IMPAACT P1086
A Phase II Study to Assess the Safety and Immunogenicity of an
Inactivated Influenza A (H1N1) 2009 Monovalent Vaccine in
HIV-1 Infected Pregnant Women

A Multicenter, Domestic Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Group (IMPAACT)

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID)
and
The Eunice Kennedy Shriver National Institute of Child Health and Human Development
(NICHD)

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Through BARDA (Biomedical Advanced Research and Development Authority), Office
of the Assistant Secretary for Preparedness and Response,
U.S. Department of Health and Human Services

In Partnership with Department of Microbiology and Infectious Diseases (DMID)

BB-IND# 14147

The IMPAACT Complications Committee Chair: Sharon Nachman, M.D.

Protocol Chairs: Sharon Nachman, M.D.
Myron Levin, M.D.

Protocol Vice Chair: Mark Abzug, M.D.

NIAID Medical Officer: Edward Handelsman, M.D.

NIAID Program Officer: Judi Miller, R.N., B.S.N.

NICHD Medical Officers: George Siberry, M.D.
Heather Watts, M.D.

Clinical Trials Specialist: Elizabeth Petzold, Ph.D.

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FINAL
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All questions concerning this protocol should be sent via e-mail to actg.teamp1086@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1086@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail rccsafetyoffice@tech-res.com or call 1-800-537-9979 or 1-301-897-1709 or fax 1-800-275-7619 or 1-301-897-1710. To order study agent, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at sdac.random.desk@fstrf.org.

Protocol Chair

Sharon Nachman, M.D.
SUNY at Stony Brook
Health Science Center
T11-080
Stony Brook, NY 11794
Phone: 631-444-7692
Email: sharon.nachman@stonybrook.edu

Protocol Co-Chair

Myron Levin, M.D.
University of Colorado at Denver and Health Sciences Center
Mail Stop C227; Building 401
1784 Racine Street
Aurora, CO 80045
Phone: 303-724-2451
Email: myron.levin@ucdenver.edu

Protocol vice Chair

Mark Abzug, M.D.
The Children's Hospital, Box B055
13123 East 16th Avenue
Aurora, Colorado 80045
Phone: 720-777-6389
Email: abzug.mark@tchden.org

NIAID Medical Officer

Edward Handelsman, M.D.
IMAP Branch
NIH, NIAID, DAIDS
6700-B Rockledge Drive, Rm 5107
Bethesda, MD 20892
Phone: 301-402-3221
Email: handelsmane@niaid.nih.gov
IMPAACT P1086 PROTOCOL TEAM ROSTER

NIAID Program Officer

Judi Miller, R.N., B.S.N.
IMAP Branch
NIH, NIAID, DAIDS
6700-B Rockledge Drive, Rm 5227
Bethesda, MD 20892
Phone: 301-496-1189
Email: jmillera@niaid.nih.gov

NICHD Medical Officers

George Siberry, M.D., M.P.H.
Pediatric Adolescent and Maternal AIDS Branch
NIH, NICHD
6700 Executive Blvd., Rm 4B11H
Bethesda, MD 20892
Phone: 301-496-7350
Email: siberryg@mail.nih.gov

Heather Watts, M.D.
Pediatric Adolescent and Maternal AIDS Branch
NIH, NICHD
6100 Executive Blvd. Rm 4B11G
Bethesda, MD 20892
Phone: 301-435-6874
Email: wattsh@mail.nih.gov

Clinical Trials Specialists

Elizabeth Petzold, Ph.D.
IMPAACT Operations
Social & Scientific Systems
1009 Slater Road, Suite 120
Durham, NC 27703
Phone: 919-287-4314
Email: epetzold@s-3.com

Protocol Statisticians

Terrence Fenton, Ed.D.
Statistical & Data Analysis Center
Harvard School of Public Health
651 Huntington Avenue
Boston, MA 02115
Phone: 617-632-2009
Email: fenton@sdac.harvard.edu

Petronella Muresan, M.S.
FSTRF-Harvard School of Public Health
900 Commonwealth Avenue, 2nd floor
Boston, MA 02215
Phone: 617-632-2059
Email: petronm@sdac.harvard.edu

Protocol Data Manager

Barbara Heckman, B.S.
Frontier Science and Technology Research Foundation (FSTRF), Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x 7231
Email: heckman.barbara@fstrf.org

Wende Levy, R.N., M.S.
IMPAACT Operations
Social & Scientific Systems
8757 Georgia Avenue
Silver Spring, MD 20910
Phone: 301-628-3384
Email: w levy@s-3.com
IMPAACT P1086 PROTOCOL TEAM ROSTER

Protocol Pharmacist
Ruth Ebiasah, Pharm.D. M.S., R.Ph.
Pharmaceutical Affairs Branch
NIH, NIAID, DAIDS
6700-B Rockledge Drive, Rm 4223
Bethesda, MD 20892
Phone: 301-402-0128
Email: ebiasahrp@niaid.nih.gov

Protocol Immunologist
Adriana Weinberg, M.D.
University of Colorado at Denver and Health Sciences Center
Mail Stop 8604
12700 E. 19th Avenue, Rm 11126
Aurora, CO 80045
Phone: 303-724-4480
Email: adriana.weinberg@ucdenver.edu

Protocol Virologist
Paul Palumbo, M.D.
Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756
Phone: 603-650-8840
Email: paul.palumbo@dartmouth.edu

Laboratory Technologist
Joan Dragavon, M.L.M.
University of Washington
Research & Training Building
300 9th Avenue, Rm 725
Seattle, WA  98104
Phone: 206-897-5210
Email: dragavon@u.washington.edu

Westat Clinical Research Associate
Lori Donelson, R.N., B.S.N., C.C.R.C.
Clinical Research Associate
Westat, WB 290
1441 West Montgomery Ave.
Rockville, MD 20882
Phone: 301-610-5118
Email: loriдонelson@westat.com

Field Representative
Andrea Jurgrau, M.S.R.N., C.P.N.P.
Columbia-Presbyterian Medical Center
622 West 168th Street, VC4, Rm 412
New York, NY 10032
Phone: 212-305-5000
Email: jurgrau@nyp.org

Obstetrician
David J. Garry, DO FACOG
Jacobi Medical Center
Department of OB/GYN and Women’s Health
Building 1, BS-22
1400 Pelham Parkway South
Bronx, NY 10461
Phone: (718) 918-6300
Email: david.garry@nbhn.net

Lab Data Coordinator
Anthony Bloom, M.S.
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x 7431
Email: bloom.anthony@fstrf.org
### List of Commonly Used Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONE (1) DOSE of vaccine</td>
<td>Each 30mcg vaccine dose consists of <strong>TWO</strong> separate 15mcg intramuscular (IM) injections</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event/Adverse Experience</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute Neutrophil Count</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BARDA</td>
<td>Biomedical Advanced Research &amp; Development Authority, DHHS</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-Mediated Immunity</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic T Lymphocytes</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Management Center</td>
</tr>
<tr>
<td>DMID</td>
<td>Division of Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>Evaluable</td>
<td>Evaluable mother-infant pairs are defined as having received <strong>two</strong> doses of inactivated <strong>Influenza A (H1N1) 2009 monovalent vaccine</strong> and had samples for immunogenicity laboratory assays obtained prior to delivery, as per protocol.</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FHR</td>
<td>Fetal Heart Rate</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titer</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HA</td>
<td>Hemagglutinin</td>
</tr>
<tr>
<td>HAI</td>
<td>Hemagglutination Inhibition</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent or Institutional Ethics Committee</td>
</tr>
<tr>
<td>ILI</td>
<td>Influenza-like-illness</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISM</td>
<td>Independent Safety Monitor</td>
</tr>
<tr>
<td>MCG</td>
<td>Microgram</td>
</tr>
<tr>
<td>MedDRA®</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MN</td>
<td>Microneutralization Assay</td>
</tr>
<tr>
<td>N</td>
<td>Number (typically refers to subjects)</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NICHD</td>
<td>The Eunice Kennedy Shriver National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>Nt</td>
<td>Neutralizing</td>
</tr>
<tr>
<td>OCRA</td>
<td>Office of Clinical Research Affairs, DMID</td>
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<tr>
<td>OHRP</td>
<td>Office for Human Research Protections, DHHS</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PID</td>
<td>Patient Identifier</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event/Serious Adverse Experience</td>
</tr>
<tr>
<td>SDMC</td>
<td>Statistical and Data Management Center</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
</tr>
<tr>
<td>TIV</td>
<td>Trivalent Influenza Vaccine</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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APPENDICES

IA MATERNAL SCHEDULE OF EVALUATIONS

IB INFANT SCHEDULE OF EVALUATIONS

IC MATERNAL SCHEDULE OF EVALUATIONS FOR WOMEN WHO DELIVER PRIOR TO DOSE #2

II PUBLIC READINESS AND EMERGENCY PREPAREDNESS ACT (PREP Act)

III DAIDS SAMPLE INFORMED CONSENT
SUMMARY OF CHANGES

All changes in this version appear in boldface type. Editorial changes including corrections of typographical errors and other changes required to update information that does not affect regulatory issues or patient consent may also be included. These changes contain all the information contained in Clarification Memo #1, dated 9/15/09 and in Letter of Amendment #1, dated 10/6/09:

1. The Influenza A (H1N1) 2009 Monovalent Vaccine manufactured by Novartis has been approved by the FDA. All references to the study product have been modified to indicate that the study vaccine is a licensed product and is no longer considered as investigational.

2. The vaccine is now referred to as “Influenza A (H1N1) 2009 Monovalent Vaccine” throughout the protocol. The virus is now referred to as “2009 H1N1 Influenza A virus” throughout the protocol. Similarly, all references to ‘S-OIV’ or ‘swine-origin’ have been removed.

3. The Table of Contents has been updated.

4. Schema and Section 2.2 – Secondary Objectives. An additional secondary objective has been added: “To explore factors related to HIV and its treatment that might affect the responses to H1N1 vaccinations.”

5. Section 1.1 – Introduction: Some preliminary data from ongoing H1N1 vaccine studies has been added:

   "Preliminary immune response results from ongoing studies of the Influenza A (H1N1) 2009 Monovalent Vaccines are now available. In general, the preliminary immune response data available from approximately 350 adult subjects, 18 – 64 years of age enrolled in studies of the influenza A (H1N1) 2009 Monovalent Vaccine show that at 21-29 days after intramuscular (IM) administration of one dose of 15µg HA/strain, between 60 and 80% of subjects achieved either a titer of 1:40 or greater (for those seronegative at baseline), or a fourfold or greater rise from baseline (for those seropositive at baseline). Differences in immune response between the 15µg HA/strain and 30µg/strain dose levels have not been identified.

   Updated results from clinical trials can also be found at the CDC website: http://www.cdc.gov/H1N1FLU"

6. Section 4.1 – Clarification of the definition of HIV-1 infection as follows: HIV-1 infection, defined as 2 positive test results obtained from 2 different samples. Tests may include two of the same type OR two different types of
tests listed below, as long as there are 2 positive test results obtained from 2 different samples:
  - HIV-1 antibody (ELISA and WB)
  - HIV-1 culture
  - HIV-1 DNA PCR
  - HIV-1 RNA PCR > 1,000 copies/ml
  - Neutralizable HIV-1 p24 antigen

7. Section 4.2 – Exclusion Criteria; Informed Consent: “Individuals with egg or egg product allergies should not receive this vaccine.”

8. Section 4.2 – Exclusion Criteria; Informed Consent: None of the following allergens are included in Influenza A (H1N1) 2009 Monovalent Vaccine (Novartis) - Gelatin, formaldehyde, octoxinol or chicken protein, but the vaccine does contain neomycin and polymyxin. Therefore, exclusion criterion 4.21 has been updated to: “Has a known allergy to eggs, egg products, neomycin or polymyxin.”

9. Section 4.51 – Vaccines: The following text has been added to Section 4.51: “The 2009-2010 seasonal TIV is recommended for all pregnant women and should be given as outlined in this section.” The following text has also been added to Section 4.51 – Vaccines: “Any vaccines deemed necessary per the site investigator are also allowed.”

10. Section 4.53: Enrollment procedures have been updated.

11. Section 5.12; Needle Length Chart: All adult subjects should have study vaccine administered in the deltoid muscle. No vaccinations with study vaccine should be given in the lateral thigh.

12. Section 5.121 – Novartis Pre-Filled Syringes – Administration: The following text has been added: “The vaccine should be allowed to reach room temperature shortly before use. Shake the syringe before administering the vaccine.”

13. Section 5.21 – Novartis Vaccine Pre-filled Syringes: Text has been added to confirm that the vaccine should be “protected from light.”

14. Section 6.1 – Toxicity Management: All grades of adverse events should be documented in the CRFs and will be assessed in the safety outcomes. In the ‘Toxicity Management’ section: the first bullet has been revised to read: “ALL Grades of adverse events should be recorded on the appropriate CRF.”
15. Section 6.2 – Subject Management: The following text has been added: “If a subject experiences documented H1N1 infection, as defined in Section 4.24, between Step I and Step II of the protocol, the subject should NOT receive the second dose of vaccine but should continue to be seen at the scheduled study visits, and have blood collected, as per the Schedule of Evaluations.

16. Section 8.5 – Study Safety Monitoring: The following text has been added: “For safety monitoring, a vaccine related SAE is an SAE that is judged to be “definitely”, “probably” or “possibly related” to study vaccine.

17. Appendix IA, table and footnote #7: The second telephone call should be placed at Day 10 (± 3 days) after the first vaccination.


19. WHY IS THIS STUDY BEING DONE? (IC page 1/11)
   Text has been modified to read: “H1N1 virus, historically known as ‘swine flu virus’, is a new strain of influenza (flu) virus that causes illness in people.”

20. WHY IS THIS STUDY BEING DONE? (IC page 2/11)
   Text has been modified to read: “If you are allergic to eggs or egg products you would not be able to receive this vaccine.”

