ICDDRB: Centre for Health & Population Research **RRC APPLICATION FORM**

RESEARCH PROTOCOL

Protocol No.: 2001-011

FOR OFFICE USE ONLY

RRC Approval: Yes/ No Date:

ERC Approval: Yes/No Date:

AEEC Approval: Yes/No Date:

Project Title: A prospective, randomised, partially-blinded, placebo-controlled, Phase III, multicentre trial to assess safety, tolerability and imunogenicity of liquid influenza virus vaccine, trivalent, types A & B, live cold-adapted (liquid CAIV-T) administered concomitantly with live, attenuated, poliovirus vaccine in healthy children

Theme: *(Check all that apply)*

- ☐ Nutrition
- ☑ Emerging and Re-emerging Infectious Diseases
- ☐ Population Dynamics
- ☐ Reproductive Health
- ☑ Vaccine evaluation
- ☐ Environmental Health
- ☐ Health Services
  - ☐ Child Health
- ☐ Clinical Case Management
- ☐ Social and Behavioural Sciences

Key words: Influenza, cold-adapted, vaccine, oral polio vaccine

Principal Investigator: **Dr. Robert F. Breiman** **Division: PHSD** **Phone:** x2255

Address: **Programme on Infectious Diseases and Vaccine Sciences**
Email: breiman@icddrb.org

Co-Principal Investigator(s): Dr. Abdullah Brooks

Co-Investigator(s): Dr. Aliya Naheed

Student Investigator/Intern: none

Collaborating Institute(s):Wyeth-Lederle Vaccines

Population: Inclusion of special groups *(Check all that apply)*:

Gender
- ☑ Male
- ☑ Females

Age
- ☑ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
  - ☐ CSW
- ☐ Others (specify _____)
- ☐ Animal

Project / study Site *(Check all the apply)*:

- ☐ Dhaka Hospital
- ☐ Matlab Hospital
- ☐ Matlab DSS area
- ☐ Matlab non-DSS area
- ☑ Mirzapur
- ☑ Dhaka Community
  Chakaria
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh: Kamalapur
- ☐ Outside Bangladesh
  name of country: _____
- ☐ Multi centre trial: Thailand, Philippines, Malaysia,Mexico, Turkey, India

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☑ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☐ Cross sectional surv
- ☑ Longitudinal Study (
- ☐ Record Review
- ☑ Prophylactic trial

Revised on: 17 October 2000

- ☐ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☐ Surveillance / monitoring
- ☑ Others—Vaccine trial

Targeted Population *(Check all that apply)*:

- ☑ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal groups
- ☐ Expatriates
- ☐ Immigrants
  - ☐ Refugee

Consent Process *(Check all that apply)*:

- ☑ Written
- ☐ Oral
- ☐ None
- ☑ Bengali language
- ☐ English language

Proposed Sample size: 2400 (all sites) Total sample size: 400 from Bangladesh ☐

Sub-group _____ ☐ _____ ☐

_____ ☐ _____ ☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

- ☐ Human exposure to radioactive agents?
- ☐ Fetal tissue or abortus?
- ☐ Investigational new device?
  (specify_____)
- ☐ Existing data available from Co-investigator
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug
- ☐ Existing data available via public archives/source
- ☐ Pathological or diagnostic clinical specimen only
- ☐ Observation of public behaviour
- ☐ New treatment regime

Yes/No

☐ ☑ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☑ Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☑ a. place the subject at risk of criminal or civil liability?

☐ ☑ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

- ☐ greater than minimal risk
- ☐ no risk
- ☑ no more than minimal risk
- ☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☑ ☐ Is the proposal funded?

If yes, sponsor Name: Wyeth-Lederle Vaccines

Yes/No

☐ ☐ Is the proposal being submitted for funding ?

If yes, name of funding agency: (1) ______________________

(2) ______________________

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support	Cost Required for the Budget Period ($)
(Day, Month, Year - DD/MM/YY)	***a.*** ***1st Year*** ***2nd Year*** ***3rd Year*** ***Other years***
Beginning date 01/08/01	$99,788 ______ ______ ______
End date: 31/01/02	***b.*** ***Direct Cost :*** $79,831 ***Total Cost*** $99,788

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Name of the Division Director ______ Signature ______ Date of Approval ______

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI

Date: ______

Name of Contact Person (if applicable)

______

Table of Contents

Page Numbers

☐ Check here if appendix is included

PROJECT SUMMARY

Principal Investigator Robert F. Breiman, M.D.

