exposure to light.

9.2 Dangers of Unsafe Needle-syringe Injections

Only recently has the magnitude of unsafe injection practices in developing countries been widely recognized.[Holding1998] The World Health Organization (WHO) estimates that up to half of all injections in the world are unsafe because the needle or syringe has been improperly reused without sterilization.[Simonsen1999, Kane1999]

Transmission of blood borne pathogens such as human immunodeficiency virus (HIV) and hepatitis B virus to patients, healthcare workers and community members can occur from unsterile injections, accidental needle sticks, and improper "recycling" of needles and syringes.[Aylward1995a] A study which modeled unsafe injections found that one nonsterile reuse of each clean needle and syringe would result in 980 new cases of hepatitis B for every 100,000 fully immunized infants in areas of high hepatitis B prevalence.[Aylward1995b] This rate increased to 3740 cases of hepatitis B per 100,000 if each sterilized or new needle was reused just four times.[Simonsen1999] For HIV, an unsterile needle reused four times in areas where the HIV prevalence is 20% was estimated to cause up to 190 new cases of HIV infection per 100,000 fully immunized patients.[Aylward1995b]

Causes of improper use of needles and syringes include (1) inadequate training, knowledge, and motivation of health staff, (2) frequent shortages of supplies or fuel and the disrepair of equipment to sterilize needles and syringes, (3) inadequate disposal policies and facilities, and (4) a black market of recycled syringes used in the informal medical sector. To address the problem WHO and the United Nations Children's Fund (UNICEF) recommend the use of auto-disabling disposable syringes that cannot be reused.[WHO1997] But the additional cost, compared to conventional syringes, has been a barrier to their use.

The Global Alliance for Vaccines and Immunization (GAVI), created with the initiative and financial support of the Gates Foundation and others, has focused attention on vaccination technology. Among its priorities are knowledge, methods, and products to reduce the dangers of re-use of injection equipment and to ensure proper management of "sharps" waste.[Birmingham2000, Jacobs2001]

9.3 Needle-free Jet Injection Technology

9.3.1 Description and Clinical History

Needle-free jet injection offers one potential solution to the dangers and drawbacks of using needles and syringes to administer vaccines. Jet injectors (once referred to as "jet guns") use high pressure to deliver a fine stream of liquid medication or vaccines through the skin. Such devices have been used by patients themselves, by immunization clinics, and in mass vaccination campaigns since the late 1940's and early 1950s successfully to administer a wide variety of medications (e.g., anesthetics, antibiotics, corticosteroids, hormones, immunodiagnostics, immunomodulators, and vitamins) as well as vaccines.[Reis1998; NIP2005a] At least 15 million doses of measles vaccine were administered by jet injectors equipped with subcutaneous nozzles from 1967-1969 alone (along with 92 million smallpox vaccine doses via intradermal nozzles in the opposite arm) in West Africa's smallpox eradication program (Figure 3).[Millar1969, Fenner1988] In Brazil, tens of millions of doses of smallpox vaccine in the 1960s,[Veronesi1966] and tens of millions more measles vaccine doses in the 1990s[deQuadros1998] were given by jet injectors in Brazil's successful campaigns against those diseases.

The fluid injected by jet injectors is generally distributed conically, following paths of least resistance into either the subcutaneous (SC) tissues, or further into intramuscular (IM) tissue. The site of deposition where most of the dose is delivered – SC, IM, or intradermal (ID) – depends on such variables as the power of the device, its orifice size, shape, distance and angle relative to the skin, the viscosity of the fluid, the angle of injection relative to the muscle fascia plane, the skin thickness injected, and other factors.[Bennett1971, Schramm2002] Even while using the same power source, orifice, and perpendicular injection as for IM or SC delivery, ID injection can be achieved by creating a gap with tubing or a spacer inserted between the nozzle orifice and the skin, thus reducing the force of the jet stream (see section 9.6.3).[Meyer1964, Kalabus1967, Dull1968, Zsigmond1999a, Zsigmond1999b, Sugibayashi2000]