21. WHY IS THIS STUDY BEING DONE? (IC page 2/11)
   Text has been modified to read: “The vaccine is made with products from eggs.”

22. WHY IS THIS STUDY BEING DONE? (IC page 2/11)
   The following text has been added: “The vaccine also contains small amounts of the antibiotics neomycin and polymyxin. If you are allergic to one of these antibiotics, you will not be able to receive this study vaccine.”

23. WHY IS THIS STUDY BEING DONE? (IC page 2/11)
   Text has been modified to read: “This vaccine contains a trace amount of thimerosal (mercury).”

24. WHY IS THIS STUDY BEING DONE? (IC page 2/11)
   The following text has been deleted: “Also, if you do not eat pork for religious reasons, you may choose not to be part of this research study.”

Text has been modified to read: “The purpose of this research study is to determine if this vaccine which has been licensed by the United States Food and Drug Administration (FDA) is safe and will help the body’s normal defenses against the effects of H1N1 influenza in HIV-infected pregnant women. The licensed vaccine to be used in this study may not prevent all cases of influenza virus, but may prevent severe disease and possibly death which has been associated with this H1N1 virus in pregnant women.”

26. After you have received the vaccine (IC Page 4/11)
“Myalgia” (muscle aches) has been added to the list of symptoms of influenza-like illness.

27. WHAT ARE THE RISKS OF THE STUDY? (IC Page 6/11)
Symptoms of vaccine related reactions have been modified to read:

Systemic Vaccine Related Reactions:
• skin rash (hives)
• fever
• nausea
• vomiting
• diarrhea
• abdominal pain
• cough
• sore throat
• achiness
• feeling tired (fatigue)
• general feeling of illness

Serious Vaccine Related Reactions:
• Difficulty breathing
• Sweating
• Fast pulse
• Swelling around the mouth, throat or eyes

28. ARE THERE RISKS RELATED TO RECEIVING THIS VACCINE DURING PREGNANCY? (IC page 7/11)
The following statement has been removed: “Safety is being evaluated prior to mass vaccination to be certain that the H1N1 influenza vaccine is safe for pregnant women.”

29. WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY? (IC page 9/11)
Text has been modified to read: 
“Alternatives to your participation in this study include receiving from your health care provider the seasonal flu vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine. Alternatively, you may choose not to receive any vaccine.”

SCHEMA

A Phase II Study to Assess the Safety and Immunogenicity of an Inactivated Influenza A (H1N1) 2009 Monovalent Vaccine in HIV-1 Infected Pregnant Women

DESIGN: Multi-site, open label Phase II study
STEP I: Dose 1 of vaccine
STEP II: Dose 2 of vaccine

NOTE: Each 30mcg dose is defined as TWO separate 15mcg intramuscular (IM) vaccine injections

SAMPLE SIZE: 130 pregnant women to obtain 100 evaluable* women and their infants.
*Evaluable mother-infant pairs are defined as having received two doses of Influenza A (H1N1) 2009 monovalent vaccine and had a complete set of samples for immunogenicity laboratory assays obtained prior to delivery as per protocol.

POPULATION: HIV-1 infected pregnant women ≥ 18 years and ≤ 39 years old, in their second or third trimester (≥ 14 weeks to < 35 weeks of gestation).

STRATIFICATION: None

REGIMEN: In Step I, the initial dose of inactivated Influenza A (H1N1) 2009 monovalent vaccine will be administered to all eligible subjects during the study entry visit (Day 0) as a 30mcg dose; (given as two 15mcg intramuscular injections). Step II is the second dose of inactivated Influenza A (H1N1) 2009 monovalent vaccine, administered as two 15mcg IM injections at Day 21 (+ 7 days).
Note: A second set of exclusion/inclusion criteria must be met prior to administration of the second dose of vaccine.

TREATMENT DURATION: Treatment duration is 21 days (+7 days).

STUDY DURATION: Study duration for the women will be from 6 - 26 weeks while pregnant and 6 months post delivery. Study duration for the infant will be through 6 months of life.

OBJECTIVES:

Primary Objectives

1. To assess the safety after each of two doses of inactivated Influenza A (H1N1) 2009 monovalent vaccine in HIV-1 infected pregnant women.

2. To assess the antibody response after each of two doses of inactivated Influenza A (H1N1) 2009 monovalent vaccine in HIV-1 infected pregnant women.

Secondary Objectives

1. To assess the maternal level of 2009 H1N1 Influenza A virus specific antibodies at delivery, as well as at 3 and 6** months post delivery, following administration of two doses of inactivated Influenza A (H1N1) 2009 monovalent vaccine to HIV-1 infected pregnant women.

2. To assess the extent of placental transport of 2009 H1N1 Influenza A virus specific antibodies from mother to the infant by measuring antibodies in maternal blood and cord / infant blood.

3. To assess the persistence in the infant of maternal 2009 H1N1 Influenza A virus specific antibodies at 3 and 6** months of age.

4. To assess maternal cell-mediated immunity (CMI) responses to the inactivated Influenza A (H1N1) 2009 monovalent vaccine.

5. To assess maternal and infant antibody titers to the seasonal (2009-2010) trivalent influenza vaccine (TIV).

6. To explore factors related to HIV and its treatment that might affect the responses to H1N1 vaccinations.

**First 50 evaluable mother-infant pairs
1.0 INTRODUCTION

1.1 Background

The nature of influenza pandemics. The dissemination of animal influenza A viruses in human populations [including subtypes A/H5N1, H7N7, H9N2 and, most recently, 2009 H1N1 Influenza A virus; also designated “pandemic influenza” herein] has added urgency to ongoing efforts to develop plans for responding to potential influenza pandemics (1-4). Three pandemics have occurred during the last century. During the 1918 influenza A/H1N1 pandemic, an estimated 40 million deaths occurred worldwide (5;6). Excess mortality, high morbidity, and social disruption were all noted during the 1957 influenza A/H2N2 and the 1968 influenza A/H3N2 pandemics (7). In both of these pandemics, human populations lacked significant levels of pre-existing immunity to the pandemic virus, resulting in rapid spread of the novel influenza A virus subtypes. Thus, the emergence of a new influenza subtype in a human population has the potential to produce a public health emergency. The 2009 H1N1 Influenza A virus has reached pandemic levels as defined by the World Health Organization (WHO) (“an influenza virus that is causing sustained community level outbreaks in at least two countries in at least two WHO regions”) (8). Animal models indicate that the pandemic H1N1 influenza virus replicates better in the lung and the gastro-intestinal tract compared with seasonal H1N1, suggesting that the pandemic virus may cause higher morbidity than the seasonal one.(9;10)

The virulence of the pandemic strain in humans is still uncertain.

The cornerstones of pandemic influenza preparedness include enhanced surveillance for the identification of emerging viruses, expanded capacity to produce and deliver relevant vaccines, availability of antiviral medications for prevention and treatment of infections caused by pandemic viruses, and improved public health infrastructure to manage and coordinate control efforts. The threat of pandemic influenza in 1976 (swine influenza) and again in 1977 (Russian influenza) resulted in an inactivated influenza virus vaccine development program that provided important insights into variables influencing the immune responses to immunization (5;6). These included dosage of hemagglutinin (HA) in the vaccine, the number of doses administered to a vaccinee (1 or 2), and the type of vaccine administered (whole virus, split virus, or purified surface antigen). Host factors that influence immune responses included age, prior priming, and presence of underlying disease and immunosuppressive medications.

Immune response to influenza vaccines. The HA is the viral receptor that binds to the host’s epithelial cell receptor, allowing the virus to enter the host cell. Hence, antibodies to the HA play a major role in protective
immunity to influenza virus infection (11;12), and are the basis for the licensure of influenza vaccines in developed countries. Resistance to infection with seasonal influenza virus strains correlates directly with both serum hemagglutination inhibition (HAI) and neutralizing (Nt) antibody levels. Measurements of serum HAI and Nt antibodies are used to assess the immunogenicity of both seasonal and pandemic influenza vaccines (11;12).

The magnitude of the immune response to an inactivated influenza vaccine is greatly affected by the dosage of antigen (usually expressed as weight of HA) contained in the vaccine. Studies evaluating the effect of HA dosage on immune responses to seasonal inactivated influenza vaccines performed over the past 35 years demonstrated dose-related increases in serum and mucosal antibody responses (12-20). Higher vaccine dosages are also associated with the development of higher levels of serum antibodies that recognize antigenically distinct drift variants (20) and can overcome suboptimal responses in immunologically challenged vaccinees, such as elderly patients (19;21).

The effect of HA dosage on the immunogenicity of inactivated vaccines targeting potential pandemic influenza virus strains (H9N2, H5N1) has been evaluated (22-24). Although higher doses of HA routinely induce a significantly greater response than a single dose, the response may still be poor if the antigen is not highly immunogenic. For example, H5N1 vaccines are much less immunogenic than seasonal vaccines or H9N2 vaccines, and two doses of 90mcg of either recombinant baculovirus-expressed H5N1 HA or of an inactivated subvirion antigen vaccine elicited antibody responses in only approximately 50% of young healthy adult subjects (22;23). Higher dosages of HA are also associated with more frequent adverse events.

The route of administration may affect the immune response. Intranasal administration of live attenuated or virosomal vaccines has been purported to enhance local responses including those of HIV-1 infected patients (25;26). Intradermal administration of inactivated influenza vaccines generates higher antibody titers compared with intramuscular administration of the same HA-containing preparations (27-29). Both the vaccine and the vehicle for vaccination for all H1N1 vaccines have been developed for vaccination via the intramuscular route. This study will only be evaluating the current IM vaccine.

The use of adjuvants is another approach to improve the immunogenicity of influenza vaccines (30;31). Adjuvants have the potential to improve serum immune responses at a given dose of antigen, to decrease the amount of antigen needed in the vaccine (dose-sparing), and to improve the immune responses by groups that generally respond poorly to
inactivated antigens (e.g., immunocompromised, elderly) (32). New and more potent adjuvants have not been evaluated in HIV-infected patients.

**Novel pandemic strain of influenza.** Recently, a novel 2009 H1N1 Influenza A virus was identified as a significant cause of febrile respiratory illnesses in Mexico and the United States (US) (3;4;6). It rapidly spread to many countries around the world, prompting the WHO to declare a pandemic on June 11, 2009 (8). Serologic data from several cohorts in different age groups that received the licensed seasonal TIV suggest that these vaccines are unlikely to provide protection against the new virus (33). However, approximately 33% of adults older than 60 years of age have measurable levels of serum HAI or Nt antibody against the 2009 H1N1 Influenza A virus, whereas young adults and children completely lack protective titers. These data indicate the need to develop vaccines against the new H1N1 strain that will be suitably protective for persons in different age groups especially for those with one or more risk factors for severe disease.

**Influenza in pregnant women.** Influenza-associated deaths among pregnant women were reported during the pandemics of 1918 – 1919 and 1957 – 1958. Case reports and epidemiologic studies also indicate that pregnancy increases the risk for influenza complications for women. Most studies have demonstrated that during influenza epidemics there is an excess of hospitalizations of pregnant women for respiratory illness, although these studies are not based on laboratory-confirmed influenza hospitalizations (34). Rates of hospitalization for respiratory illness were twice as common during influenza season. The risk for hospitalization increases significantly with latter stages of pregnancy where the relative risk is approximately 5-fold compared to age-matched non-pregnant women. Pregnant women also have an increased number of medical visits for respiratory illnesses during influenza season compared with non-pregnant women.

**Morbidity of H1N1 infection in pregnant women.** From April 15 to May 18, 2009, 34 confirmed or probable cases of pandemic H1N1 in pregnant women were reported to Centers for Disease Control & Prevention (CDC) (34;35). Eleven (32%) women were admitted to the hospital. The estimated rate of admission during the first month of the outbreak was higher than it was in the general population (0·32/10^5 pregnant women, 95% CI 0·13–0·52 vs. 0·076/10^5 population at risk, 95% CI 0·07–0·09). Furthermore, this comparator rate for non-pregnant individuals includes many that had other risk factors for severe influenza, suggesting that the risk imposed by pregnancy is an underestimate compared to otherwise healthy young women. Nearly half of the women were Hispanic and a fifth was nulliparous. Nine (26%) women were in the third trimester. By June 16, 2009, six deaths in pregnant women were reported to the CDC
(out of 45 total deaths; i.e., 13% of the deaths). Of the pregnant women who died, one was in the first trimester, one in the second trimester, and four were in the third trimester. All the women were fairly healthy before their influenza illness. All deaths were the result of pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation.

**Influenza in HIV-1 infected patients.** HIV-1 infected patients not only suffer the morbidity typical of seasonal influenza and potential interference with their HIV therapy, but there is also the potential for influenza infection that is more severe than that typical of age-matched uninfected people (36,37). The antibody responses to seasonal TIV are blunted in HIV-1 infected children and adults who are not receiving antiretroviral therapy (ART) (38-40). In patients who do not have progressive HIV-1 disease and/or are receiving highly active ART (HAART), these responses are improved (41-43). Efficacy of seasonal influenza vaccine has been established in four controlled trials (44).

**Vaccination of pregnant women to prevent influenza.** Serological studies of influenza vaccines in pregnant women suggest that their antibody response is similar to that of non-pregnant women. In the 1970s, two studies were conducted with inactivated “Swine Flu vaccine” (monovalent influenza A/New Jersey/8/76) administered to 115 pregnant women. In one study, 59 pregnant women and 27 non-pregnant women were enrolled. When data was age matched (age 24-34) for subjects who attained an HAI titer $\geq 20$, no significant difference was found in response to the vaccine antigen – approximately 65-70 seroconversion in both groups (45). However, when the total patient population was analyzed, regardless of age, a significantly lower geometric mean titer was found in pregnant vaccinees compared to non-pregnant vaccinees. The disparity in antibody response might be explained by the younger age of pregnant vaccinees (mean age, 24.3) as compared to non-pregnant vaccinees (mean age, 30.7), but more likely also indicate that the pregnant vaccinees were less responsive to the new influenza virus hemagglutinin. In another study of 56 pregnant women, the antibody response was similar to non-pregnant adults that participated in national vaccine trials. Of the maternal sera available at delivery, 19/26 (73%) had a titers of $\geq 20$ to the vaccine antigen (46).