A prospective, randomised, partially-blinded, placebo-controlled, Phase III, multicentre trial to assess safety, tolerability and imunogenicity of liquid influenza virus vaccine, trivalent, types A & B, live cold-adapted (liquid CAIV-T) administered concomitantly with live, attenuated, poliovirus vaccine in healthy children

Total Budget $ 99,788 Beginning Date Sept. 1, 2001 Ending Date Jam 30, 2002

In Asia, influenza rates are highest in young children. In community surveillance of children under 5 years with acute lower respiratory infections (ALRI) in Manila and Dhaka, influenza was confirmed by culture as the probable aetiology in 22% and 14% cases if ALRI, respectively. Similarly, in Singapore, children under 4 years of age accounted for approximately 22% of all influenza isolations, representing the highest age-specific rates, and among those infants hospitalised for acute respiratory tract infections, influenza was associated with 11%.

Cold adapted influenza virus vaccine (CAIV-T) produced by Aviron Inc. (Mountain View, CA, USA) and Wyeth Lederle Vaccines (Marietta, PA, USA) is a live, trivalent, cold-adapted, temperature sensitive and attenuated influenza vaccine consisting of two influenza strains of type A and one influenza strain of type B. CAIV-T is based on two master donor strains, A/Ann Arbor/6/60 and B/Ann Arbor/1/66, that were developed three decades ago by H.F. Maassab. The vaccine is administered via nasal spray. It is well tolerated and a variety of studies have demonstrated high efficacy in prevention of influenza and influenza-related conditions including lower respiratory infections and otitis media. Because of the role of influenza as a direct cause of respiratory illness and because of its role in predisposing patients to secondary bacterial pneumonia, this vaccine may be of substantial use in prevention of morbidity and mortality in developing countries.

For this vaccine to be used routinely in Bangladesh and other developing countries, it is necessary to show that administration of this nasal vaccine would not interfere with immune responses to another non-parenteral vaccine, oral polio vaccine (OPV) that could potentially be given simultaneously. Likewise, it is important to evaluate whether OPV administered concomitantly interferes with protective immune responses elicited by the influenza vaccine (CAIV-T).

At the present time, no data exist on the effect if any on the immune responses to the components of OPV and CAIV-T when co-administered. In clinical trials to date, no other live virus vaccine has been administered within 1 month of a dose of CAIV-T. However, in many settings where children might benefit from an effective live influenza vaccine such as CAIV-T, its use would be severely restricted should the timing of influenza vaccination coincide with a mass OPV immunisation campaign. Therefore, the purpose of this clinical trial is to investigate the effect, if any, of the co-administration of CAIV-T and OPV on the immune responses to the components of the vaccine, respectively.

This is a multi-centre study coordinated and funded by Wyeth_Lederle Vaccines. Other proposed sites include Malaysia, India, Philippines, Thailand, Mexico, and Turkey. Overall 2400 participants will be entered into the study, including an estimated 350-400 from Bangladesh. The Bangladesh site will be Kamalapur an urban slum within Dhaka, where ICDDR,B operates a clinic and currently is conducting surveillance and risk factor evaluations for dengue fever and where studies on incidence of acute lower respiratory infections have been conducted.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	Professional Discipline/ Specialty	Role in the Project
1. Dr. Robert Breiman	Epidemiology	Principal Investigator

2. Dr. Abdullah Brooks	Epidemiology	Co-principal investigator
3. Dr. Aliya Naheed	Epidemiology	Project Manager
4.		

DESCRIPTION OF THE RESEARCH PROJECT

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

Hypothesis to be tested: Simultaneous administration liquid trivalent cold adapted influenza vaccine and oral polio vaccine will yield antibody levels to both influenza and polio viruses that are not inferior to those produced when the vaccines are given separately.

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods **(TYPE WITHIN LIMITS).**

0. **To demonstrate that the immune responses to the vaccine influenza viruses, as measured by serum hemagglutination inhibition assay, in children 6 to 36 months of age given influenza virus vaccine, trivalent, types A and B, live, cold-adapted (CAIV-T) concomitantly with a live, attenuated, orally-administered poliovirus vaccine (OPV), are not inferior to those immune responses in children only receiving CAIV-T.**

0. **To demonstrate that the immune responses to each of the three viruses contained in OPV, as measured by serum neutralisation assay, in children 6 to 36 months of age, given CAIV-T concomitantly with OPV, are not inferior to those immune responses in children only receiving OPV.**

0. **To assess the safety and tolerability of concomitant administration of CAIV-T with OPV.**

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyse available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. **(DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).**