9.3.2 MUNJIs vs. DCJIs

Safety concerns arose over **multi-use-nozzle jet injectors** (MUNJIs), example illustrated in Figure 3, which use the same nozzle to inject consecutive patients without intervening sterilization. A hepatitis B outbreak in the mid 1980s caused by one MUNJI,[CDC1986, WHO1986, Canter1990] as well as other published[Kremer1970, Darlow1970, Brink1985, Zachoval1988, Lukin1997, Weintraub1998, Hoffman2001, Souto2001] and unpublished[deSouzaBrito1994] studies of this and other devices, indicated blood and tissue fluid containing pathogenic agents could be transmitted among patients. This led to discontinuation and recommendations against their use in public health,[CDC2002, WHO1997] and market removal in 1997 of the most common device, the Ped-O-Jet®.[NIP2005a]

Since the 1990s, a new generation of safer **disposable-cartridge jet injectors** (DCJIs) have appeared. DCJIs avoid the inherently unsafe design of MUNJIs, since the disposable cartridge has its own sterile orifice and nozzle and is discarded between patients. One such DCJI device is the Biojector® 2000 (http://www.bioject.com/biojector2000.html), which has been studied in a number of clinical trials (see section 10.4.3), and is licensed in the U.S., Europe, and elsewhere for either subcutaneous or intramuscular injection, depending on cartridge orifice size.

9.3.3 Jet Injectors in Children

Needle-free injections have been studied and used before in pediatric populations. The Biojector® 2000 is used routinely for immunization of infants, toddlers, and older children in a number of county health department clinics in the U.S. (http://www.bioject.com/biojector2000.html). For example, the public health clinics of Cobb County, a suburban jurisdiction just outside of Atlanta, Georgia, has been using jet injectors for several years for all routine childhood immunizations, including vaccines for diphtheria-tetanus-pertussis (**DTP)**, *Haemophilus influenzae* type B (**HIB**), and hepatitis B (**HBV**) (personal communications: Richard Stout, Bioject, Inc., 1999 and Jan Smith, Cobb County Immunization Program, 1999).[Dodson1997]

As a result of the abandonment of MUNJIs in the late 1990s as described in section 9.3 above, since 2000 the U.S. Navy and Coast Guard have used the Biojector® 2000 to administer vaccines to both military recruits at basic training sites, as well as to pediatric and adult dependents at regional health facilities. In the year from October 2003 to October 2004, nearly half a million Biojector cartridges were thus used by the military (personal communication, Kurt Lynam, Bioject, Inc., 2004).

Another DCJI device, the INJEX® 50 (http://www.injex.com/products/injex30.asp), has been studied in the administration of **MMR** vaccine to teenagers and found to produce satisfactory immune responses and no significant difference in pain score compared to control needle injections.[Sarno2000] The INJEX®, however, is not used for routine

vaccination in the United States because it currently lacks capability for intramuscular injection, which are recommended for several common vaccines.

9.3.4 Immunogenicity of Jet-injected Vaccines

A large body of clinical literature documents jet injector immunogenicity, which is usually equal to or better than that induced by conventional needle and syringe for a variety of conventional inactivated and live vaccines.[Reis1998; NIP2005b] Vaccines that have been successfully administered via jet injection include typhoid,[ParentduChatelet1997] cholera,[McBean1972, PhillipinesCholeraCommittee1973] bacille Calmette-Guérin (**BCG**),[Parker1948] typhoid-diphtheria (**Td**),[Wegmann1976] whole cell diphtheria-tetanus-pertussis (**DTP**),[Stanfield1972, Ruben1973, ParentduChatelet1997, Rossier1998] measles,[Meyer1964, Ruben1973] meningococcal A and C,[Rey1989] smallpox,[Meyer1964, Veronesi1966, Ruben1973, Fenner1988] yellow fever,[Meyer1964, Ruben1973] hepatitis A,[ParentduChatelet1997, Fisch1996] hepatitis B,[Lemon1983, Whittle1987, Mathei1997] influenza,[Davies1969, Spiegel1994a, ParentduChatelet1997] plague,[Lipson1958] polio,[Lipson1958] and tetanus.[Veronesi1966, Rey1967, Rey1973, ParentduChatelet1997, Schlumberger1999]

The reported increased immunogenicity via jet injector may result because injection inevitably leaves a small amount of vaccine in the skin, which is richly endowed with dendritic (Langerhans) cells which have important roles in processing and presenting antigens in the immune system.[ParentduChatelet1997] Various studies have suggested this improved immunogenicity may allow lower doses of vaccine to be administered. For example, Hendrickse, et al demonstrated adequate levels of protective antibodies against measles after administration SC of a reduced dosage with the most widespread device, the Ped-O-Jet®.[Hendrickse1968, Macintosh1977]