Preliminary results are available from an ongoing study at the University of Colorado Denver and The Children’s Hospital Immunodeficiency Program comparing immune responses to seasonal influenza vaccines of HIV-infected and uninfected pregnant women. Sera were collected before and 6 weeks after immunization and antibodies were measured for the 3 serotypes contained in the vaccine. Both HIV-1 infected and uninfected women had significant increases in HAI titers at 6 weeks post-
immunization (p=0.02 for both groups). However, uninfected women had more robust antibody responses to the seasonal TIV than HIV-1 infected pregnant women (Fig 1).

Immunization of pregnant women against seasonal influenza (TIV) is currently recommended by the Advisory Committee on Immunization Practices of the CDC (47). The safety of TIV during pregnancy has been previously demonstrated (48).

Figure 1: HAI responses to seasonal TIV in HIV-1 infected and uninfected pregnant women. Data were derived from 14 HIV-1 infected and uninfected women immunized with seasonal TIV during pregnancy as per CDC recommendations.

**Effect of maternal immunization on influenza in infants.** In addition to the protection provided to mothers, influenza vaccination provides benefit, either directly or indirectly, to infants. In a randomized study in Bangladesh, seasonal influenza vaccine reduced proven influenza illness by 63% in infants aged 6 months or younger born to recently immunized mothers compared to infants born to unimmunized mothers (49).

Guillain-Barré Syndrome (GBS) associated with influenza vaccine. Guillain-Barré Syndrome has not typically been considered a complication of seasonal influenza vaccination. However, an excess of Guillain-Barré Syndrome was reported in association with the novel 1976 swine influenza strain that prompted mass immunization in preparation for a possible pandemic (50;51). This experience will dictate certain features of the safety assessment planned for this protocol.

This protocol has been developed in collaboration with the Department of Microbiology and Infectious Diseases. DMID has sponsored a parallel study of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** in pregnant women (≥14 to <34 weeks gestation) in the United States. Vaccine timing, immunogenicity assays and vaccine safety will occur in parallel across the two studies.
Preliminary immune response results from ongoing studies of the Influenza A (H1N1) 2009 Monovalent Vaccines are now available. In general, the preliminary immune response data available from approximately 350 adult subjects, 18 – 64 years of age enrolled in studies of the influenza A (H1N1) 2009 Monovalent Vaccine show that at 21-29 days after intramuscular (IM) administration of one dose of 15µg HA/strain, between 60 and 80% of subjects achieved either a titer of 1:40 or greater (for those seronegative at baseline), or a fourfold or greater rise from baseline (for those seropositive at baseline). Differences in immune response between the 15µg HA/strain and 30µg/strain dose levels have not been identified.

Updated results from clinical trials can also be found at the CDC website: http://www.cdc.gov/H1N1FLU

1.2 Rationale

1.21 Overview

1. Pregnant women are at increased risk of influenza illnesses in general and have been identified at very high risk of severe illness and mortality from the 2009 H1N1 Influenza A virus.
2. HIV infection increases the risk of complications from influenza infection, especially secondary bacterial infections.
3. Prior swine flu vaccine data (1976) suggests that pregnant women appear to have lower antibody response as compared to non-pregnant vaccinees.
4. HIV-infected pregnant women have lower antibody response to seasonal flu vaccine than HIV-uninfected pregnant women.
5. Data with other vaccines such as Hepatitis B vaccine (HBV vaccine) has suggested that increasing antigen titer of the vaccine dose improves antibody response in HIV infected individuals. Higher doses of inactivated vaccine (HBV vaccine) have been shown to improve antibody response in HIV-infected youth.
6. Data from other populations suggests an increased antibody response to higher dosed seasonal influenza vaccine.
7. The P1086 study team believes that HIV-1 infected pregnant women are at extremely high risk of severe illness and death from the 2009 H1N1 Influenza A virus. Both their HIV infection and their pregnancy increase their risk of poor response to doses of vaccine that are immunogenic in other populations. Use of higher dose (30mcg) of inactivated Influenza A (H1N1) 2009 monovalent vaccine in this study of HIV-1 infected women will achieve scientific objectives of timely assessment of safety and
immunogenicity in these high-risk populations while maximizing the potential for study participants to be protected by study vaccine from 2009 H1N1 Influenza A virus this season.

1.22 Justification Discussion

It is very likely that the continuing epidemic spread of H1N1 infection in the US will greatly increase in the fall-winter season when social interactions and climactic conditions are especially conducive to spread of influenza viruses. Women of childbearing age lack antibody that will interact with the HA of the pandemic strain and neutralize it, and thus they lack measurable protection against this influenza virus.

Pregnant women are at an increased risk for the complications of influenza. This risk is likely to increase for pregnant women that are also infected with HIV-1, especially if their HIV infection is poorly controlled, and they have perhaps only recently been started on antiretrovirals the most feasible approach to mitigate potential complications from the pandemic strain in these women is to administer a safe and immunogenic vaccine prepared against this strain. Seasonal influenza vaccines have been efficacious in HIV-1 infected patients in the past, although they have not been sufficiently evaluated in a pregnant cohort.

TIV vaccination of HIV-infected individuals before HAART has been associated with transient increases in HIV viral load in 4-18% of individuals (52;53). This may be related to T cell activation (54), and/or down regulation of CMI (55). Increases in HIV viral load are less common in individuals on antiretrovirals (ART), with CD4+ counts of 200-500 cells/ml at vaccination, and generally are not considered clinically significant (42;56-59). Other vaccines, including tetanus toxoid, reportedly have similar adverse effects in HIV-infected individuals. These effects do not constitute a contraindication to vaccination, but it is important to establish the magnitude of the problem or the lack thereof when studying immunization of HIV-infected pregnant women, because of the high association between the maternal HIV viral load and HIV vertical transmission.

In an ongoing study at the University of Colorado Denver and The Children’s Human Immunodeficiency Program comparing immune responses to seasonal influenza vaccines in HIV-1 infected and uninfected pregnant women showed that HIV-1 infected pregnant women had significant antibody increases in response to seasonal influenza vaccines. We, therefore, surmise that HIV-1 infected pregnant women may produce specific antibodies in response to the administration of the pandemic inactivated Influenza A (H1N1) 2009 monovalent vaccine. However, we
anticipate the antibodies will be of lower titer than uninfected non-pregnant populations. Being both HIV-1 infected and pregnant are risk factors for having lower immune defenses.

The study team anticipates widespread infection with H1N1 during the study. Therefore, it is imperative that this study not only be completed as soon as possible but also evaluates a vaccine dose that is most likely to produce a high titer protective response in this high risk population. Since women of childbearing age have had no prior exposure to the pandemic strain of influenza it will be necessary to immunize with two doses of the vaccine. This study will assess the safety and immune response following each of the two doses of inactivated *Influenza A (H1N1) 2009 monovalent vaccine*. A higher titer dose vaccine (30mcg) will be evaluated, since the target populations are at risk for sub-optimal responses to the lower dose of vaccine. Time constraints and available subject sample size will not support a dose-ranging study. It is also likely that in this population the risk-benefit ratio supports use of the higher dose of vaccine.

Data are not currently available on either dose of the inactivated *Influenza A (H1N1) 2009 monovalent vaccine*; however, in view of prior influenza vaccine studies in pregnant women suggesting lower response rates and HIV-1 infected individuals having confirmed lower responses, we feel it is justified to use the higher titer dose.

If any data becomes available to indicate if a dose of 30mcg is not optimal, we will consider amending the protocol to evaluate another dose.

Safety is being evaluated prior to mass vaccination to be certain that inactivated *Influenza A (H1N1) 2009 monovalent vaccine* is safe in HIV-1 infected pregnant women. Efficacy evaluation is not a primary objective of this protocol. HAI antibody responses will be evaluated as the magnitude of these responses has been correlated (in uninfected and non-pregnant vaccinees that received seasonal TIV) with protection against influenza infection and/or disease.

The immunologic assessment will focus on:

1) The number of vaccines achieving a predefined “protective level” (1:40 in the HAI assay as established per seasonal influenza vaccine).

2) Induction of specific B and T cell-mediated immunity (CMI).

3) Persistence of these responses.

Influenza-specific memory B cells are evaluated because they are key elements for antibody persistence. HIV-1 infected individuals with or
without HAART tends to produce lower titers of specific antibodies in response to vaccines and also lose specific antibodies faster than HIV-1 uninfected individuals. The pathogenesis of the antibody loss is incompletely understood, but is related to a defect in the generation of memory B cells. CMI is being evaluated because it may play a large role in recovery from influenza infection, and this response to a novel vaccine may be especially problematic in HIV-1 infected pregnant women. Furthermore, with a virus that may predominantly replicate in the lower respiratory tract, it is important to verify that cytotoxic T lymphocytes (CTL) are being generated by the vaccine, because animal models have clearly established an association between influenza-specific CTL and clearance of influenza viruses from the lungs. P1086 will include immunologic measurements at 3 months and 6 months (in a subgroup of subjects) after delivery, thereby providing an evaluation of the persistence of immune responses.

Transplacental antibody transfer and persistence of maternal antibodies in the infant are measured at delivery (cord blood) 3 months and 6 months, respectively. Transplacental antibody transfer may be impaired in HIV-1 infected women by low production of specific antibodies in response to the vaccine and by their high titer of nonspecific IgG, which competes for the IgG transport sites in the placenta. Hence, it is extremely important to determine the level of transplacental influenza-specific IgG transfer to the infant and persistence of this antibody during the first 6 months of life. During these first 6 months, infants cannot be vaccinated with the seasonal TIV vaccine, nor is antiviral prophylaxis generally recommended due to lack of safety data. Antiviral prophylaxis in the younger age group may be considered, however, under special circumstances. Thus, to inform this decision we will determine the extent to which infants born to HIV-1 infected mothers receive potential passive protection as a result of their mothers having been immunized with an inactivated Influenza A (H1N1) 2009 monovalent vaccine.

1.3 Potential Risks and Benefits

1.31 Potential Risks

Clinical trials to evaluate Novartis and other manufacturer’s unadjuvanted and adjuvanted, inactivated Influenza A (H1N1) 2009 monovalent vaccine have been initiated. Due to the similarity of the starting material, manufacturing product and composition of the final container product, it is expected that the adverse event (AE) profile of inactivated H1N1 influenza vaccines will be similar to similar licensed influenza vaccines.
Occasionally, adult recipients of influenza vaccines may develop reactions such as fever, body aches, headache, malaise, myalgia, and/or nausea. These may occur more frequently in people who are given the higher dose level of vaccine. These reactions are usually greatest within the first 24 hours after vaccination and last 1 to 2 days. Some subjects may develop reactions at the site of vaccination (redness, swelling, pain, or tenderness). Analgesics (e.g., acetaminophen) and rest will generally relieve or moderate these symptoms. These reactions should go away in 1 to 4 days and should not require additional treatment.

Acute and potentially life-threatening allergic reactions are also possible. Very rarely, occurring in about 1 in 4 million people given a vaccination, there can be a serious allergic reaction to a vaccine. These reactions can cause skin rash (hives), difficulty breathing, swelling around the mouth, throat, or eyes, a fast pulse, sweating, or loss of blood pressure. If these reactions occur they can usually be stopped by the study staff giving emergency medications. As with any vaccine or medication, there is a very small chance of a fatal reaction, although researchers do not expect this to occur.

Guillain-Barré Syndrome (GBS) is an acute inflammatory neuropathy characterized by weakness, hyporeflexia or areflexia, and elevated protein concentrations in cerebrospinal fluid. The rate of Guillain-Barré Syndrome was significantly increased in individuals receiving the 1976 Swine Influenza (H1N1) vaccine at about 1 per 100,000 vaccine recipients. This has not been seen consistently with other influenza vaccines. Most persons who develop Guillain-Barré Syndrome recover completely, although the recovery period may be as little as a few weeks or as long as a few years. About 30% of those with Guillain-Barré Syndrome still have residual weakness after 3 years and about 3% may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack. Intensive surveillance of Guillain-Barré Syndrome after administration of inactivated influenza vaccines since 1976 has shown a slight increase in risk over background cases (more than one additional case of Guillain-Barré Syndrome per million persons) following vaccination, typically with onset within 6 weeks after vaccination. Interestingly, although vaccination rates have increased in the last 10 years the numbers of reported cases of vaccine-associated Guillain-Barré Syndrome have declined. It is unknown if the currently produced Novartis and other manufacturer’s, unadjuvanted and adjuvanted, inactivated *Influenza A (H1N1) 2009 monovalent vaccine* will result in the incidence of Guillain-Barré Syndrome that was seen.
with the 1976 vaccine product as the mechanism leading to this response has not been completely elucidated.

There may be other unknown risks of participation. The risk to the fetus/infant is unknown because animal reproduction studies with the vaccine have not been conducted. There may be other unknown side effects. This protocol would most likely be categorized as more than minimal risk with possible direct benefit.

Babies under 6 months of age are not eligible to receive influenza vaccines, thus any protection that they may receive will be directly related to maternal vaccinations and transmission of protective antibodies across the placenta. We believe that babies born to HIV-1 infected mothers on this study may receive benefit from maternal vaccinations. Cord blood, as well as infant blood at 3 and 6 months of age will be used to evaluate for the presence of circulating antibodies to both H1N1 study vaccine as well as seasonal influenza (in mothers who were also vaccinated with seasonal TIV).

Known Potential Benefits

It is possible that vaccination with the inactivated **Influenza A (H1N1) 2009 monovalent vaccine** will result in some protection against infection caused by the H1N1 virus, and may or may not provide protection against a serious infection with H1N1 influenza, should the virus be contracted. The duration of any such protection is currently unknown. In addition, there may be potential protection from H1N1 influenza illness in the infant from passive antibody transfer. However, the inactivated **Influenza A (H1N1) 2009 monovalent vaccine** is not expected to offer protection against circulating seasonal influenza.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To assess the safety after each of two doses of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** in HIV-1 infected pregnant women.