Name and Description of the Investigational Material

Cold adapted influenza virus vaccine (CAIV-T) produced by Aviron Inc. (Mountain View, CA, USA) and Wyeth Lederle Vaccines (Marietta, PA, USA) is a live, trivalent, cold-adapted, temperature sensitive and attenuated influenza vaccine consisting of two influenza strains of type A and one influenza strain of type B. CAIV-T is based on two master donor strains, A/Ann Arbor/6/60 and B/Ann Arbor/1/66, that were developed three decades ago by H.F. Maassab.[1,2] CAIV-T contains three components: two attenuated influenza A strains, H1N1 and H3N2, based on the
influenza A master donor strain and one attenuated influenza B strain based on the influenza B master donor strain. Two of the eight gene segments of the master donor are replaced by gene segments coding for the haemagglutinin (HA) and neuraminidase (NA) genes from wild type influenza strains A (H1N1 and H3N2) and B. The reassorted cold-adapted strains are called 6:2 reassortments. All three influenza strains are cold-adapted so that the virus is able to replicate in the relatively cool temperatures of the nose and nasopharynx (25°C); temperature sensitive so
that they are not able to replicate efficiently in the warm temperature of the lungs (37°C for type B and 39°C for type A) and attenuated so that the virus does not spread and replicate in the lungs.

Frozen CAIV-T

Clinical trials of a frozen formulation of CAIV-T have been conducted by Aviron in over 6,500 children, over 3,700 healthy adults and approximately 100 high risk adults (co-administered with the licensed injectable influenza vaccine). Prior to Aviron's trials, cold-adapted influenza vaccines derived from type A or type B cold-adapted master strains [2] were used since 1976 in clinical trials sponsored by the National Institute of Health (NIH) and from 1991-1993 in clinical trials sponsored by Wyeth-Ayerst Research. Monovalent and bivalent type A, monovalent type B, and trivalent CAIV-T were administered in trials prior to Aviron sponsorship to more than 8,000 subjects whose ages ranged from 2 months to more than 100 years. The frozen CAIV-T formulation requires storage at –20°C or below.

Liquid CAIV-T

The liquid formulation of CAIV-T jointly developed by Aviron, Inc. and Wyeth Lederle Vaccines is derived from the same three attenuated influenza strains that are used to manufacture the frozen formulation. The difference in the production of the liquid formulation from the frozen formulation occurs after the harvest of allantoic fluid from SPF
chicken eggs infected with the three cold-adapted influenza strains. The harvested material for the liquid formulation is concentrated and purified by centrifugation (refer to the Clinical Investigator's Brochure). The liquid CAIV-T formulation is stable at 2 to 8°C and was developed for more convenient storage and simplified administration of the vaccine, enabling distribution outside of North America.

In ferrets, a liquid CAIV-T formulation was found to be favourable to the frozen CAIV-T for immunogenicity, safety and protection against wild-type influenza virus challenge. To date, four (4) clinical trials of the liquid formulation of CAIV-T have been performed in children aged 6 months to 36 months, and children and adolescents aged 6 years to 17 years. In total approximately 2700 children aged 17 years or younger, including approximately 2200 children aged 6 months to 36 months in a total of 16 countries, have received the liquid formulation of CAIV-T. Three of these four trials remain ongoing, and all four at this time remain blinded.

Influenza

Influenza is an acute viral respiratory illness characterised by abrupt onset of fever, myalgia, non-productive cough, headache, sore throat, nasal congestion and malaise. The infection is spread primarily as an aerosol by transfer of virus-containing droplets from an infected to a susceptible person. In cool and temperate climates, influenza occurs annually in the autumn and winter months causing widespread infection and morbidity in all age groups.[3] The infection is frequently epidemic with an acute community onset and rapid spread. During epidemic periods, it may be responsible for 25% of all respiratory illnesses.[4] The attack rate is greatest in individuals with minimal prior exposure to influenza,

particularly children. Although complete recovery occurs in uncomplicated influenza, pneumonia and other serious complications may occur in the very young, the elderly, the immune compromised and persons with underlying conditions such as chronic pulmonary or heart diseases.

The currently approved trivalent inactivated influenza vaccines (TIV) are most commonly recommended for the prevention of influenza in adults and children with chronic disorders, residents of chronic care facilities, and healthy persons 65 years of age or older.[4] Vaccination recommendations vary by region, but some countries recommend vaccination for persons who desire to avoid influenza infection and to reduce the severity of disease or the chance of transmitting influenza to high-risk persons with whom the individual has frequent contact. However, these recommendations do not include healthy children, who serve as a source of endemic spread of influenza in the community. The variable efficacy of the inactivated vaccines in the youngest and oldest age groups and the poor acceptance of annual administration by injection, particularly in children, have delayed widespread use of influenza vaccination outside the high-risk populations and have stimulated research to identify alternative, practical vaccination methods.