9.3.4.1 Non-adjuvanted Vaccines Delivered by Jet Injection

9.3.4.1.1 Influenza Vaccines

Since the adaptation of needle-free jet injectors for mass vaccination in the early 1950s, there has been a long and well-documented history for comparable immunogenicity (to needle-syringes) and tolerable reactogenicity in their use for the administration of influenza vaccines.[Anderson1958, Clark1965, Wright1968, Davies1969, Vibes1971, Ivannikov1980, Spiegel1994a, ParentduChatelet1997] During the swine influenza mass campaign of 1976-1977 in the U.S., a substantial proportion of the approximately 80 million doses administered that season were delivered by jet injectors (CDC, unpublished data).[Ehrengut1977]

9.3.4.1.2 Measles Vaccines

Studies have well documented the immune response of the hundreds of millions of doses of measles vaccine administered by jet injectors, particularly in mass campaigns in Africa and South America (see section 9.3.1).[Meyer1964, Kalabus1967, Ruben1973, Kok1983, deQuadros1998]

9.3.4.1.3 Meningococcal Vaccines

Traditional meningococcal polysaccharide (**MEN_{ps}**) vaccines have been extensively administered by needle-free jet injection technology.[AmatoNeto1974, Artenstein1971, Binkin1982; Chippaux1998, Gotschlich1972a, Gotschlich1972b, Greenwood1980, Mohammed1981, Mohammed1984, Rey1989, Spiegel1994b, Taunay1974, Taunay1978] Most of these citations reported on the use of monovalent serogroup A polysaccharide vaccine, which more commonly causes serious epidemics in the so-called "meningitis belt" of western Sub-Saharan Africa. Amato Neto *et al*, both Taunay *et al* reports. and Rey *et al*. describe the administration of meningococcal C vaccine by this method.

9.3.5 Reactogenicity of Jet-injected IM and SC Vaccines

The medical literature reports varying results in studies regarding the pain and reactogenicity of needle-free injectors compared to needles to deliver intramuscular (IM) and subcutaneous (SC) injections. Insulin and other non-irritating drugs and non-adjuvanted vaccines generally result in either reduced or equivalent pain for jet injectors compared to needles,[Hingson1947, Hughes1949, Anderson1958, Kutscher1962, Meyer1964, Greenberg1995] but not always.[Jackson2001]

Vaccines with irritating adjuvants like aluminum salts usually result in somewhat higher frequencies of local reactions (e.g., edema, erythema, tenderness) when jet injected, but this has not generally been of a magnitude sufficient to compromise clinical tolerance and safety.[Barrett1962, Lenz1966, Edwards1974, Agafonov1974, Agafonov1978, Hoke1992, Hoke1995, ParentduChatelet1997] The irritation probably results from the residual vaccine remaining in the skin and superficial subcutaneous tissues, even if most of the dose administered is deposited more deeply. (Most modern influenza vaccines, including Vaxigrip®, have no adjuvant.)

9.3.5.1 Alum-adjuvanted Vaccines Delivered by Jet Injection

In addition to some of the papers mentioned in preceding sections, a number of reports have been published on the administration by jet injection of the following alum-adjuvanted vaccines by either the IM or SC routes. In general, these papers reported somewhat increased -- but tolerable -- rates of local reactions compared to needle-syringe administration. Such reactions are usually mild and resolve within days without treatment.

- Diphtheria-Tetanus-Pertussis (whole-cell) (**DTP_{w}**)[Stanfield1972, Ruben1973, ParentduChâtelet1997]
- Hepatitis A (**HAV**)[Hoke1992, Hoke1995, Parent du Châtelet1997, Williams2000]
- Hepatitis B (**HBV**)[Lemon1983, Whittle1987, Mathei1997]
- Tetanus (**TET**)[Veronesi1966, Rey1967, Rey1973, Parent du Châtelet1997, Schlumberger1999]
- Tetanus-Diphtheria (**Td**)[Wegman1976]
- Tetanus-Diphtheria-polio (**$Td\text{-}POL_{IPV}$**)[Barrett1962]