2. To assess the antibody response after each of two doses of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** in HIV-1 infected pregnant women.
2.2. Secondary Objectives

1. To assess the maternal level of 2009 H1N1 Influenza A virus specific antibodies at delivery, as well as at 3 and 6** months post delivery, following administration of two doses of inactivated Influenza A (H1N1) 2009 monovalent vaccine to HIV-1 infected pregnant women.

2. To assess the extent of placental transport of 2009 H1N1 Influenza A virus specific antibodies from mother to the infant by measuring antibodies in maternal blood and cord / infant blood.

3. To assess the persistence in the infant of maternal 2009 H1N1 Influenza A virus specific antibodies at 3 and 6** months of age.

4. To assess maternal CMI responses to the inactivated Influenza A (H1N1) 2009 monovalent vaccine.

5. To assess maternal and infant antibody titers to the seasonal (2009-2010) trivalent influenza vaccine (TIV).

6. To explore factors related to HIV and its treatment that might affect the responses to H1N1 vaccinations.

**First 50 evaluable mother-infant pairs

3.0 STUDY DESIGN

This is a multi-site, open label, Phase II study in 130 HIV-1 infected > 18 years and ≤ 39 years old, pregnant women in their second or third trimester (≥ 14 weeks and < 35 weeks of gestation) and their infants. This study is designed to investigate the safety, reactogenicity, and immunogenicity of a two dose regimen of Novartis unadjuvanted and inactivated Influenza A (H1N1) 2009 monovalent vaccine.

Note: Other manufacturers, unadjuvanted and adjuvanted, inactivated Influenza A (H1N1) 2009 monovalent vaccine may be studied as part of this protocol in the future.

STEP I: Subjects who meet the entry criteria for the study will receive an initial dose of 30 mcg, given as TWO 15mcg IM injections, of inactivated Influenza A (H1N1) 2009 monovalent vaccine at Day 0.
STEP II: Eligible subjects will receive a second dose of 30 mcg given as TWO 15mcg IM injections, inactivated Influenza A (H1N1) 2009 monovalent vaccine at Day 21 (+ 7 days, no earlier than Day 21) post first vaccination.

The schedule of laboratory and clinical evaluations for this study is outlined in Appendix IA “Maternal Schedule of Evaluations”, IB “Infant Schedule of Evaluations” and IC “Maternal Schedule of Evaluations for Delivery Prior to Dose #2.

NOTE: Other H1N1 influenza vaccines are currently under study in HIV-1 positive, pregnant and non-pregnant populations. These vaccines include both 15mcg and 30mcg doses of adjuvanted and unadjuvanted, inactivated Influenza A (H1N1) 2009 monovalent vaccine from Novartis, as well as vaccines from other manufacturers. If a different preparation is found to be sufficiently safe and immunogenic as a result of other ongoing NIH trials, an additional cohort of HIV-1 positive pregnant women may be added to the P1086 study. However, this study will complete enrollment and vaccination of the subjects at the 30 mcg dose of Novartis study vaccine. Subjects will be followed as per the Schedule of Evaluations described in Appendix IA, IB and IC.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

Approximately 130 HIV-1 infected pregnant women, > 18 years to < 39 years old, in their second or third trimester (≥ 14 weeks to < 35 weeks of gestation) will be enrolled at sites located in various geographic locations at NIAID and NICHD sites throughout the United States and Puerto Rico. The local Institutional Review Boards (IRBs) will approve all materials prior to their use.

4.1 Inclusion Criteria for Study Entry (Step I)

4.11 HIV-1 infection, defined as 2 positive test results obtained from 2 different samples. Tests may include two of the same type OR two different types of tests listed below, as long as there are 2 positive test results obtained from 2 different samples:
- HIV-1 antibody (ELISA and WB)
- HIV-1 culture
- HIV-1 DNA PCR
- HIV-1 RNA PCR > 1,000 copies/ml
- Neutralizable HIV-1 p24 antigen

4.12 Pregnant female ≥ 18 years and ≤ 39 years.

4.13 ≥14 weeks and < 35 weeks of gestation.
4.14 Subjects should have a documented platelet count of >50,000 mm$^3$ and an ANC of >500 mm$^3$ within the 28 days prior to study entry.

4.15 Able to understand and comply with planned study procedures.

4.16 Provides written informed consent prior to initiation of any study procedures.

4.17 Subject should be on antiretroviral therapy as outlined in the treatment guidelines for pregnant HIV-1 infected women. Women must be currently taking ART or should initiate ART either prior to or concomitantly with, the first dose of the vaccine.

Note: HIV-1 infected women who are pregnant should be treated according to the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States: Tables - April 29, 2009 (http://www.aidsinfo.nih.gov/Guidelines/)

4.2 Exclusion Criteria for Study Entry (Step I)

4.21 Has a known allergy to eggs, egg products, neomycin or polymyxin

4.22 Has a history, in the opinion of the site investigator, of severe reactions following previous immunization with seasonal TIV.

4.23 Participation in a novel H1N1 influenza vaccine study in the past two years.

4.24 Proven history, by RT-PCR, of novel influenza H1N1 infection, or, has a positive influenza diagnostic testing since June 2009 (specificity to H1N1 not required) prior to study entry.

4.25 Received any other live licensed vaccine within 4 weeks or inactivated licensed vaccine within 2 weeks prior to study entry.

4.26 Received a non-licensed agent (vaccine, drug, biologic, device, blood product, or medication) within 4 weeks prior to vaccination in this study, or expects to receive another non-licensed agent before delivery.

4.27 An acute illness and/or an oral temperature greater than or equal to 100.0°F within 24 hours prior to study entry.
4.28 Use of anti-cancer chemotherapy or radiation therapy within the preceding 36 months of study enrollment, or has immunosuppression as a result of an underlying illness or treatment (other than HIV-1 infection).

4.29 Active neoplastic disease (excluding non-melanoma skin cancer, and HPV-related cervical dysplasia, CIN grades 1, 2 or 3).

4.210 Long term use of glucocorticoids, including oral or parenteral prednisone or equivalent (≥ 2.0 mg/kg per day or ≥ 20 mg total dose) for more than 2 consecutive weeks (or 2 weeks total) in the past 3 months, or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the past 3 months (nasal and topical steroids are allowed).

4.211 Received immunoglobulin or other blood products (with exception of Rho D immune globulin) within the 3 months prior to enrollment in this study.

4.212 Current diagnosis of uncontrolled major psychiatric disorder.

4.213 History of Guillain-Barré Syndrome in the subject or subject’s family (parents, siblings, half siblings, or children).

4.214 Onset of a neurological disorder including (but not limited to) absent ankle and patellar deep tendon reflexes (DTRs) in both legs (all four absent) within the past 6 months.

4.215 Disproportionate loss of strength in lower extremity or extremities, compared to the upper extremities (not thought to be related to pregnancy) within the past 6 months.

4.216 Any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

NOTE: Pregnancy complications such as pre-term labor, hypertension and pre-eclampsia are not exclusion criteria for this study.

4.3 Inclusion Criteria for Step II

4.31 Received the first dose of inactivated Influenza A (H1N1) 2009 monovalent vaccine.

4.32 Has a documented platelet count of >50,000 mm$^3$ and an ANC of >500 mm$^3$ within the 28 days prior to Step II entry.
4.4 Exclusion Criteria for Step II

4.41 Received a non-licensed agent (vaccine, drug, biologic, device, blood product, or medication), other than from participation in this study, since the study vaccine dose #1, or expects to receive another non-licensed agent before delivery.

4.42 Use of anti-cancer chemotherapy or radiation therapy since study vaccine dose #1, new diagnosis of an active malignancy, or is immunosuppressed as a result of an underlying illness (other than HIV-1 infection) or treatment.

4.43 Use of glucocorticoids, including oral or parenteral prednisone or equivalent (≥ 2.0 mg/kg per day or ≥ 20 mg total dose) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) for more than 2 consecutive weeks (or 2 weeks total), since study vaccine dose #1.
NOTE: Nasal and topical steroids are allowed.

4.44 Received immunoglobulin or other blood products (with exception of Rho D immune globulin) since study vaccine dose #1.

4.45 A new diagnosis of uncontrolled major psychiatric disorder since study vaccine dose #1.

4.46 New occurrence or new awareness of Guillain-Barré Syndrome in the subject or subject’s family (parents, siblings, half siblings, or children) since study vaccine dose #1.

4.47 A new onset of a neurological disorder including (but not limited to) absent ankle and patellar DTRs in both legs (all four absent) since study vaccine dose #1.

4.48 Disproportionate loss of strength in lower extremity or extremities, compared to the upper extremities (not thought to be related to pregnancy) since study vaccine dose #1.

4.49 Any Grade 3 toxicity or AE experienced by a subject unless the investigator has received protocol team approval.

4.410 Any Grade 4 toxicity or AE (other than injection site reaction or fever) that is definitely, probably or possibly related to the study vaccine dose #1.
4.411 Any Grade 4 injection site reactions or fever experienced by a subject, unless the investigator has received protocol team approval.

4.412 Any Grade 4 AEs that are definitely not or probably not related to study vaccine, unless the investigator has received protocol team approval.

4.413 Any new clinical findings since the study vaccine dose #1, which in the investigator’s opinion, would compromise the safety of the subject.

4.414 Subject refuses further vaccination. The subject will still be asked to complete safety visits and be followed in the study.

4.415 Subject withdraws consent. The subject may withdraw their consent for study participation at any time and for any reason, without penalty.

4.5 **Concomitant Medication Guidelines**

Administration of any medication, therapies or vaccines will be documented in the study case report forms (CRFs). Concomitant medications will include all medications taken during the following periods: within the 28 days prior to enrollment through end of study or early termination, whichever occurs first.

4.51 **Vaccines**

Receipt of any vaccines besides the study product will be collected throughout the study from enrollment to the off study visit. The administration of inactivated licensed vaccines, including inactivated seasonal influenza vaccine (TIV), should be at least 2 weeks (14 days) prior to the first dose of the *Influenza A (H1N1) 2009 monovalent vaccine* OR delayed until 21 days after the second dose of study vaccine has been administered.

The administration of live licensed vaccines, including seasonal cold-adapted live influenza vaccine, should be at least 4 weeks (28 days) before the first dose of the inactivated *Influenza A (2009) monovalent vaccine* OR delayed until 21 days after the second dose of study vaccine has been administered.

*The 2009-2010 seasonal TIV is recommended for all pregnant women and should be given as outlined in this section.*
If administration of the seasonal flu vaccine outside of the windows described above is necessary for clinical care, the investigator should notify the protocol team at actg.teamp1086@fstrf.org.

Allowable vaccines administered to the mother pre-partum include inactivated TIV (see above) and post-partum include diphtheria, tetanus and pertussis vaccine and measles, mumps and rubella vaccine. Any vaccines deemed necessary per the site investigator are also allowed.

4.52 Disallowed / Precautionary Medications

The following medications should be avoided, if possible, and alternative treatments sought. Medications that might interfere with the evaluation of the vaccine should not be used unless absolutely necessary. Medications in this category include, but are not limited to:

- Glucocorticoids, i.e., oral, parenteral and high-dose inhaled steroids,
- Immunosuppressive or cytotoxic drugs.

Please contact the protocol team at actg.teamp1086@fstrf.org if treatment with any of these medications, is necessary for clinical care.

4.53 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration
process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RCC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.


4.54 Management of Pre-term Delivery

Any women who deliver before the second dose of study vaccine will receive study vaccine dose #2 after they deliver. These women will continue to be followed as per the schedule of evaluations (Appendix IC). For statistical analysis, these women will be placed into a non-evaluable category for the primary immunogenicity objective but immunogenicity and safety data will continue to be recorded and evaluated. Preterm delivery data will also be collected and will be reported.

4.55 Co-enrollment Procedures

Co-enrollment is encouraged, except for protocols that would violate the exclusion criteria. All co-enrollments with IMPAACT P1025 do not require prior P1086 team approval. Co-enrollments into interventional studies will require approval from both protocol chairs.
5.0 STUDY TREATMENT

All eligible subjects will receive the inactivated Influenza A (H1N1) 2009 monovalent vaccine at Day 0. If eligible, subjects will receive a second dose of the study vaccine at Day 21 (+ 7 days).

5.1 Drug Regimens and Administration

5.11 Regimen

**Step I (DAY 0):** Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine 30 mcg administered as two-0.5mL (15mcg) injections intramuscularly.

**Step II (DAY 21 [+ 7 days]):** Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine 30 mcg administered as two-0.5mL (15mcg) injections intramuscularly.

Subjects must be registered to Step II through the SDAC/DMC randomization system. A new prescription with the new SID number must be written for the pharmacist to dispense the second dose of the study vaccine.

5.12 Preparation and Administration

The Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine will be provided in pre-filled syringes.

Note: If another product becomes available that requires additional preparation (e.g., single-dose vials) prior to administration or if the pre-filled syringes are no longer available, refer to the table below for injection site and needle length guidelines.
Injection Site and Needle Size

<table>
<thead>
<tr>
<th>Age</th>
<th>Needle Length</th>
<th>Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teens (18 years)</td>
<td>5/8” – 1”</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td></td>
<td>1” – 1 ¼”</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>Female Adults (19 years or older)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 130 lbs</td>
<td>5/8” – 1”</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>130-200 lbs</td>
<td>1” – 1 ½”</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>200+ lbs</td>
<td>1 ½”</td>
<td>Deltoid muscle of arm</td>
</tr>
</tbody>
</table>

*A 5/8” needle may be used only if skin is stretched tight, subcutaneous tissue is not bunched, and injection is made at a 90-degree angle.

