COVER PAGE for document upload to Record **NCT00386542** at https://ClinicalTrials.gov ("*Needle-free Jet Injection of Reduced-dose, Intradermal, Influenza Vaccine in >= 6 to < 24-month-old Children*")

Filename: **4785-INF-ID-ConsentEnglish-Annotated-2007Mar16_A-1b.pdf**

Study Title - English: **Clinical Trial of Safety (Reactogenicity) and Immunogenicity of Needle-free Jet Injection of Reduced-dose, Intradermal, Influenza Vaccine (INF) Administered to ≥6 -to- <24 Month-old Infants and Toddlers in the Dominican Republic**

Study Title - Español: **Ensayo Clínico de Seguridad y Respuesta Inmunológica de Inmunización Administrada sin Aguja con Inyector a Chorro en Dosis Reducida por vía Intradérmica con Vacuna Influenza (Gripe) (INF) en Niños de ≥6 - <24 Meses de Edad en la República Dominicana**

Document Type: **Informed Consent [English translation of Spanish provided to participating parent(s)/guardian(s), dated "2007Mar16"]**

Document Description: **English translation of revised, final Spanish informed-consent form dated 2007-03-16, submitted to and approved by the *Consejo Nacional de Bioética en Salud*, the *Comité de Ética/Investigaciones de la Fundación Dominicana de Infectología*, and the Investigational Review Board (IRB) "G" at the U.S. Centers for Disease Control and Prevention (additions from original version in underlined brown ochre font color; deletions in ~~red strikeout~~)**

After signing this form, share a complete copy of all pages with the parents, as well as the additional information document.

Participant (ID) number: ___ ___ ___

INFORMED CONSENT

Study of Needle-free Immunization against the Flu

Clinical Trial of Safety (Reactogenicity) and Immunogenicity of Needle-free Jet Injection of Reduced-dose, Intradermal, Influenza Vaccine (INF) Administered to ≥6 -to- <24 Month-old Infants and Toddlers in the Dominican Republic

Department of Infectious Diseases
Hospital Infantil Dr. Robert Reid Cabral (HIRRC)
Secretariat of State of Public Health and Welfare
Santo Domingo, Dominican Republic
&
Centers for Disease Control and Prevention (CDC)
Department de Health and Human Services, Atlanta, Georgia, USA

Esteemed parents,

Today we inform you of the chance to enroll your child in a study that offers the vaccine against the flu (influenza). Please read the separate document INFORMED CONSENT - ADDITIONAL INFORMATION FOR THE PARENTS for other details.

The sponsors of the study are the Centers for Disease Control and Prevention (CDC) of the United States and the Dr Robert Reid Cabral Children's Hospital (HIRRC). The World Health Organization (WHO), the Program for Appropriate Technology in Health (PATH), and others also collaborate.

The children in the study will not be exposed to unnecessary risks. The rights of the children and their parents will be respected and protected. This study will be carried out according to international ethical principles, and according to the laws of the Dominican Republic.

The study compares a reduced dose given in the skin by jet injector with a regular dose by needle and syringe. This permits us to know if the reduced dose is as good as the regular dose. The reduced dose is about 2 drops. The regular amount is 5 drops in children less than 3 years. In older children and adults it is 10 drops. Twenty drops equal 1 milliliter (mL). A teaspoon contains about 5 milliliters (100 drops).

If the reduced dose works, it can protect more people in an epidemic. In addition, the jet injector can be safer and faster than needles. This study uses Vaxigrip® vaccine. This vaccine is made in France by the international company Sanofi Pasteur. Two doses of Vaxigrip are recommended children younger than 9 years if they have not received the vaccine before.

What are the benefits to the child of the study?

Your child will receive two doses of Vaxigrip vaccine to study its protection. They might be full doses or reduced doses. If your child receives reduced doses, at the end of the study he will receive a third complete dose to assure that he or she is protected. Six months later, we will give to the children a bonus vaccination of the regular dose so the children are protected for the next flu season. The vaccines, the return visits to the clinic, and the necessary medical examinations of the study are all free of charge. The parents will not pay anything.

Who can participate in this study?