- Typhoid (**TYD**)[Agafonov1974, Edwards1974, Agafonov1978]

9.3.5.1.1 Diphtheria-Tetanus-Pertussis (whole cell) Vaccines

Parent du Châtelet *et al* administered three monthly injections of **$DTP_{w(PMSV)}$** to African infants recruited at age 2-to-3 months, using prefilled disposable jet injection cartridges (Imule®) and an investigational Mini-Imojet® needle-free jet injector (JI), and compared it to similar controls receiving the same vaccine and doses by needle-syringe (N-S).[Parent du Châtelet1997] Comparing the JI and N-S groups, frequencies of delayed reactions for pain were 34.2% and 27.4%, respectively (not significant [NS]), 68.3% and 51.2% for induration ($p<0.05$), 1.2% and 2.4% for adenopathy (NS), and 4.9% and 2.4% for fever (NS).

9.3.5.1.2 Hepatitis A Vaccines

Local redness was reported by significantly more soldiers (23%) who received their first dose of Merck **HAV** vaccine IM by Ped-O-Jet® injector, compared to 3% among those vaccinated IM by needle-syringe.[Hoke1995] After the second dose, the significantly-different jet injector/needle-syringe frequencies were 14%/0% for redness, and 8%/0% for swelling. After the third dose, only redness occurred with significantly increased frequency among the jet injector recipients (18%) versus the needle-syringe group (5%). Nevertheless, the investigators concluded that "the jet injector is a highly satisfactory means for mass inoculation of military recruits with hepatitis A vaccine".[Hoke1992]

The Pasteur-Mérieux (now Sanofi-Pasteur) **HAV** vaccine was administered SC by Mini-Imojet® jet injector to 48 adults, and compared to needle-syringe injections by the IM (n=50) and SC (n=49) routes.[Parent du Châtelet1997] Relative frequencies of side effects for SC jet injector, IM needle, and SC needle were 35% / 13% / 26%, respectively, for delayed pain (p=0.05). No significant difference in proportions were found between the three injection groups for delayed erythema (9% / 0% / 13%, respectively), induration (2% / 0% / 0%), hematoma (7% / 0% / 7%), adenopathy (0% / 2% / 2%), and fever (11% / 9% / 9%).

A Biojector® 2000 needle-free jet injector (JI), [redacted], was used to administer two doses IM of GlaxoSmithKline **HAV** vaccine, which was also administered IM by needle-syringe (N-S).[Williams2000] There was no significant difference in the frequencies of systemic side effects between the two study groups. But local reactions were more frequent in the JI group: redness after 58 (20%) of 289 doses (compared to 6 [2%] of 288 N-S doses); swelling after 57 (20%) doses (N-S: 9 [3%]); and bruising after 75 (26%) doses (N-S: 7 [2%]).

9.3.5.1.3 Hepatitis B Vaccines

Three doses of Merck **HBV** vaccine were administered SC in unblinded fashion by Ped-O-Jet® injector above the deltoid insertion region of the non-dominant arms of 19 volunteer adults. These injections were compared with simultaneous saline injection by needle-syringe (N-S) into the dominant arms.[Lemon1983] Induration of >5 mm was reported after 9 (16%) of 57 jet injections, compared to only 1 (2%) of placebo N-S control injections. Erythema of >5 mm reported in 5 (9%) of jet injections, compared to none from N-S placebo. Firm, indurated, painless nodules from 5-to-10 mm in diameter appeared one or two days after 9 (16% of 57) jet injections. All eventually disappeared, at times leaving a pigmented macule.

A Biojector® 2000 device was used to administer GlaxoSmithKline **HBV** vaccine IM to 47 randomly selected adult volunteers, and to 50 vaccinees by needle-syringe.[Matheï1997] Local side effects of soreness, redness, or swelling were reported significantly more frequently (126 adverse effects) after 93 jet injections (doses 1 and 2) than after 98 needle-syringe injections (49 adverse effects).

9.3.5.1.4 Tetanus and Diphtheria Vaccines

Reactogenicity at 3 days to a monovalent tetanus toxoid vaccine adsorbed on aluminum hydroxide (Tetavax®, Pasteur Mérieux Sérums et Vaccins, now Sanofi Pasteur) was examined in 213 African adults vaccinated with the investigational Imule® disposable cartridge and Mini-Imojet® needle-free injector, without the use of a control group receiving needle-syringe injection to compare adverse reactions.[ParentduChâtelet1997] Frequencies of AE were reported for pain (68.5%), fever (35.9%), induration (26.0%), erythema (7.7%), and hematoma (0%).