5.121 Novartis Pre-Filled Syringes

Two pre-filled syringes of Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine 15mcg/0.5mL will be required for the 30mcg dose. No reconstitution or dilution is necessary.

Administration

Two-0.5mL (15mcg) pre-filled syringes will be used to administer the total 30mcg dose. Two separate, individual injections will be required. The vaccine should be allowed to reach room temperature shortly before use. Shake the syringe before administering the vaccine.

It is recommended that when using the pre-filled syringe, 0.5mL (15mcg) is injected into one of the subject’s deltoid muscles, with the second pre-filled syringe of 0.5mL (15mcg) administered into the other deltoid muscle. However, if the subject requests that both vaccine injections be given in the same deltoid muscle, the injections must be given at least 2 inches apart (see Appendix IA and IC).

A total of 1mL (30mcg), divided into two-0.5ml (15mcg) injections (pre-filled syringes), must be administered to complete the total vaccination dose.

This product should not be administered intravenously, subcutaneously, or intradermally.
5.2 Drug Formulation

5.21 Novartis Vaccine Pre-filled Syringes

The Novartis unadjuvanted inactivated **Influenza A (H1N1) 2009 monovalent vaccine** is supplied in a single-dose, pre-filled syringe of 0.5mL at a concentration of 15mcg / 0.5mL.

The Novartis unadjuvanted inactivated **Influenza A (H1N1) 2009 monovalent vaccines** must be stored at 2° to 8° C (35° to 46°F), **protected from light**. DO NOT FREEZE. Product that has been exposed to freezing should not be used. For additional information regarding formulation, packaging, and stability please refer to the Investigator’s Brochure.

5.3 Dose Modifications

There will be no dose modifications. Subjects who do not receive the second vaccination will be asked to return for safety assessments and for scheduled blood sample collections for immunogenicity assessments.

5.4 Drug Supply, Distribution and Pharmacy

The Novartis unadjuvanted inactivated **Influenza A (H1N1) 2009 monovalent vaccine** is manufactured by Novartis, Inc and is being provided by the Biomedical Advanced Research and Development Authority (BARDA).

Study product will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT pharmacist can obtain study product for the protocol by following the instructions in the manual “Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks” in the section entitled “Study Product Management Responsibilities”.

The NIAID CRPMC will not provide antiretroviral therapy (e.g., HAART), seasonal trivalent influenza vaccine, syringes or supplies for administration of vaccines as part of this study.

The IMPAACT pharmacist is required to maintain complete records of all study vaccine received from the NIAID CRPMC and subsequently dispensed. All unused study vaccine must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are given in the manual, “Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks” in the section “Study Product Management Responsibilities”.

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6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, Clarification August 2009, must be used and is available on the RCC web site (http://rcc.tech-res.com/safetyandpharmacovigilance/).

- ALL Grades of adverse events should be recorded on the appropriate CRF.

- The site investigator must receive permission from the study team (actg.teamp1086@fstrf.org) before giving the second vaccination for the following events:
  - All Grade 3 adverse events
  - All Grade 4 injection site reactions or fever
  - All Grade 4 adverse events that are definitely not or probably not related to study vaccine

- For Grade 4 adverse events, other than a local injection site reaction or fever that are definitely, probably or possibly related to study vaccine, the second study vaccination should not be given.

If you have questions, please contact the study team at actg.teamp1086@fstrf.org

6.2 Study Management Plan

Screening and entry visits may be completed on the same day.

Subjects will remain in the clinic for at least 30 minutes after each vaccination so that clinic personnel can observe for any potential adverse reactions to the vaccine. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction.

Antipyretics should not be routinely given in anticipation of adverse events after vaccination, but should not be withheld if symptoms occur. Antipyretics should be recorded on the memory aid and reported to the site staff.

Subjects will be contacted on Day 2 and Day 10 post first vaccination, and then again on Day 2 post second vaccination (see Appendix IA).
Data about mothers and infants related to delivery will be collected and recorded. In addition, mothers and infants will be contacted at 3 months and 6 months post delivery. Only the first 50 evaluable women who have received the two doses of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** within 28 days and immunogenicity evaluations post first dose, will be asked to come back to clinic for an in person visit at 6 months. All other women will be contacted by telephone at 6 months. See Appendix IA.

Subjects will be asked to come into clinic for a sick visit within 72 hours if they show any signs of fever >100.0°F and/or symptoms of an influenza-like illness (ILI) such as coryza, sore throat, cough, or pneumonia (see Appendix IA). Respiratory specimens will be collected at this visit.

**If a subject experiences documented H1N1 infection, as defined in Section 4.24, between Step I and Step II of the protocol, the subject should NOT receive the second dose of vaccine but should continue to be seen at the scheduled study visits, and have blood collected, as per the Schedule of Evaluations.**

It is anticipated that vaccine-associated AEs will occur frequently, but will be minor local reactions and side effects that will rarely necessitate interruption of the vaccination schedule. All AEs must be documented in the study CRFs. Management of AEs will be according to the best clinical practice and the judgment of the site investigator. If a subject exhibits signs of a vaccine related reaction, the subject will be requested to return to clinic within 72 hours.

**NOTE:** A clinic visit is required within 24 hours if any response during a telephone query describes a new onset of weakness of legs, tingling of hands and/or feet, or difficulty walking.

Data will be collected at all visits (in clinic and by phone) for any signs and symptoms related to Guillain-Barré Syndrome, and other serious adverse events such as:

- Death (will be obtained from the medical record)
- Life threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Weakness of legs
- Tingling of hands and/or feet
- New onset of difficulty walking not related to pregnancy
The Guillain-Barré Syndrome monitoring tool questionnaire to be completed at the clinic may be accessed by going to the www.fstrf.org website and clicking on the ‘QUALITY OF LIFE’ link.

6.3 **Criteria for Deferral of Second Dose of Vaccine**

If a subject meets any of the following criteria, the second dose of study vaccine should be deferred for up to 7 days. If this period elapses, the site must obtain prior approval from the study team to administer the second dose of study vaccine. If the second dose is not received, the subject will continue to be followed for the duration of the study according to Appendix IA. Any questions should be sent to the study team at actg.teamp1086@fstrf.org.

6.31 Presence of signs or symptoms that could confound or confuse assessment of vaccine reactogenicity.

6.32 Body temperature ≥ 100.0°F orally determined, within 24 hours prior to Step II entry.

6.33 Presence of a serious, acute non-bacterial or bacterial infection within seven days of vaccination.

6.34 For those patients who have received >6 -13 days of steroids, within the past 21 days, will require at least 14 days off of steroids prior to administration of the second dose of study vaccine. Under 6 days of steroids, no deferral of study vaccine is needed.

6.4 **Criteria for Permanent Discontinuation in the Study**

Criteria for discontinuation in the study are as follows:

- Loss to follow up.
- Subject withdrawal of consent.
- The investigator determines that further participation would be detrimental to the subject’s health or well-being.
- The subject fails to comply with the study requirements so as to cause harm to herself.

This study may be terminated for safety concerns of the PI, FDA, OHRP, DMID, DAIDS, the SMC or participating Institutional Review Boards or ethics committees, and other governmental agencies.
7.0 EXPEDITED ADVERSE EVENT REPORTING

Adverse Event Reporting to DAIDS

The adverse events (AEs) that must be reported in an expedited fashion to DAIDS Regulatory Compliance Center (RCC) Safety Office include all serious adverse events (SAEs) as defined by ICH guidelines regardless of relationship to the study agent(s).

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above must also be reported in an expedited timeframe to DAIDS. Such determination may be made through medical or scientific judgment [ICH E2A].

In addition to reporting all SAEs as defined above, other events that sites must report in an expedited fashion include:

- Symptoms of Guillain-Barre Syndrome such as tingling of hands and/or feet, weakness of legs and new onset of difficulty walking

For all SAE’s submitted to RCC, sites must file an updated SAE report to RCC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

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1 The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event.
2 Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting.

The following types of hospitalization do not require expedited reporting to DAIDS:

- Any admission unrelated to an AE (e.g. for labor/delivery, aging-related cosmetic surgery, administrative admission, or social admission for temporary placement for lack of place to sleep)
- Protocol-specified admission (e.g. for procedure required by protocol)
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) (unless it is a worsening or increasing in frequency as judged by the clinical investigator)

Note: A new AIDS-defining event in a subject already known to be HIV-infected would be considered a worsening of a pre-existing condition (HIV infection).
The study agents for which relationship assessments are required are Novartis inactivated Influenza A (H1N1) 2009 monovalent vaccine.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, Clarification August 2009, must be used and is available on the RCC web site (http://rcc.techres.com/safetyandpharmacovigilance/).

The protocol-defined expedited event reporting period for this protocol is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

After the end of the protocol-defined reporting period defined above, sites must report clinical events that are serious, unexpected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

The timelines and mechanisms for reporting all the events listed above to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in the “Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: http://rcc.techres.com/safetyandpharmacovigilance/ (and in study manual of Operations (MOP), if applicable).

Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow DAERS processes as outlined in DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within DAERS application itself.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: http://rcc.techres.com/safetyandpharmacovigilance/ (and the study MOP if applicable), and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase II study in HIV-1 infected pregnant women, designed to investigate the safety, reactogenicity, and immunogenicity of 2 doses of inactivated Influenza A (H1N1) 2009 monovalent vaccine given at 30 mcg (as TWO 15mcg doses), with an initial dose given prior to 35 weeks gestation and a second dose given 21-28 days after the initial dose. This study will generate descriptive data on whether:
1) The inactivated Influenza A (H1N1) 2009 monovalent vaccine is well tolerated;
2) It elicits adequate immune responses among pregnant women; and
3) It elicits potentially protective levels of antibodies transferred from mothers to their infants.

There are a number of issues which may have an impact on maternal response to the vaccine including: immune status at the time of first immunization, change in immune status during the pregnancy (especially among HIV-1 infected women previously untreated who have just been started on antiretroviral therapy in an attempt to prevent HIV transmission) and gestational age at the time of immunization. In addition, there will be women who receive the first immunization, but who deliver before the second can be administered. These factors may split the study sample into a number of subgroups whose adverse event rates, response to the vaccine or transfer of maternal antibodies to infants may differ. The study will not have an adequate sample size to provide precise estimates of immune response and adverse events rates for all subgroups which may exhibit differing results. Section 8.6 presents confidence intervals around potential subgroups of various sizes with a range of potential results to provide an indication of the precision with which these rates can be estimated.

The study will be monitored intensely by the protocol team, which will review data every other week while subjects are accruing and the vaccine is being administered; and at least once a month after the last dose of study vaccine is administered (See Section 8.5). A Safety Monitoring Committee (SMC) will be convened by IMPAACT to review safety information gathered from all study participants.

8.2 Endpoints and Outcome Measures

8.21 Primary Endpoints:

8.211 Adverse Events of Grade 3 or higher severity, including:

- Abnormal laboratory values, signs and symptoms or diagnoses.
- Solicited local AEs, including pain, tenderness, redness, and swelling post each vaccination.
- Solicited systemic AEs, including feverishness, malaise, body aches (exclusive of the injection site), nausea, and headache post each vaccination.
- Adverse pregnancy outcomes, including maternal, fetal and infant complications.
8.212 Adverse Events of Grade 3 or higher severity attributed to the study vaccine.

8.213 Second vaccine dose withheld, due to adverse reactions attributed to study vaccine dose #1.

8.214 Immunologic response, defined as HAI titer $\geq 1:40$, at 21 days after first dose and at 10 days after the second dose of study vaccine.

8.22 Secondary endpoints

8.221 Maternal immunologic response (HAI $\geq 1:40$) at 21 days after the second dose of study vaccine, delivery of the baby, and then 3 months and 6 months* after delivery.

8.222 Infant HAI $\geq 1:40$ at birth (via cord blood) and at 3 months and 6 months* of age.

8.23 Secondary response variables

8.231 Maternal Geometric Mean Antibody Titers (GMT) HAI following: 1) the first and second dose of the vaccine, 2) at delivery, 3) at 3 months post-delivery and 4) at 6 months post-delivery*.

8.232 Infant GMT HAI measured at birth and at 3 months and 6 months* of age.

*first 50 mother-infant pairs who received both of two doses of inactivated *Influenza A (H1N1) 2009 monovalent vaccine* and had a complete set of immunogenicity laboratory assays obtained prior to delivery, as per protocol

8.233 Maternal CMI responses, as measured by B-cell and T-cell ELISPOT values.

8.234 CD4 count at entry and at time of second dose.

8.235 HIV RNA copies/ml.

8.236 Response to seasonal TIV.

8.3 Randomization and Stratification

There will be no randomization or stratification.
8.4 Sample Size and Accrual

Approximately 130 pregnant women, \(\geq 18\) years and \(\leq 39\) years of age, in their second or third trimester (\(\geq 14\) weeks and \(< 35\) weeks of gestation), will be enrolled into this study for the purpose of gathering information on the safety and immunogenicity of the inactivated **Influenza A (H1N1) 2009 monovalent vaccine**. This sample size is expected to yield at least 100 evaluable* mother and infant pairs, which will provide reasonably precise estimates of rates of adverse events and immunogenic response.

The infants born to these women will also be enrolled into the study, yielding a total sample of approximately 130 mother/infant pairs, with evaluable data from at least 100 mothers and 100 infants. If the infant is not evaluable, the protocol team will continue to follow the mother to complete the data for the maternal secondary objectives.

Anticipated accrual for P1086 is 6 weeks, prior to and during the 2009-2010 influenza seasons.

* Evaluable mother-infant pairs are defined as having received two doses of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** and had samples for immunogenicity laboratory assays obtained prior to delivery, as per protocol.

8.5 Study Safety Monitoring

It is the responsibility of the Protocol Team to interpret safety data and make decisions regarding adverse events to protect subjects from undue risk. In addition, the IMPAACT Network will appoint a SMC to provide independent reviews to ensure subject safety. The SMC is composed of three clinicians and a statistician independent of the P1086 protocol team and vaccine manufacturer.