The children must be healthy, without serious medical problems. They must be at least 6 months old, but not yet reached the 2nd birthday. They must have received in prior visits all vaccines recommended for their age (diphtheria, tetanus, whooping cough, polio, Haemophilus influenzae type b, hepatitis B, measles, mumps, and rubella). They must not have received a vaccine against the influenza. Plus, it is necessary that the parents can be contacted at their home telephone or that of a neighbor. The parents must be able to make and write down certain measurements of the child at home. They must promise to bring the child to this clinic for followup 7 times after today. The final visit for the bonus is 8 months from today.

Who cannot be included in this study?

Children with some medical conditions cannot participate. The doctor will ask you about each of these conditions to decide if your child can be included.

What will the participants get in the study?

The parents of children in the study will be paid the cost of roundtrip travel by taxi. They will get a snack or lunch in the hospital on each followup visit. They will receive disposable thermometers to take the child's temperature. They will receive a tape and a plastic ruler to measure skin reactions. They will receive a notebook to write down these measurements and other changes in the health of the child. The parents may keep all these.

What are the inconveniences and discomforts of the study?

The parents must observe the child, take measurements, and write them down at home. The parent must bring to the child for seven additional return visits to this clinic. The child will feel the pain of injection three or four times. The child will feel the pain of blood collection three times. The parents must leave the room during each the first three injections. This is to keep secret the vaccination method until the end of the study. Also, the doctors recommend that the parents leave when blood is taken. If the child has illness like the flu, a sample will be taken from the nose, which is also uncomfortable.

What are the risks of participating in the study?

As is common with many vaccines, some patients who get Vaxigrip will have reactions. Most frequent is soreness at the site of the injection for up to two days. It happens in 10% to 64% of patients. These reactions are generally mild. Redness, swelling, and local bruising can occur more rarely.

Fever is also common in young children who have not been vaccinated before. It can begin six to twelve hours after the vaccination and can last one to two days. (To reduce the fever, the doctor can provide acetaminofen to give to the child in the afternoon after vaccination.) Other reactions can include feeling bad and muscle pains. Very, very rarely allergic reactions and nerve disorders can happen. These can be facial paralysis, changes in brain function and the syndrome called Guillain-Barré.

The jet injector can leave a drop of blood on the skin. In very rare cases, it can cut the skin. The collection of blood from a vein can cause bruising and pain at the site of the needle. If illness like flu

occurs, the cotton swab applied in the nose to collect fluids can cause temporary discomfort. More serious or permanent injury because of these procedures would be very rare.

There is always the chance a child could have a harmful effect that neither the parents nor the investigators know about before. The study is ready to detect and to treat the complications that can result from participation of the child.

What will happen if my child suffers any harm during the study?

If your child suffers harm as a direct result of the study, medical care will be provided by the Dr. Robert Reid Cabral Children's Hospital (HIRRC). This includes services without charge in any of its clinics and wards, including the intensive care unit.

If the HIRRC cannot provide the needed treatment you can take your child to another hospital or clinic. The costs of transfer and later treatment will have to be paid by the parents. Nevertheless, you have the legal right to demand payment for such costs from those who lead the study. An insurance policy from an international insurance company has been acquired. This policy covers the legal responsibility to the participants of the HIRRC, CDC, WHO, and PATH. The policy will pay the medical expenses in case of harm that is the direct result of the study.

How will the study be carried out?

The study lasts two months for each patient, plus six months more until the "bonus" vaccine. It has a total of eight visits to the clinic, including the one today.

Children will be assigned by chance (like a lottery) to one of three groups. Each one of the groups will be vaccinated with Vaxigrip. One group will receive 5 drops (0.25 mL) of the vaccine in the muscle with needle and syringe. A second group will be vaccinated with only 2 drops (0.1 mL) in the muscle with needle and syringe. A third group will be vaccinated with only 2 drops in the skin with the needle-free jet injector, Biojector® 2000. Four weeks after the first vaccination, all groups will receive a second dose in the same way as the first dose.

Four weeks after the second vaccination, a third full "insurance" dose will be given to children who earlier received reduced doses. This third dose ensures that the children are protected against the flu. The group that received full doses before will receive a simulated third vaccination.

Six months later all children will receive a bonus vaccination. This will ensure protection from the flu for the next year.