Brazilian investigators administered via Press-O-Jet™ needle-free injector a dose volume of 1.0 mL of tetanus toxoid precipitated on alum to 300 adults and 350 children in São Paulo, and reported "no disagreeable reactions".[Veronesi1966]

An aluminum-phosphate-adsorbed bivalent **Td** vaccine was administered via needle-free Dermo-Jet® injector in a 0.1 mL intradermal dose to 19 adults, and found by the investigators to be "well-tolerated" and equivalent to an SC injection.[Wegmann1976]

Barrett studied immunization of high-school students with combination **Td-POL$_{IPV}$** vaccine using the American Hypospray® jet injector, finding 12 percent to have a transient local erythema of "3+ severity", defined as a reddened area of 80 square millimeters, with accompanying induration, heat, and tenderness.[Barrett1962]

9.3.5.1.5 Typhoid Vaccines

Agafonov reported on typhoid vaccine via jet injection with a Soviet jet injector, finding the frequency of systemic reactions to the typhoid vaccine was 6.9%, while local reactions were 82% - 93%.[Agafonov1978] Comparing jet injection with needle-syringe for other typhoid and typhoid-paratyphoid vaccines (**TYD_{AKD}** and **$TYD\text{-}PTD_{TAB}$**), Edwards found 82 - 88 percent of jet injection vaccinees had one or more local reactions (pain, erythema, heat, swelling, tenderness, induration, or nodes), compared to only 24 percent of needle-syringe recipients.[Edwards1974] By 72 hours, only 8 percent of the jet-injected **TYD_{AKD}** vaccinees and none of the **$TYD\text{-}PTD_{TAB}$** vaccinees still had such local reactions.

9.4 Intradermal Route of Vaccination

9.4.1 Vaccines other than Influenza

The intradermal (ID) route has been described in the literature for at least 16 different vaccine types. There are numerous reports, of course, for those vaccines in which the ID route is the normal one, such as **BCG**,[Chambon1970a, Chambon1970b, Chambon1970c, Collas1973, Carnus1973, Carnus1974, Fillastre1970] smallpox,[Fenner1988] and combined **BCG**-smallpox vaccine.[Vaughan1972, Vaughan1973] The intradermal route has also been studied with good results for killed vaccines such as typhoid[Tufts1931] and rabies,[Briggs2000] the latter of which has been used widely for dose-sparing purposes in the developing world.[Wilde2005] Generally good results have been reported for hepatitis B,[Bryan1990] but not always,[Coberly1994] while mixed results have been reported for cholera,[McBean1972] hepatitis A,[Brindle1994, Pancharoen2003, Pancharoen2005] and measles.[Calafiore1966, Kok1983, deMoraes1994] Other vaccines studied rarely by this route include polio,[Salk1953a, 1953b] meningococcal A, diphtheria-tetanus-pertussis, tetanus-diphtheria, tick-borne encephalitis, and Rift Valley fever).

In addition, intradermal jet injection has been used to administer immunomodulators like interferon,[Nathan1986] as well as tuberculin (purified protein derivative, PPD) for tuberculosis skin testing among patients of all ages.[Bettag1967, Brólio1976, Cockburn1965, DePartearroyo1966, Dull1968, Hendrix1966, Luby1968, Marsallon1972, Morse1967, Neumann1973, Wijsmuller1975]

9.4.2 Influenza by Intradermal Needle Injection

There is a substantial literature, since the 1930s, starting with Thomas Francis (of Salk polio vaccine trial fame),[Francis1937] documenting the equivalence and occasionally improved immunogenicity of intradermal influenza vaccination by needle-syringe compared to larger doses by the subcutaneous and intramuscular routes.[Bruyn1947, VanGelder1947, Weller1948, Bruyn1949a, Bruyn1949b, Edwards1958, Hilleman1958, Kirkham1958, Sanger1959, Stille1959, Beasley1960, Saslaw1964, Clark1965, Tauraso1969, Marks1971, Brown1977, Halperin1979, Spiegel1994a, Belshe2004, Kenney2004,] On the other hand, a few studies found ID influenza responses less then IM or SC on some or all of the antigens that were studied.[Boger1957, Saslaw1963, Phillips1970, Sigel1975, Hutchinson1977, Herbert1979]