It is required that the data required for the toxicity reports be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

For safety monitoring, a vaccine related SAE is an SAE that is judged to be “definitely”, “probably” or “possibly related” to study vaccine.

Reports compiled by the Data Management Center (DMC) will be reviewed and discussed by the Protocol Team on biweekly conference calls while subjects are accruing and the vaccine is being administered. The Protocol Team will meet at least once a month after the last dose of study vaccine is given. Reports may also be reviewed by the SMC, if the need arises.
Adverse events will be monitored throughout the follow-up period. If the protocol team identifies any potentially treatment-related toxicity that may compromise subject safety, it will determine whether further enrollment and vaccinations will be paused. Should this occur, the SMC will review all relevant data and will determine whether, and under what conditions, the study will be allowed to proceed or will be stopped.

Further enrollment and vaccinations will be paused for SMC review and recommendation if any of the following are reported across ongoing NIH studies evaluating the 15mcg or 30mcg dose of the Novartis unadjuvanted, inactivated \textbf{Influenza A (H1N1) 2009 monovalent vaccine}.

- Any death occurring within the 10 days following administration of study vaccine that was not the result of trauma or accident.
- Any subject having laryngospasm, bronchospasm, or systemic anaphylaxis within 24 hours of administration of study vaccine.
- Two or more subjects with generalized urticaria associated with product administration within 72 hours of administration of study vaccine.
- Three or more subjects with ulcerations or abscesses associated with study vaccine administration.
- Any subject with any necrosis at the injection site.
- Any subject with a vaccine-related SAE, as per ICH guidelines listed in section 7.2.
- Any subject with acute weakness of limbs and or cranial nerve innervated muscles (description of potential signal of Guillain-Barré Syndrome).

The study will also be halted for SMC review and recommendation if, during the 10 days after each vaccination, any of the following occurs:

- 15\% or more (minimum of 2 if less than 20 subjects have been vaccinated) of the subjects enrolled in this study, experience the same severe (Grade 3 or higher by the DAIDS Toxicity Table) vaccine-related local reaction that interferes with daily activities. Dimensions of a local reaction are not included in stopping decisions.
- 15\% or more (minimum of 2 if less than 20 subjects have been vaccinated) of the subjects in this study experience the same severe (Grade 3 or higher by the DAIDS Toxicity Table) vaccine-related quantitative systemic reactions.
- 15\% or more (minimum of 2 if less than 20 subjects have been vaccinated) of the subjects enrolled in this study experience the same
severe (Grade 3 or higher by the DAIDS Toxicity Table) vaccine-related subjective systemic reactions, the severity (grade) of which is corroborated by study personnel.

If the study is stopped for any of the above reasons, the SMC will instruct the protocol team under what conditions the study would stop again for a repeat of the same reason.

8.6 Analysis

8.6.1 Primary Analyses

8.6.1.1 Safety

The proportion of mothers experiencing grade 3 or grade 4 adverse events following the first and second doses of vaccine will be presented. The precision with which this sample result estimates the rate of similar adverse events in the population represented by the study sample will be reported in terms of 90% confidence intervals (CI) around the sample proportions. This will provide 95% confidence that the rate of severe adverse effects is not greater than the upper limit of the CI around the proportion of subjects with grade 3+ events in the study sample.

Table 1 illustrates the confidence intervals for a range of hypothetical proportions of adverse events. This table shows (e.g.) that a sample finding of no grade 3 or grade 4 adverse events in a total evaluable sample of 100 subjects would provide 95% confidence that the rate in the population from which the sample was drawn is no greater than 3%. A similar finding within a subsample of 20 subjects would provide 95% confidence that the population rate was no greater than 14%.
Table 1: Exact 90% Confidence Intervals Around Potential Proportions of Subjects Exhibiting Grade 3+ Adverse Events (Total Sample and Selected Subsample Sizes)

<table>
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<th>N</th>
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<td>28%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>10%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>30%</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows the probability of detecting at least 1 adverse event of a given type and/or level of severity in the study sample, given a range of hypothesized rates in the population from which the sample was drawn. The table demonstrates that the probability of observing one or more events in a sample of 100 subjects is >87% with events whose population probabilities are at least 2%, while the probability of observing two or more events is >81% for events whose population probabilities are at least 3%.

Table 2. Probability of detecting Adverse Events

<table>
<thead>
<tr>
<th>True Event Rate in the Population Represented by the Study Sample</th>
<th>Probability of Observing Event(s) in the Study Sample (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 or more Event</td>
</tr>
<tr>
<td>0.5%</td>
<td>39%</td>
</tr>
<tr>
<td>1%</td>
<td>63%</td>
</tr>
<tr>
<td>2%</td>
<td>87%</td>
</tr>
<tr>
<td>3%</td>
<td>95%</td>
</tr>
<tr>
<td>4%</td>
<td>98%</td>
</tr>
<tr>
<td>5%</td>
<td>99%</td>
</tr>
</tbody>
</table>

8.612 Immunogenicity

The proportion of mothers meeting the criteria for immunologic response following the first and second doses
of vaccine will be presented. The precision with which this sample result estimates the rate of immunologic response rates in the population represented by the study sample will be reported in terms of 90% CIs around the sample proportions. This will provide 95% confidence that the rate of immune response is not less than the lower limit of the proportion of study subjects meeting immune response criteria.

The primary immunogenicity analysis will include all subjects having evaluable data. However, immunologic response rates may vary among subgroups of mothers who differ with respect to factors such as: 1) baseline immune status, 2) whether they have been on HAART for their own care or are just starting HAART to prevent transmission of HIV to their infant, 3) length of time on current HAART regimen, 4) weeks of gestation when receiving the first dose of vaccine, 5) age of the mother, and 6) whether the mother received the seasonal TIV before the study vaccine. Because of these factors, secondary analyses which focus on subgroups analyses may be of considerable interest.

Table 3: Exact 90% Confidence Intervals around Potential Proportions of Subjects Meeting Immunologic Response Criteria (Total Sample and Selected Subsample Sizes)

<table>
<thead>
<tr>
<th>N</th>
<th>Sample rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>25%</td>
<td>18%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>67%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>84%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>95%</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>40</td>
<td>25%</td>
<td>14%</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>61%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>79%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>95%</td>
<td>85%</td>
<td>99%</td>
</tr>
<tr>
<td>20</td>
<td>25%</td>
<td>10%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>54%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>72%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>95%</td>
<td>78%</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

Table 3 illustrates the confidence intervals for a range of hypothetical proportions of immunologic response. This table shows (e.g.) that a sample finding of 75 responders in the total sample of 100 subjects would provide 95% confidence that the rate in the population from which the
sample was drawn was no lower than 67%. If a subsample of 20 subjects exhibited a 75% response rate, this would provide 95% confidence that the population rate was no lower than 54%.

8.62 Key Secondary Analyses

Prediction of maternal immune response and transfer of maternal antibody to the infant are key issues to be addressed in secondary analyses. Since this is a new vaccine about which there is considerable uncertainty with respect to the distribution of antibody titers which it may elicit, alternative outcome variables will be explored. These include:

1) The log (10) HAI titer,
2) HAI titer >10, considered indicative of an immune response; and
3) HAI titer >40, which is considered to be likely to be protective.

The distribution of log (10) HAI titer will be examined to determine whether it satisfies the normality assumption required for linear regression analysis. If this is not true, then this method will be not be used. Since the other potential outcome variables listed above are categorical, the method of analysis for those outcomes will be logistic regression.

Factors predicting immune response will be examined on data collected after the first vaccination and, again, after the second. Predictors of maternal response will include factors such as: maternal CD4 count at baseline, maternal viral load at baseline; gestational age at the time of first vaccination and HAI titers to the seasonal influenza vaccine. Predictors of infant antibody levels will include: gestational age at time of first maternal vaccination, maternal HAI titers to the vaccine, whether the mother actually received both vaccinations or delivered before the second could be given, time to delivery after receiving the 2nd dose of study vaccine and an indicator of whether this was a full term delivery. Additional predictors may be explored as additional data concerning the H1N1 virus and the study vaccine become available.

Descriptive analyses examining CMI will make use of ELISPOT data reflecting B and T cell responses to the vaccine and of cytotoxic T cell lymphocyte (CTL) frequencies specific against 2009 H1N1 Influenza A virus and armed with homing receptors that will direct to the lungs. The distributions of baseline ELISPOT
values will be examined, and summary statistics including medians and interquartile ranges will be presented. The numbers of spot forming cells measured after the first and second doses of vaccine will be compared. The method of analysis will depend upon the distributions of the ELISPOT data and will consist of paired t-tests, if normality assumptions are met, and Wilcoxon Matched Pairs Signed Ranks tests, if they are not.

The persistence of memory B cells will be evaluated on specimens collected 3 and 6 months after delivery. The change in memory B cells from post-dose 2 measurement to 3 and 6 months after delivery will be evaluated by paired t-tests (or the Wilcoxon test if the data are not normally distributed) to determine whether a significant difference persists. Correlations between B and T cell ELISPOT values will be computed, along with correlations between these values and antibody titers. These will consist of Pearson correlations, if the data are normally distributed or Spearman correlations if normality assumptions are not met. The CTL analyses will consist of descriptive analyses at baseline and after each dose of vaccine. Comparison of CTL frequencies across the 3 time points will be made to determine whether the vaccine increases the percentage of CTL specific against H1N1 that have homing markers for the lung. As with the ELISPOT data, the method of analysis will be paired t-tests or Wilcoxon tests, depending upon whether normality assumptions are met.

9.0 HUMAN SUBJECTS

9.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix III), and any subsequent modifications must be reviewed and approved by the IRB responsible for oversight of the study. Written informed consent must be obtained from the subject. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject.

Each site that receives US HHS funding, will follow the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects. The plan should follow all IRB/EC, local, state and national guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.
9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee and by the study staff, and study monitors.

9.3 Exclusion of Women, Minorities and Children (Special Populations)

This study will be inclusive of pregnant adult women who meet the inclusion/exclusion criteria, regardless of religion or ethnic background. Only women who are 18–39 years old and are ≥ 14 to <35 weeks of gestation, inclusive, are eligible.

9.4 Study Discontinuation

The study may be discontinued at any time by the NIH, the FDA, OHRP, SMC, the IRB or Ethics Committee, or other governmental agencies as part of their duties to ensure that research subjects are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 BIOHAZARD CONTAINMENT

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory viruses are transmitted by droplet aerosolization and fomites. Appropriate blood and secretion precautions will be employed by all personnel in the collection of samples and the shipping and handling of all specimens for this study, as currently recommended by the CDC.

All infectious specimens will be transported in compliance with Federal Regulations and the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions and to the ACTN.
12.0 REFERENCES


(20) Keitel WA, Atmar RL, Nino D, Cate TR, Couch RB. Increasing doses of an inactivated influenza A/H1N1 vaccine induce increasing levels of cross-reacting antibody to subsequent, antigenically different, variants. J Infect Dis 2008; 198(7):1016-1018.


(25) Hammitt LL, Li S, Patterson-Bartlett J, et.al. Kinetics of viral shedding and immune responses to cold-adapted influenza vaccine. 10th International


## APPENDIX IA
### MATERNAL SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>STEP I</th>
<th>STEP II</th>
<th>STEP I &amp; STEP II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 2†</td>
<td>Day 10 (±3d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±1d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±3d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±3d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±1d)</td>
<td></td>
</tr>
<tr>
<td><strong>Dose #1</strong></td>
<td>Entry†</td>
<td>1-3 days post 1st dose</td>
<td>7-13 days post 1st dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose #2</td>
<td>1-3 days post 2nd dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-22 days post 2nd dose</td>
</tr>
<tr>
<td><strong>L&amp;D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screen</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Informed Consent</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Neurological Exam</strong></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Documentation of HIV status</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fetal Heart Rate</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H1N1 Vaccination</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow up phone call</strong></td>
<td>X†</td>
<td>X†</td>
<td></td>
</tr>
<tr>
<td><strong>Reactogenicity assessment</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete Blood Count</strong></td>
<td>X²</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Chemistries</strong></td>
<td>1ml²</td>
<td>1ml²</td>
<td>1ml²</td>
</tr>
<tr>
<td><strong>Immunophenotyping (CD4/CD8/CD19)</strong></td>
<td>2ml</td>
<td>2ml</td>
<td>Xargon</td>
</tr>
<tr>
<td><strong>HIV-1 RNA PCR</strong></td>
<td>3ml</td>
<td>3ml</td>
<td>Xargon</td>
</tr>
<tr>
<td><strong>Cryopreserved PBMC &amp; plasma for CMI &amp; neutralizing antibodies</strong></td>
<td>15ml</td>
<td>15ml</td>
<td>15ml</td>
</tr>
<tr>
<td><strong>Serum for DMID (HAI)</strong></td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
</tr>
<tr>
<td><strong>Serum for IMPAACT (HAI)</strong></td>
<td>2ml²²</td>
<td>2ml²²</td>
<td>2ml²²</td>
</tr>
<tr>
<td><strong>Umbilical cord blood for DMID</strong></td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
</tr>
<tr>
<td><strong>Umbilical cord blood for IMPAACT</strong></td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
</tr>
<tr>
<td><strong>Respiratory Specimen</strong></td>
<td>15ml</td>
<td>15ml</td>
<td>15ml</td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUMES</strong></td>
<td>23ml</td>
<td>22ml</td>
<td>22ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
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<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

**NOTE:** ± indicates a range of dates.
Footnotes: APPENDIX IA, MATERNAL SCHEDULE OF EVALUATIONS

1. It is preferred that screening and study entry occur on the same day; however, entry may be delayed up to 7 days after screening, if required.