Separation from the parents during the vaccination

In order to assure scientific quality, neither the parents nor the doctors will know the method of vaccination used. This will be revealed at the time of receiving the bonus vaccine. Only the nurses who vaccinate will know how it is given.

The nurse will take the child to the injection room without the parents. The parent waiting area is next to the vaccination room. The separation will last about five minutes: three for the taking of blood and one or two more for the vaccination.

The separation during vaccination is necessary so that the parents and the doctors do not know the method. If the parents do not agree to this separation, they should not participate in the study. (If the parents ask, they may watch the blood collection only.)

Tasks of the parents

After each of the first two vaccinations, the parents must observe the child carefully. They must write down certain measurements in a form. The parents also have to bring the child back to the clinic

two days and seven days after these vaccinations. Only one parent needs to be with the child on these visits. The nurses will write down the dates and remind the parents when to return to the clinic.

After the third vaccination, the parents do not need to write down anything in a diary. But they should call the doctors or nurses if the child becomes sick. And they should bring the child six months later for the final vaccination.

Laboratory samples

A teaspoon of blood will be taken from the child three times: 1) The day of 1st vaccination (normally today). 2) The day of 2nd vaccination (4 weeks after the 1st). 3) The day of 3rd vaccination (4 weeks after the 2nd). This is to know if the vaccine works.

In case of illness like flu, a cotton swab will gently take liquid from inside the nose. This will help identify the flu virus.

If the parents agree, leftover samples after the study will be stored to do other tests of scientific value in the future (except NOT testing for HIV and human genes). A second signature in this form authorizes the storage and future testing of these samples. If you do not want this, indicate your disagreement by NOT SIGNING in the designated place. Not signing about these stored samples will not disqualify your child to enter the study.

Protection of identifying personal information

The names and identity of the parents and children will be handled strictly confidentially. It will be maintained in private by the investigators and staff of the HIRRC. They will not be given outside of the HIRRC without permission of the parents, unless the law requires it. Other information without names and identities will be shared with the investigators at the CDC and a committee to supervise the safety of the study.

Notifying parents of the results

At any time, the parents can ask that the laboratory results of the study for their child be provided to them when they are available. They can ask for a copy of any printed report of the study. Also, they can contact the doctors of the study with any question.

What are my rights?

Your permission and consent for the participation of your child this study are voluntary. You can take it back at any time without explanation. You can now decline to participate. Or, later, you can take your child out of the study. If you do, your child will suffer no harm. Your child will not lose access to medical services or benefits. Your child will receive necessary vaccines to complete the recommended schedule for immunizations in the Dominican Republic.

The doctors can take your child out of the study for medical reasons. The doctors must tell you any new information that may be important in deciding to remain or leave the study. You have the right to request more information at any time. Before deciding to join the study, you may ask any question to the investigator.

Contacts for more information

The doctors named below are in charge of your child in this study. If you have any worry or question, do not hesitate to contact one of the doctors.

Dominican Principal Investigator:

Dr. Virgen Gómez, MD
Director de of Followup Clinic
Department de Infectious Diseases
Dr. Robert Reid Cabral Children's Hospital
Avenue Abraham Lincoln No. 2, Centro de los Héroes, National District
Santo Domingo, Dominican Republic
Tel: [+1] (809) 532-5872
Fax: [+1] (809) 532-2564
Mobile: [+1] (809) 449-2913
virgen.gomez@verizon.net.do

Dominican Co-Investigators:

Dr. Josefina Fernández, MD
Director of Research
Department of Infectious Diseases
Dr. Robert Reid Cabral Children's Hospital
Tel: [+1] (809) 532-5872
Fax: [+1] (809) 532-2564
Mobile: [+1] (809) 223-5129
infectologia1@verizon.net.do

Dr. Glenny Gúzman, MD
Medical Investigator
Department of Infectious Diseases
Dr. Robert Reid Cabral Children's Hospital
Tel: [+1] (809) 532-5872
Fax: [+1] (809) 532-2564
Mobile: [+1] (809) 258-0667
guzman.glenny@gmail.com

Dominican Senior Investigator:

Dr. Jesús M. Feris Iglesias, MD
Director, Department of Infectious Diseases
Dr. Robert Reid Cabral Children's Hospital
Tel: [+1] (809) 532-5872 (mornings), 685-2552 (afternoons)
Mobiles: (809) 222-4516, (809) 732-0820
infectologia@verizon.net.do

American Principal Investigator:

Bruce G. Weniger, MD, MPH
Assistant Chief for Vaccine Development
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)
1600 Clifton Road (D-26 ~~E-61~~), Atlanta, Georgia 30333 USA
Tel: [+1] (404) 639-8779
Fax: [+1] (404) 639-8834
Mobile: [+1] (678) 478-1101
bgw2@cdc.gov

For the Physician Investigator

In a detailed conversation, I have explained the nature of this study to the

parents _____

of child _____

I will give the parents a copy of this signed document for them to keep.

Signature of the investigator: _____

Date and place of signing: __ __ - __ __ __ - 200__ _____

For the Parents

Child: _____ _____
(First names) (Last names)

The doctor who signs above has informed me in a detailed conversation about the study in which my child will participate. He has given me the opportunity to think about my decision. I understand the information provided me.

I hereby voluntarily grant my consent to the participation of my child in the study. A copy of this signed form will be given to me today to keep.

I know that my consent can be taken back at any time without explanation. I know that the study doctor can remove my child from participation if my child's health can be affected by continuing. I know that any withdrawal will not affect the right to medical assistance that my child may need.

I understand the benefits, discomforts, and risks of the study. I have the right to be notified of any new information that might be important for continuing my child in the study. If I have any worry I can contact the doctor at any time

They have promised me to cover the reasonable costs of travel and snacks or lunch during the study visits. I have been informed that my child will receive free medical care in this hospital for any harm resulting from participation in this study. I have been informed that the organizers of this study have purchased an insurance policy. It covers their legal responsibility to pay for any harm resulting from the participation of my child in the study. This includes necessary costs for medical and hospital care if it cannot be provided by the hospital and doctors responsible for the study.

I promise to follow the instructions of the study doctors. I will inform them immediately if I think my child suffers any serious health problem. I must consult with the study doctor before giving or my child receives other medical treatment (except in case of emergency).

I give my consent for medical information on my child to be kept confidentially by the HIRRC and the study staff. HIRRC can share with the CDC sponsor only data in an anonymous form. It will not be possible for them to identify my child or me. I consent that the sponsor and its collaborators can examine, and analyze these anonymous data.

_____

Signature of ❑ mother or ❑ father or ❑ guardian (check one box)

_____ _____

First names (BLOCK LETTERS) Last names (BLOCK LETTERS)

_____ _____

Date of signature * Place *

_____

Other signature, if any (the ❑ mother, the ❑ father, the ❑ guardian – mark one box)

_____ _____

First names (BLOCK LETTERS) Last names (BLOCK LETTERS)

_____ _____

Date of signature * Place *

* The date and place must be written by the hand of the signers

Consent for the storage of samples:

□ ***I agree*** *that the leftover serum and virus samples be stored and can be used for future studies.* (Sign below)

□ ***I do NOT agree*** *that the leftover serum and virus samples be stored and can be used for future studies.* (Do NOT sign below)

_____

Signature of ❑ mother or ❑ father or ❑ guardian (check one box)

_____ _____

Date of signature * Place *

_____

Other signature, if any (the ❑ mother, the ❑ father, the ❑ guardian – mark one box)

_____ _____

Date of signature * Place *

* The date and place must be written by the hand of the signers

After the signing of the "Informed Consent", share with the parents complete copies of all pages of this form of additional information.

INFORMED CONSENT - ADDITIONAL INFORMATION

For the Parents

Study of Needle-free Immunization against the Flu

Clinical Trial of Safety (Reactogenicity) and Immunogenicity of Needle-free Jet Injection of Reduced-dose, Intradermal, Influenza Vaccine (INF) Administered to ≥6 -to- <24 Month-old Infants and Toddlers in the Dominican Republic

Department of Infectious Diseases
Hospital Infantil Dr. Robert Reid Cabral (HIRRC)
Secretariat of State of Public Health and Welfare
Santo Domingo, Dominican Republic
&
Centers for Disease Control and Prevention (CDC)
Department de Health and Human Services, Atlanta, Georgia, USA

Esteemed parents,

In this document we provide you additional information about the study. This information is given in a series of questions and answers. Please ask the doctor or nurse about any question you have. Figure 1 is a photo of the Biojector® 2000 injector to be used in the study. If you want to see it, ask that the injector be shown.