9.4.3 Reduced-dose Influenza Vaccination by Different Routes

When the same reduced dosage of influenza antigen was compared via the intradermal versus IM or SC routes, there were conflicting results from clinical trials. Bruyn *et al* found GMTs in children receiving 0.2 mL intradermally of **INF** to be higher than those receiving the same dose SC,[Bruyn1949a] as did Davies *et al*.[Davies1969] and Tauraso *et al*[Tauraso1969] administering 0.1 mL by both routes. Stille *et al* also found greater ID responses when administering small antigen masses, but conversely, SC responses exceeded ID ones when delivering larger doses.[Stille1959] On the other hand, McCarroll *et al*,[McCarroll1958] studying hospital employees 18 to 65 years of age, and Klein *et al*,[Klein1961] studying infants 2 months to 5 years of age, both found no difference in responses between the ID and SC routes.

Regarding systemic reactions, among 101 infants from 2 months to 2 years of age receiving 0.1 mL of influenza vaccine in the Klein *et al* study, febrile reactions were reported among 34.7% (17/49) in the intradermal group and only 19.2% (10/52) in the subcutaneous group getting the same reduced dose.[Klein1961] Similarly, local reactions of small areas of erythema and induration with 2 to 3 days of slight tenderness and itching were described for "all" intradermal participants (ages 2 month to 5 years, n = 96), while only 2 of 94 children vaccinated subcutaneously had local pain and induration.

9.4.4 Influenza by Intradermal Needle-free Jet Injection

The use of needle-free jet injectors to administer influenza vaccine intradermally (ID) has been studied and documented since the 1940s.[Parker1948] Two studies of jet injected ID influenza vaccination in particular were performed. Davies *et al* studied monovalent A_2/Australia/54 and found significantly higher GMTs for 0.1 mL administered ID by JI (114) than for 0.5 mL by the SC route (75.8).[Davies1969] Although there was no statistically significant difference between the proportion with a 4-fold titer rise in the JI ID group (58%) versus the full-dose SC one (40%). On the other hand, Payler *et al* studied a trivalent product, administering 1.0 mL SC compared to 0.15 mL ID by JI, and found a trend to SC to be superior, but the difference did not reach statistical significance.[Payler1974]

9.5 Influenza Disease Burden

In 2004, recognizing the morbidity and mortality of influenza disease in young children, the Advisory Committee on Immunization Practices (ACIP) of the CDC first recommended universal vaccination of all children from the ages of 6 through 23 months, healthy and otherwise,[CDC2004] and continues to recommend so in 2005.[CDC2005] Similarly, the Pan American Health Organization encourages countries to introduce yearly seasonal influenza vaccination in routine programs for children from 6-23 months of age.[PAHO2005]

Influenza causes both epidemic and pandemic disease with the 1918-19 pandemic as the most devastating, with an estimated 40-50 million deaths worldwide.[Nicholson2003] In the United States, influenza is associated with an average of 36,000 underlying respiratory and circulatory deaths annually and more than 200,000 hospitalizations.[Thompson2003]

Each year between 5% and 20% of the population is infected with influenza.[Monto1986] Based on the 1980 population, among persons age <20 years, the annual burden of influenza in the United States includes an average of:

- 13.8 to 16.0 million excess influenza-related illnesses
- 152.0 to 176.4 million excess influenza-related illness days
- 47.1 to 54.7 million excess influenza-related excess bed and restricted activity days.

Among persons age ≥20 years, the annual burden of influenza in the United States is on average:

- 4.1 to 4.4 million excess influenza-related illnesses
- 65.7 to 70.6 million excess influenza related illness days
- 16.6 to 17.9 million excess influenza-related excess bed and restricted activity days [Sullivan1993]

About 90% of influenza-associated deaths occur among persons aged 65 years and older. The influenza-attributable mortality rate for persons aged 85 years and up is significantly higher as compared to persons 65 to 69 years.[Thompson 2003]

Table 1

Estimated Annual Influenza Associated Mortality 1990-91 Through 1998-99 Seasons [1]

Age Group	Rate per 100,00 person-years
<1	0.6
1-4	0.4
5-49	0.5
50-64	7.5
≥65	98.3
Total	13.8

[1] Underlying respiratory and circulatory deaths
Source: Unpublished, CDC
(http://inside.nip.cdc.gov/divisions/isd/irl/dis_ep_burd.asp)

Influenza A (H3N2) viruses are associated with the highest annual rates of influenza-associated hospitalizations. Persons aged 65 and up have the highest rates of influenza-associated hospitalization followed by children younger than 5.