2. A targeted medical history is required at screening/entry, as well as subsequent clinic visits, and should include information on:
   - Cancer, allergies and a vaccination history in the 6 months prior to study entry and during study participation.
   - Information regarding current status of the subject’s pregnancy; history of previous pregnancies will be recorded at the screening visit.
   - List of medications taken currently as well as within the 28 days prior to enrollment.
   - CDC classification for HIV status at screening/entry and 3 months post delivery/early discontinuation.
   - Review of symptoms for Guillain-Barre Syndrome

3. Physical exam should include height, weight, vital signs (oral temperature, heart rate and blood pressure), and additional examination as directed by intercurrent signs and symptoms.

4. A neurological exam must include formal gait, strength and reflex assessments should be performed at all clinic visits on every subject. Additional tests should be performed based on subject symptoms.

5. A fetal heart rate (FHR) exam should be performed within 1 hour prior to vaccination and at least 30 minutes post vaccination for BOTH vaccine doses.

6. TWO pre-filled syringes of 15mcg Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine MUST be administered, for a total dose of 30mcg. We recommend one injection per deltoid OR two injections in the same deltoid, at a minimum of 2 inches apart. This total dose (30mcg) must be given at BOTH Day 0 (Step I) and Day 21 (Step II).

7. All subjects will be contacted by telephone to inquire about adverse events, to obtain the information collected on the subject memory aid and to remind the subject to continue the memory aid for the first 10 days post vaccination. At the time of the next visit the memory aids may be discarded. If a subject is seen in clinic a clinic evaluation may be substituted for the telephone call evaluation. An interval history should also be obtained. Follow up calls will take place at Day 2 post vaccine #1, at Day 10 post vaccine #1 and at Day 2 post vaccine #2. Some subjects will also receive a phone call at 6 months post delivery.

8. Reactogenicity assessments will include the subject’s history and provide an assessment of AEs, which includes review for any of the following symptoms: Erythema, induration, pain and tenderness at the injection site, fever, fatigue, myalgia (exclusive of the injection site), headache, nausea and rash.

9. The subject must have a CBC result within the previous 28 days prior to each vaccination dose, in order to confirm a documented platelet count of >50,000/mm$^3$ and an ANC>500/mm$^3$. Results from a clinically obtained CBC from within the previous 28 days may be used for the first vaccine visit and the results of the entry CBC may then be used for randomization for the 2nd vaccine visit if the vaccination occurs no greater than 28 days after the entry visit.

10. The subject must have chemistry tests that include an SGPT, SGOT and creatinine levels within the past 28 days for entry. Clinically obtained results within the previous 28 days may be used; if not available chemistry tests should be obtained.

11. Immunophenotyping may be run in a CLIA certified laboratory, at the clinical site. The test does not need to be run at a DAIDS IQA certified laboratory.

12. HIV-1 RNA may be run in a CLIA certified laboratory, at the clinical site. The test does not need to be run at a DAIDS VQA certified laboratory.

13. Directions for H1N1, TIV and other specimen processing, storage and shipping of samples can be found in the P1086 Manual of Operations (MOP).

14. Nasal pharyngeal swab, nasal washing, tracheal aspirate specimen, or bronchoalveolar lavage will be taken from any subject presenting with fever $\geq$100.0°F AND signs/symptoms indicative of an influenza-like illness (ILI), such as coryza, sore throat, cough and pneumonia. However, if either fever OR ILI symptoms are present, a respiratory specimen should be obtained at the discretion of the site investigator. Please see P1086 MOPs for collection, processing and storage instructions.
15. STEP I Day 21 and STEP II Day 0 visits are recommended to be completed on the same day. Vaccine dose #2 may be deferred up to 7 days if indicated (see section 6.3 for more information). Please email the team at actg.teamp1086@fstrf.org with questions.

16. Data about mothers and infants related to labor and delivery will be collected and recorded.

17. The most recent results for these tests from standard of care should be reported.

18. The first 50 mothers who received both of two doses of inactivated **Influenza A (H1N1) 2009 monovalent vaccine** and immunogenicity laboratory assays drawn prior to delivery, as per the protocol, will be requested to come in for a clinic visit with their babies at 6 months. The remainder of the subjects will have a phone call evaluation.

19. For an ILI associated sick visit, an interval history and physical exam should be performed and a respiratory specimen should be obtained as indicated in footnote 14.

20. For a Guillain-Barre Syndrome-associated sick visit, an event targeted history, physical exam and neurological exam (which should include formal gait, strength and reflex assessment) should be collected.

21. This should include an interval history since the last visit, reporting any unreported adverse events that have occurred.

22. HAI will be performed for **2009 H1N1 Influenza A virus** and influenza viruses in TIV.

23. HAI will be performed for H1N1 **2009 H1N1 Influenza A virus** only.

**NOTE:**
For insufficient blood draws, priorities are as follows:

1. Serum for DMID
2. Serum for shipping to the University of Colorado, IMPAACT Immunology Laboratory
3. HIV-1 RNA and CD4/CD8/CD19
4. PBMC’s and plasma for shipping to the University of Colorado, IMPAACT Immunology Laboratory
## APPENDIX IB
### INFANT SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Footnotes:</th>
<th>Birth(^1)</th>
<th>3 month visit (± 1 month)</th>
<th>6 month visit (± 1 month)(^7)</th>
<th>Early study discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinic visit</td>
<td>Phone call</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Interval History(^3)</td>
<td>X(^3)</td>
<td>X(^3)</td>
<td>X(^5)</td>
<td>X(^5)</td>
</tr>
<tr>
<td>Documentation of HIV status(^4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum for IMPAACT (HAI)</td>
<td>(1ml)(^6)</td>
<td>1ml</td>
<td>1ml</td>
<td>1ml</td>
</tr>
<tr>
<td>Serum for DMID (HAI)</td>
<td>(1ml)(^6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUMES</td>
<td>(2ml)(^6)</td>
<td>1ml</td>
<td>1ml</td>
<td>1 ml</td>
</tr>
</tbody>
</table>

**Footnotes:**

1. Neonates will receive their own PID at the time of maternal study enrollment.
2. Physical exam will include: height, weight, head circumference, Apgar score (at birth), and a neuromuscular evaluation.
3. Interval history will include reporting of any congenital abnormalities. Infant SAE data will be collected when obtaining data on pregnancy outcome from birth until discharge after delivery.
4. HIV status should be obtained through chart abstraction.
5. Interval history will include any newly identified congenital anomalies.
6. If a cord blood sample was not obtained, a total of 2mls of blood should be drawn from the baby within 7 days of delivery.
7. Only babies of mothers who fulfill the evaluable* definition and are asked to return at 6 months for an in-person visit.

*These will be the infants of the first 50 mothers who received both of two doses of the inactivated **Influenza A (H1N1) 2009 monovalent vaccine**, and had samples for immunogenicity laboratory assays drawn prior to delivery, as per the protocol.

**NOTE:**
If cord blood was not obtained and insufficient serum is collected from the baby at the birth visit, the priority of draw is as follows:
1. Serum for DMID
2. Serum for IMPAACT
**APPENDIX IC**

**MATERNAL SCHEDULE OF EVALUATIONS FOR WOMEN WHO DELIVER PRIOR TO DOSE #2**

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Dose #2 (&lt; 4 wks post delivery)</th>
<th>Day 2 1-3 days post 2nd dose</th>
<th>Day 10 7-13 days post 2nd dose</th>
<th>3 months post delivery ±1 month</th>
<th>6 months post delivery Phone call (±1 month)</th>
<th>Sick visit14,15</th>
<th>Early discontinuation from the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1N1 Vaccination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up phone call</td>
<td></td>
<td>X7</td>
<td>X7</td>
<td>X</td>
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<td>Cryopreserved PBMC &amp; plasma for CMI &amp; neutralizing antibodies</td>
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<tr>
<td>Serum to DMID (HAI)</td>
<td>5ml</td>
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<tr>
<td>Serum to IMPAACT (HAI)</td>
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<tr>
<td>Umbilical cord blood for DMID</td>
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<td>Respiratory Specimen</td>
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<tr>
<td>TOTAL BLOOD VOLUMES</td>
<td>13ml blood (mom)</td>
<td>22ml</td>
<td></td>
<td>25ml</td>
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**TOTAL BLOOD VOLUMES**

13ml blood (mom) 10ml cord blood
Footnotes: APPENDIX IC - MATERNAL SCHEDULE OF EVALUATIONS FOR DELIVERY PRIOR TO DOSE #2

1. A targeted medical history should include interval history since delivery. Data about mothers and infants related to labor and delivery will be collected and recorded.
2. Physical exam should include height, weight, vital signs (oral temperature, heart rate and blood pressure), and additional examination as directed by intercurrent signs and symptoms.
3. TWO pre-filled syringes of 15mcg Novartis unadjuvanted inactivated Influenza A (H1N1) 2009 monovalent vaccine MUST be administered, for a total dose of 30mcg. We recommend one injection per deltoid OR two injections in the same deltoid, at a minimum of 2 inches apart. This total dose (30mcg) must be given at BOTH Day 0 (Step I) and Day 21 (Step II).
4. A neurological exam must include formal gait, strength and reflex assessments should be performed at all clinic visits on every subject. Additional tests should be performed based on subject symptoms.
5. If a subject is seen in clinic a clinic evaluation may be substituted for the telephone call evaluation.
6. Reactogenicity assessments will include the subject’s history and provide an assessment of AEs, which includes review for any of the following symptoms: Erythema, induration, pain and tenderness at the injection site, fever, fatigue, myalgia (exclusive of the injection site), headache and nausea.
7. All subjects will be contacted by telephone, to inquire about adverse events, to obtain the information collected on the subject memory aid and to remind the subject to continue the memory aid for the first 10 days post vaccination. At the time of the next visit the memory aids may be discarded.
8. Results from a clinically obtained CBC from within the previous 28 days may be used to document a platelet count of >50,000 mm$^3$ and an ANC>500 mm$^3$.
9. The subject must have chemistry tests that include an SGPT, SGOT and creatinine levels within the past 28 days.
10. Immunophenotyping may be run in the CLIA certified laboratory, at the clinical site. The test does not need to be run at a DAIDS IQA certified laboratory.
11. HIV-1 RNA may be run in the CLIA certified laboratory, at the clinical site. The test does not need to be run at a DAIDS VQA certified laboratory.
12. Directions for processing, storage and shipping of samples can be found in the P1086 Manual of Operations (MOP).
13. Nasal pharyngeal swab, nasal washing, tracheal aspirate specimen, or bronchoalveolar lavage will be taken from any subject presenting with fever >100.0°F AND signs/symptoms indicative of an influenza-like illness (ILI), such as coryza, sore throat, cough and pneumonia. However, if either fever OR ILI symptoms are present, a respiratory specimen should be obtained at the discretion of the site investigator. Please see P1086 MOPs for collection, processing and storage instructions.
14. For an ILI associated sick visit collect an interval history and physical exam should be performed and a respiratory specimen should be obtained as indicated in footnote 13;
15. For a Guillain-Barre Syndrome associated sick visit collect an event targeted history, physical exam and neurological exam which should include formal gait, strength and reflex assessments, but does not need a respiratory specimen.
16. HAI will be performed for **2009 H1N1 Influenza A virus** and influenza viruses in TIV.

NOTE:
For insufficient blood draws, priorities are as follows:
1. Serum for shipping to DMID
2. Serum for shipping to the University of Colorado, IMPAACT Immunology Laboratory
3. HIV-1 RNA and CD4/CD8/CD19
4. PBMC’s and plasma for shipping to the University of Colorado, IMPAACT Immunology Laboratory
APPENDIX II

Public Readiness and Emergency Preparedness Act (PREP act).

This protocol and the vaccine tested are covered under the Public Readiness and Emergency Preparedness act (PREP act). Under the PREP Act, covered persons are immune from liability actions brought from the administration or use of a covered countermeasure that is the subject of a declaration.

On June 15, 2009, HHS secretary Kathleen Sebelius had issued an amendment to the Declaration for use of the PREP act to include the H1N1 vaccines and any associated adjuvants (Federal Register, Volume 74, Number 121, Pages: 30294-30297). The PREP act provides immunity for covered persons (such as Manufacturers, Distributers, Program planners and other Qualified persons who prescribe, administer or dispense the vaccine) from tort liability, unless the injury was caused by willful misconduct.

The PREP Act also authorized a “Covered Countermeasures Process Fund” to provide compensation to eligible individuals who suffer specified injuries from administration or use of a countermeasure pursuant to the declaration. Any requests for compensation must be filed within one year of administration or use of the countermeasure. Requests would go to the HRSA Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/countermeasurescomp/default.htm). Compensation may then be available for medical benefits, lost wages and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from administration and use of the vaccine must first seek compensation from the Covered Countermeasures Process Fund. A serious physical injury means an injury that is life threatening, results in, or requires medical or surgical intervention to prevent, permanent impairment of a body function or permanent damage to body structure. Any compensation will be reduced by public or private insurance or worker’s compensation available to the injured individual.

If no funds have been appropriated to the compensation program, the Secretary does not make a final determination on the individual’s request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the United States District Court for the District of Columbia, but only if the claim involves willful misconduct, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. Any award is reduced by any public or private insurance or worker’s compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, the individual does not have a tort claim that can be filed in a United States Federal or a State court.
APPENDIX III

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT

P1086
Phase II Study to Assess the Safety and Immunogenicity of an Inactivated Influenza A (H1N1) 2009 Monovalent Vaccine in HIV-1 Infected Pregnant Women
Version 2.0, dated April 23, 2010

SHORT TITLE FOR IMPAACT P1086: Safety of an H1N1 Influenza Vaccine in HIV-1 infected pregnant women.

INTRODUCTION
You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS, and are pregnant. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Your baby will also be a participant on the study once he or she is born.

WHY IS THIS STUDY BEING DONE?
H1N1 virus, historically known as ‘swine flu virus’, is a new strain of influenza (flu) virus that causes illness in people. However, H1N1 influenza virus has recently been identified as the cause of serious, sometimes life-threatening illness in some previously healthy people. This illness can result in severe pneumonia, which requires hospitalization, and is life-threatening.