General Questions and Answers about the Study

What is the flu?

The flu (influenza) is a contagious disease caused by the influenza virus. It can cause mild or severe disease. Sometimes it can cause death. Most healthy people recover from the flu without problems. It can cause serious disease in some people. This includes older persons, young children, and people with health problems.

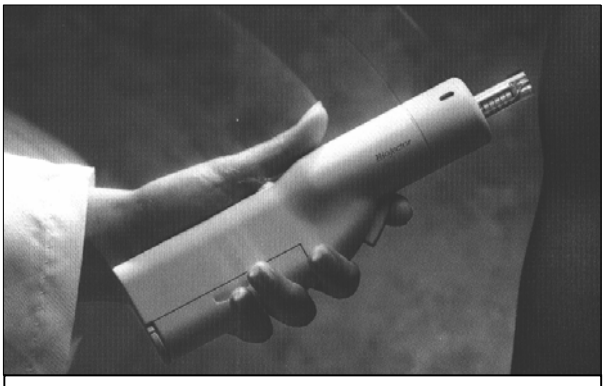

FIGURE 1. Biojector® 2000 needle-free jet injector.

The flu also can worsen asthma, diabetes, heart disease, and other conditions. The flu virus can cause epidemics (that affect many in the Dominican Republic) and pandemics (that affect many in all continents).

What is the vaccine to be studied?

This study uses Vaxigrip® vaccine. This brand is approved for sale and use in the Dominican Republic, Canada, Mexico, Australia, New Zealand, the European Union, and in many other countries. This vaccine is made in France by the international company Sanofi-Pasteur. The vaccine has been shown reliable and safe in children and adults in previous studies. It has been used routinely in millions of children from 6 months of age. Two doses of Vaxigrip are recommended for young children less than 9 years of age if they have not received the vaccine before.

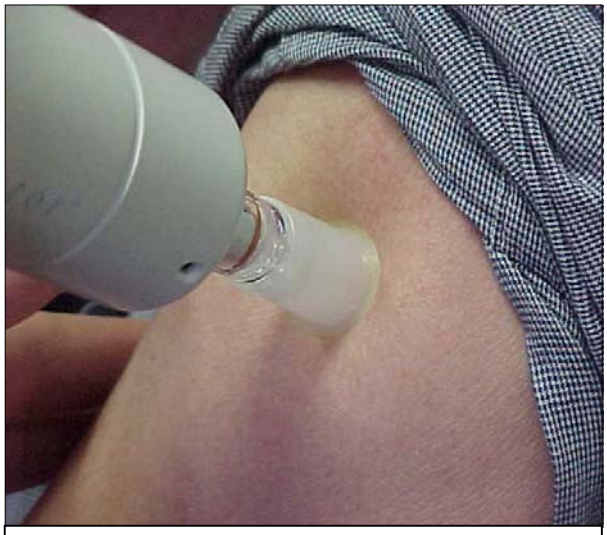

FIGURE 2. The Biojector® 2000 with plastic spacer giving an injection into the skin.

What protection do vaccines give?

Most people who receive vaccines do not become ill from the virus the vaccine was designed to prevent. Previous studies of Vaxigrip indicate that 7 to 9 of every 10 vaccinated children will be protected. This also means that about 1 to 3 of every 10 children will not respond to the vaccine. These children will not be protected. If these unprotected children come into contact with someone with the flu, it is possible they may catch the disease.

Many other germs cause illness like the flu. This vaccine will not avoid illness from these other germs. Nevertheless, the flu is one of the most severe diseases among them. The Vaxigrip vaccine provides valuable protection.