On average 94,735 primary pneumonia and influenza hospitalizations, 133,900 any listed pneumonia and influenza hospitalizations, and 226,054 primary respiratory and circulatory hospitalizations per year occur in the US.[Thompson 2004]

Table 2

Age-Specific Annual Average Numbers and Rates of Influenza-Associated Hospitalizations [1]

Age Groups	Number	Rate
<5	20,031	107.9
5-49	34,867	20.8
50-64	29,447	83.8
65-69	18,301	189.7
70-74	26,501	321.2
75-79	27,516	431.1
80-84	28,578	686.1
≥85	40,813	1194.9
Total	226,054	88.4

[1] Respiratory and circulatory hospitalizations, primary
Source: Unpublished, CDC (http://inside.nip.cdc.gov/divisions/isd/irl/dis_ep_burd.asp)
ACIP 2005 Recommendations[CDC2005]

9.5.1 Epidemiology of Influenza in Dominican Republic and Caribbean

The epidemiology of influenza in the Dominican Republic is atypical in that this Caribbean island experiences transmission more-or-less year round as a consequence of virus introductions from tourists escaping winters in North America from October through March, and winters in South America from April through September (personal communication, Dr. Jesús Feris Iglesias, 2005). There is scant quantitative data available, however, on influenza incidence from the Dominican Republic or from its neighbor, Haiti, on the island of Hispaniola.

General health indicators for the Dominican Republic are summarized by PAHO.[PAHO2004] The estimated infant (0-12 months) mortality rate between 1995 and 2000 was 40 per 1,000 live births (l.b.). In 1999, the leading cause of morbidity in such infants was acute respiratory infection (668.8 per 1,000 l.b.), followed by acute diarrheal diseases (329.3), and parasitoses (138.5). In children 1-4 years, respiratory infections were also the leading cause of illness at 221.2 cases per 1,000 population, followed by acute diarrheal diseases (69.4). The immunization infrastructure performed well, with the proportion of infants less than one year of age immunized with **POL_{OPV}**, **DTP**, and **TUB_{BCG}** measured at 87%, 72%, and 96%, respectively. Influenza vaccine is not a routine antigen included in the public immunization program in the Dominican Republic.

Puerto Rico, another island about 100 km to the east, does have somewhat more epidemiologic data on influenza, which may be relevant to the Dominican Republic because of geographic, climatic, and cultural similarities. Among Puerto Rican children less than 6 years of age, the rate of influenza incidence in the selected years 1987, 1989, 1992, 1994, and 1996 was 8.1, 38.1, 12.7, 6.6, and 2.4, respectively, per 100 persons, suggesting substantial morbidity and great year-to-year variation.[PuertoRico2005]

Among the English-speaking Caribbean members of the Caribbean Epidemiology Center (CAREC), which does not include the Dominican Republic, acute respiratory infections decreased over time, but still remain a leading cause of death in children 1-4 years of age, with an age-adjusted rate of 30 per 100,000 in 1980 and 5 per 100,000 in 1995. [Holder2000] In 2000 and 2001, a total of 71,201 and 60,236 influenza cases, respectively, were reported from the 20 CAREC member countries.

On Jamaica, an island 400 km to the southwest of the Dominican Republic, a study of etiologic agents of acute respiratory infections determined the proportion in 83 malnourished children.[Christie1990] Influenza virus was isolated from 14% (12 of 83), second only to parainfluenza viruses (18%), and more frequent than adenovirus (12%), RSV in 8%, and Mycoplasma in 8%. During the 1918-19 influenza pandemic, the virus was noted to have swept through the Caribbean and resulted in an estimated 100,000 deaths.[Killingray1994]

9.6 Objectives and Rationale for Study

9.6.1 Study Objectives

This study intends to demonstrate a dose-sparing intradermal (ID) method to allow larger numbers of young children to be protected when supplies of influenza vaccine are limited, and to prove the principle that needle-free jet injection can obviate the cost, time, expertise, and difficulty administering ID injections by the Mantoux needle-syringe method. DCJIs thus also avoid this and other drawbacks and dangers of needle-syringe injections, such as safe sharps disposal, unsterile reuse, and needlestick injury.