Recent reports by the Centers for Disease Control (CDC) indicate that pregnant women are more likely to have severe effects of H1N1 influenza, and require hospitalization more often than non-pregnant women.
The purpose of this research study is to determine if this vaccine which has been licensed by the United States Food and Drug Administration (FDA) is safe and will help the body’s normal defenses against the effects of H1N1 influenza in HIV-infected pregnant women. The licensed vaccine to be used in this study may not prevent all cases of influenza virus, but may prevent severe disease and possibly death which has been associated with this H1N1 virus in pregnant women.

This is the first time this vaccine has been tested in HIV-1 positive pregnant women. It is currently being tested in healthy adults and healthy children. The vaccine is produced by Novartis, a pharmaceutical company. The vaccine is “inactivated”, which means virus particles used to make the vaccine have been killed, and cannot cause influenza. This vaccine contains a trace amount of thimerosal (mercury). The vaccine is made with products from eggs. If you are allergic to eggs or egg products, you would not be able to receive this vaccine. The vaccine also contains small amounts of the antibiotics neomycin and polymyxin. If you are allergic to one of these antibiotics, you will not be able to receive this study vaccine.

There is no information on the safety or immune response to this vaccine in pregnant women or patients with HIV. The “immune response” is how your body recognizes and defends itself against bacteria, viruses, and substances that may be harmful to the body. We want to see if your body will produce antibodies (proteins that fight infection) that will prevent or fight H1N1 virus. We also want to know if the antibodies your body makes will transfer to your baby via the placenta and provide some protection against H1N1 infection in your baby.

The study will look at:

- The safety of the vaccine (after each of two doses). This will be done by observing you following the vaccine shots, and asking you about any adverse (bad) effects you may experience after each shot. We will also check your baby’s heart rate before and after each dose.
- Your ability to form antibodies against H1N1 in response to the vaccine shots. This will be done by doing blood tests on you (after each dose and at certain time points described below).
- The ability of your antibodies to cross the placenta into your baby. This will be done by testing both your blood and your baby’s umbilical cord blood after you give birth.
- How long your antibodies stay in your baby’s blood. This will be done by doing a blood test on your baby when he/she is three months and six months old.
- Your immune response to the vaccine if you also get the seasonal flu vaccine.
- How your body is responding to the HIV infection by looking at the number of special white blood cells (T cells) that are affected by the HIV virus (CD4 levels).
- The amount of HIV in your blood (HIV viral load).

**WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?**
If you agree to take part in this study, you will be asked some questions to be sure you can participate in this study. If you agree to take part in this study, you are also agreeing to allow your baby to be a participant in this study.

Screening Visit
At the screening visit, we will ask about your family history, including Guillain-Barré Syndrome. Guillain-Barré Syndrome is a very rare but serious disorder affecting the nervous system that is explained in more detail later in this consent. In addition, you will be asked for permission to review your medical record.

At the screening visit study staff will ask you some questions about your medical history, as well as the use of any past or present anti-HIV drugs. You will have a physical exam and a neurological exam. Up to 6 teaspoons of blood will be taken for basic tests, as well as special lab tests (to test your immune response to the flu virus). This visit will take approximately 30 minutes.

Additional Visits
You will be asked to return to clinic for an additional seven visits, where we will do the following procedures. This visit will take approximately 30 minutes.

- Study staff will ask you some questions about how you have been feeling since your last visit.
- You will have a physical exam (height and weight, blood pressure, temperature and pulse) and a neurological exam.
- Between ½ to 6 teaspoons of blood will be taken for basic tests, as well as special lab tests (to test your immune response to the flu virus).

Day of Vaccine
You will receive two doses of vaccine approximately 21 days apart. Each dose of vaccine will be given by TWO injections with a needle in a muscle in your upper arm. You may choose to have both injections in one arm or one injection in each arm. We will check your baby’s heart rate before the vaccine. After vaccine administration, you will remain in the clinic for at least 30 minutes (½ hour) to make sure that no reactions to the vaccine develop and then we will check your baby’s heart rate again. These visits will take approximately 1 hour.

After you have received the vaccine
You will need to contact the study staff immediately to report any unusual or serious reactions that occur after you leave the clinic. You will be asked to take your temperature at the same time every day for the first 10 days after the vaccine. You will also be given a memory aid so that you can record your temperature and write down any symptoms or unusual reactions that occur during these first 10 days. The study staff will call you or see you in clinic twice after each vaccination, to ask you about any reactions you may have had.
You will also be asked about any new fever or flu-like illness, such as a sore throat, myalgia (‘muscle aches’), runny nose or cough. If you are having any of these symptoms, you will be asked to come back to the clinic within 72 hours. If you have any other new symptoms, such as weakness of legs, tingling of hands and/or feet, or difficulty walking, it is important that you contact the study staff immediately and you will be asked to come back to clinic within 24 hours.

Delivery of your baby
At the delivery of your baby, about 1½ teaspoons of blood will be drawn from you for special lab tests (to test your immune response to the flu virus). We will also draw 1-2 teaspoons of blood from the umbilical cord of the placenta for similar special laboratory tests.

If the cord blood is not obtained at the time of delivery, less than 1 teaspoon of blood will be drawn from your baby before discharge from the hospital. All attempts will be made to obtain this blood at the time of other routine tests to avoid additional needle sticks.

If you deliver your baby before you receive vaccine dose #2, you will be asked to stay on study and come in for the remaining visits with your baby. You will get your second dose of vaccine within 4 weeks after your delivery.

Three Months after Delivery
Three months after the delivery of your baby, you will be asked to come back to clinic with your baby. During this visit, you will be asked about any medical problems that have occurred since your visit as well as a brief physical exam and a blood draw (3½ teaspoons). We will also ask you some questions about your baby perform a physical exam and draw less than ½ teaspoon of blood from your baby. This visit will take approximately 30 minutes.

Six Months after Delivery
The first 50 women who receive both doses of study vaccine and have all of the special lab tests (to test your immune response to the flu virus) done before delivery, will be asked to come back to clinic with their baby’s for a final study visit approximately six months after delivery. For those mothers that come into clinic, you will be asked about any medical problems that have occurred since your visit and you will have a brief physical exam. You will also have 3½ teaspoons of blood drawn. We will also ask you some questions about your baby; perform a physical exam and draw less than ½ teaspoon of blood from your baby. This visit will take approximately 30 minutes.

All other mothers will receive a telephone call at six months after delivery.
Sick visits
At any time during the course of the study, if you have fever of 100.0°F or above, or any signs or symptoms of a flu-like illness such as cough, runny nose or sore throat, you will be asked to come in to the clinic. A nasal specimen may be done on this visit, after evaluation by your healthcare provider. This test will be done to see if certain types of flu virus are found in your nasal passages and if so, how much is present. This study test will be performed after the study is completed and you will not be told your results. This visit will take approximately 30 minutes.

Off-Treatment Study Visits (Follow-up Period)
If you are unable to receive the second dose of vaccine, you and your baby will be asked to continue with the study visits at 21 days after dose #1, delivery and at 3 months after delivery.

Early Study Discontinuation Visit
If you no longer want to be in this study, or no longer can be in this study, you will be asked to come to the clinic one last time. If this visit occurs after delivery, we will ask that you bring your baby to the visit. At this last visit, some or all the laboratory tests described above will be done, if tests have not been done at a recent study visit. You will have a brief physical exam, a neurological exam and have 5 teaspoons for your blood drawn. We will also ask how you have been feeling. No vaccine will be given at this study visit. This visit will take approximately 30 minutes.

We will also ask you some questions about your baby; perform a physical exam and draw less than ½ teaspoon of blood from your baby.

OTHER INFORMATION
When the study is over, results will be available from your study site. You will be given the results of your routine lab tests when they become available. The results of special lab tests (to test your immune response to the flu virus) and any respiratory specimens will not be provided to you or your doctor. These tests will not be run at the time they are received. Instead they will be run in batches or at the end of the study. Any blood samples that are not used after 3 years following the end of the study will be destroyed.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 130 pregnant women will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?
The longest length of time you will be in this study will be 52 weeks. You will be in the study until your baby is 6 months of age.

WHAT ARE THE RISKS OF THE STUDY?
Risk of Blood Draws

You or your baby may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

Risks Related to the Vaccine

There is no information available at this time with regard to specific side effects of the H1N1 influenza vaccine. This vaccine is similar in preparation to that used in other influenza vaccines. This is one of the vaccines being prepared for general use in all people in the United States. However, it is made from a new virus, so at this time, there is limited information on the safety of the vaccine.

The dose of study drug is higher than the recommended dose for healthy children because children with HIV infection may not respond as well as healthy children to the lower dose of vaccine.

Life threatening allergic reactions to vaccines are very rare. If they do occur, it is usually within a few minutes to a few hours after the vaccination. Side effects that might be expected as a result of the H1N1 influenza vaccine would be those which are sometimes observed in other commonly used vaccines, including fever, skin redness, pain, tenderness, soreness and swelling at the site of injection. Any information on side effect or risks that is gathered from H1N1 vaccination on other groups of people will be provided to you as quickly as possible.

Occasionally, there can be a serious allergic reaction to a vaccine. These reactions can cause any of the following symptoms:

**Systemic Vaccine Related Reactions:**
- skin rash (hives)
- fever
- nausea
- vomiting
- diarrhea
- abdominal pain
- cough
- sore throat
- achiness
- feeling tired (fatigue)
- general feeling of illness

**Serious Vaccine Related Reactions:**
• Difficulty breathing
• Sweating
• Fast pulse
• Swelling around the mouth, throat or eyes

If these reactions occur they can usually be stopped by the study staff giving emergency medications. These symptoms usually occur soon after having the vaccine. As with any vaccine or medication, there is a very small chance of a fatal reaction, although researchers do not expect this to occur.

Guillain-Barré Syndrome (GBS), a very rare but serious disorder affecting the peripheral nervous system, is not usually seen following routine influenza vaccination. However, some cases of Guillain-Barré Syndrome were reported after mass public vaccination for the 1976 “swine flu”. It is unknown if the H1N1 influenza vaccine will present the same risk. The study staff will assess you for symptoms of Guillain-Barré Syndrome at each clinic visit and phone call.

About Guillain-Barré Syndrome:
The peripheral nerves send sensory information (like pain or temperature) from the body to the brain, and motor (movement) signals from the brain to the body. In Guillain-Barré Syndrome, the body’s immune system attacks the peripheral nerves. Symptoms of Guillain-Barré Syndrome include weakness and numbness or tingling in the legs and arms, and possible loss of movement and feeling in the legs, arms, upper body, and face. Complete recovery from Guillain-Barré Syndrome can take anywhere from a few months to a few years. Although most people recover completely from Guillain-Barré Syndrome, some do not. The frequency of Guillain-Barré Syndrome is about 1 to 2 cases in every 100,000 people per year in the United States. It strikes men and women, young and old equally.

ARE THERE RISKS RELATED TO RECEIVING THIS VACCINE DURING PREGNANCY?
The usual seasonal influenza vaccines are recommended for pregnant women. Safety information for pregnancy is lacking for this vaccine. Information related to pregnancy-associated risks will be provided to you as they become known.

WHY WOULD THE DOCTOR TAKE ME / MY BABY OFF THIS STUDY EARLY?
The study doctor may also decide that you should not receive the second dose of vaccine if:
• The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), or the site’s Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research subjects.
A Study Monitoring Committee (SMC) recommends that the study be stopped early. This committee is an outside group of experts that monitors the study.

You or your baby is not able to attend the study visits as required by the study.

The study doctor may also withhold the second dose of vaccine if:

- Continuing the study vaccine may be harmful to you or your baby
- You or your baby need(s) a treatment that cannot be administered if a second dose of vaccine is given.

WHAT HAPPENS IF I OR MY BABY IS INJURED?
If you or your baby suffers physical injury from this study, the study doctor will provide immediate medical treatment. The study doctor will also provide referrals to appropriate health care facilities. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). No financial compensation by the doctors that gave you the vaccine will be made for any discomfort suffered because of participation in this study. You will not be giving up any of your legal rights by signing this consent form.

This vaccine and the research study are covered by the Public Readiness and Emergency Preparedness (PREP) Act which limits your ability to sue if you develop a reaction to the vaccine. A Federal program has been created to help pay for medical care and other specific expenses of people who have serious reactions that are caused by the vaccine. To be eligible for this program, you must file a claim within one year of the vaccination. The program is administrated by the Health Resources and Services Administration. An information sheet about the PREP Act, and the Federal program, including how to file a claim will be provided to you.

WILL I RECEIVE ANY COMPENSATION?
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
If you agree to take part in this study, there may be a direct benefit to you and your baby, but no guarantee can be made. You may develop antibodies against H1N1 influenza virus which may prevent infection or lessen your symptoms if you get infected. Your baby may benefit from receiving your antibodies and may benefit if you are prevented from getting infected with H1N1 influenza. It is also possible that you and your baby may receive no benefit from being in this study. Information learned from this study may help others who have HIV and are pregnant.
WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
Alternatives to your participation in this study include receiving from your health care provider the seasonal flu vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine. Alternatively, you may choose not to receive any vaccine. Please talk to your health care provider about these and other choices available to you.

WHAT ABOUT CONFIDENTIALITY?
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your baby, or others.

Your and your baby’s records may be reviewed by the U.S. Food and Drug Administration (FDA), (insert name of site) IRB, National Institutes of Health (NIH), Office of Human Research Protections (OHRP), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?
There are no costs to you for study vaccines, study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications arise or if your doctor decides extra tests are needed. In some cases it is possible that your insurance company will not pay for these costs because you and your baby are taking part in a research study.
WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time. You/your baby will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your and your baby’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
  • name of the investigator or other study staff
  • telephone number of above

For questions about your rights or your baby’s rights as a research subject, contact:
  • name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
  • telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____________________                              ____________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________                ____________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

________________________                        ____________________________________
Study Staff Conducting    Study Staff Signature and Date
Consent Discussion (print)

________________________                        ____________________________________
Witness’ Name (print)   Witness’s Signature and Date
(As appropriate)