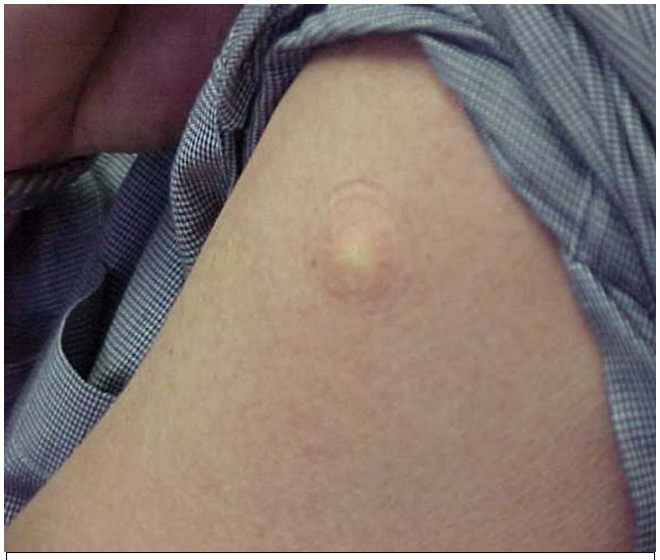

FIGURE 3. Blister of vaccine in the skin. The blister disappears in a few minutes.

Why a reduced dose of the vaccine?

In case of an outbreak of flu, there may not be enough vaccine for all persons who need it. A reduced dose of vaccine would permit more persons to be protected.

Some studies in adults showed that a reduced amount is as good as the usual amount. Other studies demonstrated that injecting reduced doses into the skin can protect as well as a full dose into the muscle. But there is no study in children from 6 to 23 months. This is the reason to do this study. Figure 2 shows the spacer for injecting into the skin.

Why is this study considered experimental?

● **The reduced dose is experimental.** The amount of 0.1 mL (2 drops) is not usual. Normally it is 0.25 mL (5 drops) in young children. This is the reason this study is experimental research.

● **Vaccine into the skin is experimental.** The skin is not the usual place to give vaccine. Usually it is given in muscle or fat. Other vaccines, the BCG against tuberculosis and smallpox, are given routinely in the skin. Dozens of studies with other vaccines against flu in the past showed that vaccination in the skin works. Nevertheless, we do not know about Vaxigrip brand administered into the skin.

● **The injector is not yet approved for use in the Dominican Republic.** The Biojector® 2000 injector is approved for use in the United States and many countries in Europe. But it is still not approved for medical use by the health authorities of the Dominican Republic. This injector has been used successfully for many vaccines like flu, yellow fever, and hepatitis A and B. Similar injectors have been used with other vaccines for tetanus, diphtheria, whooping cough, measles, polio, and smallpox.

FIGURE 4. Bottle of Vaxigrip vaccine. This packaging is not approved for sale in the Dominican Republic .

● **The plastic spacer is experimental.** The plastic spacer to be attached to the injector is new (see Figure 2). It creates a gap of 2 centimeters between the nozzle of the injector and the skin. This allows the vaccine to penetrate only into the skin. Other brands of injectors have given many millions of doses into the skin. Figure 3 shows the blister in the skin left by the vaccine. The blister disappears in a few minutes.

● **The packaging is experimental.** Vaxigrip packed in bottles is sold in other countries (see Figure 4). These bottles are still not approved for the sale by the Dominican Republic. Here, Vaxigrip is now approved only in pre-filled syringes (see Figure 5). This study will use the bottles.

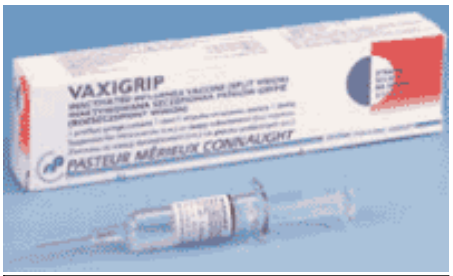

FIGURE 5. Pre-filled syringe of Vaxigrip vaccine, already registered in the Dominican Republic.

What public health benefits does the study offer?

The results can allow protecting more people against flu in case of outbreak and shortage of vaccine. It also might show that jet injectors can avoid the disadvantages of needles and syringes.

For the Physician Investigator:

In a detailed conversation, I have explained the nature of this study to the parents _____

of child _____

I will give the parents a copy of this signed document for them to keep.

Signature of the investigator: _____

Date and place of signing: __ __ - __ __ __ - 200__ _____

When assigned, write the Participant ID number: ___ ___ ___