9.6.2 Rationale

This study will provide new clinical data on the degree of safety and immunogenicity of protecting young children from influenza by a needle-free reduced-dose route. It would provide information essential for developing country public health officials, immunization programs, and clinicians who must make difficult policy decisions as they face likely vaccine shortages in the inevitable pandemic of influenza of the future.

There is already a large body of data on the immunogenicity and reactogenicity of intradermal administration of **INF** vaccine by needle-syringe (see sections 9.4.2 and 9.4.3), and prior studies of this route using needle-free jet injection in adults[Davies1969] and in schoolchildren[Payler1974] (see section 9.4.4). But there is none in the intended age group of 6-to-24 month old children. This study will fill that gap for an age group at high risk for morbidity and death from influenza disease.

9.6.3 Intended / Potential Use of Study Findings

Proving the concept of dose-sparing by intradermal (ID) injection could provide a useful strategy for public health policymakers in developing countries to protect their

populations against pandemic influenza threats for which vaccine supplies are likely to be in short supply. Demonstrating that needle-free jet injectors can accomplish this ID delivery quickly and easily without the risks of needlestick accidents can provide a valuable logistical tool for mass campaigns.

Although the particular intradermal spacer to be utilized in this study is a proprietary design of the jet injector manufacturer, the concept of creating a gap between a jet injector nozzle and the skin to achieve intradermal delivery by weakening a standard perpendicular jet stream may be considered *prior art* and thus no longer patent-protectable. It has been long described in the scientific literature and applied in the field with various jet injectors (section 9.3.1).[Meyer1964, Kalabus1967, Dull1968, Zsigmond1999a, Zsigmond1999b, Sugibayashi2000] This precedent provides "freedom to operate" for various manufacturers to adapt and study their devices in achieving ID delivery. Thus, the findings of this study may spur further competitive research and development to pursue a safer, needle-free administration route for influenza and perhaps other antigens.

9.6.4 Research Questions

1. Will the investigational study arm of children receiving two doses of 0.1 mL of influenza vaccine administered ID demonstrate *non-inferiority* to the immune responses achieved by the control study arm of children receiving two conventional, full-doses of 0.25 mL administered IM by needle-syringe? (Primary endpoint: proportion of participants achieving inverse titer of ≥40 on hemagglutination inhibition assay for each virus strain in the vaccine.)

2. What will be the safety profile of jet-injected, reduced-dose, intradermal influenza vaccination (erythema, induration, limb swelling, bleeding, and other local and systemic reactions) delivered by DCJI using an investigational spacer for ID delivery?

3. Will an investigational study arm of children receiving two reduced doses of 0.1 mL of vaccine administered IM by needle-syringe demonstrate *non-inferiority* to the immune responses achieved by the control arm of children receiving conventional, full-dose 0.25 mL administered by the same method in the same target tissue (obviating any need for intradermal delivery to achieve dose sparing)?

10. Investigational Plan

10.1 Overall Study Design and Plan

The study is a randomized, double-blinded, controlled, phases I and II clinical vaccine trial of safety and immunogenicity, among children enrolled at ≥9 -to- <24 months of age. It will compare using a *non-inferiority* statistical model two standard doses in this age group of 0.25 mL of a commercial, trivalent, inactivated, split-virus product administered

13. List of Associated Documents

- Protocol – Spanish version
- Informed Consent Form - Spanish
- Informed Consent Form - English translation
- Participant Identification Form (PIF)
- Enrollment Log / Participant Inscription Form
- Study Staff Responsibilities and Signatures Registry and Log
- Case Report Form (CRF)
- Parent's Diary Form, Vaccination 1, Days 0 – 7
- Parent's Diary Form, Vaccination 1, Days 7 – 28
- Parent's Diary Form, Vaccination 2, Days 0 – 7
- Parent's Diary Form, Vaccination 2, Days 7 – 28
- Serious Adverse Event Form (SAE)
- Data Clarification Form

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