Live, cold-adapted influenza virus vaccines that are protective against naturally circulating influenza types A and B viruses could offer certain potential advantages over inactivated influenza vaccines: Intranasal administration requires no injection; local and systemic immune responses are produced to mediate protection against influenza infection;
induction of cell-mediated immunity (e.g., cytotoxic T-cell activity) may contribute to recovery from infection; effective immunisation of young children may reduce epidemic transmission of wild-type influenza viruses in households and to the elderly and chronically ill who are at increased risk from serious illness. Live, attenuated vaccines are among the most efficacious, durable and cost-effective vaccines available.

Epidemiology of Influenza in Children

In the USA, the rate of influenza infection was found to be highest in children aged 6 to 11 years (48 per 100 person-years), and in children aged 2 to 5 years (45 per 100 person-years). The risk of lower respiratory tract infection associated with influenza was highest in children under 2 years (7.8 per 100 person-years) while in children under 2
years of age, two-thirds of influenza infections occurred in infants aged 6 to 11 months (21 per 100 person-years).[5] In recently reported studies, hospitalisation rates for influenza in healthy infants aged 1 year or less represented the highest age-specific hospitalisation rates.[6,7]

In Asia, influenza rates are also highest in young children. For example, in residential kindergartens in Beijing, 19% of acute respiratory infections of children aged 6 months to 7 years were confirmed by culture to be attributed to influenza.[8] In community surveillance of children under 5 years with acute lower respiratory infections (ALRI) in
Manila and Dhaka, influenza was confirmed by culture as the probable aetiology in 22% and 14% cases if ALRI, respectively.[9,10] Similarly, in Singapore, children under 4 years of age accounted for approximately 22% of all influenza isolations, representing the highest age-specific rates,[11] and among those infants hospitalised for acute respiratory tract infections, influenza was associated with 11%.[12] Data are available from some countries in Southern Africa and South America for influenza in children. The published data confirm the very high rates of influenza infection in young children in diverse populations in the Southern Hemisphere, with influenza rates from South Africa,[13,14,15,16] Argentina,[17,18] Brazil,[19,20,21,22] and Chile [23] also appearing to be highest in young children. These findings are comparable to those observed in the USA. Similar patterns of disease caused by influenza have been reported across a variety of European regional settings. A collaborative surveillance program involving national data
from Belgium, France, The Netherlands, Portugal, Spain, and the United Kingdom [24] reported that the highest proportions of clinical cases of influenza occurred in children under 14 years of age (ranging from

15% in Spain to 49% in northern France). Further, data from respiratory viral surveillance of the Rhône-Alpes region in France
indicated that influenza accounted for 22% of all viral isolates obtained from children aged 1 to 4 years with an influenza-like illness, and 58% of viral isolates in children aged 5 to 9 years.[25]

Similar reports from Norway, the Czech Republic, and Scotland, support the significant role of influenza in childhood respiratory illness in Europe.[26,27,28]

Oral Poliovirus Vaccine and Developing Countries

The immunogenicity of oral poliovirus vaccine (OPV) is lower in infants in developing countries than in infants in industrialised countries. The most widely used formulation of trivalent OPV is based on the 10:1:3 combination of vaccine types 1, 2, and 3 respectively. In the review by Patriarca et al. (1991), the median seroconversion rates of infants residing in developing countries for each virus strain following administration of three doses of OPV were:

- Poliovirus type 1 : 72%
- Poliovirus type 2 : 95%
- Poliovirus types 3 : 65%

A variety of factors have been proposed to explain the differences in response rates of infants between industrialised and developing countries.[29,30]

One approach to improving the seroconversion rates to OPV in developing countries has been to provide infants and children with additional vaccine doses; for example another OPV dose may be administered at 9 months of ages, and a further dose in the second year of life [31,32,33,34]. However, routinely scheduled individual immunisation visits may not be practical in some settings in developing countries in older children. As a result, some countries have introduced mass immunisation campaigns for these subsequent OPV doses. While ensuring a higher rate of vaccine coverage, some evidence exists for vaccine administered in such campaigns to evoke better immune responses and higher seroconversion rates [35,36].

Purpose of study

At the present time, no data exist on the effect if any on the immune responses to the components of OPV and CAIV-T when co-administered. In clinical trials to date, no other live virus vaccine has been administered within 1 month of a dose of CAIV-T. However, in many settings where children might benefit from an effective live influenza vaccine such as CAIV-T, its use would be severely restricted should the timing of influenza vaccination coincide with a mass OPV immunisation campaign. Therefore, the purpose of this clinical trial is to investigate the effect, if any, of the co-administration of CAIV-T and OPV on the immune responses to the components of the vaccine, respectively.

Risks and Benefits

The frozen formulation of CAIV-T, manufactured by Aviron, Inc. has been evaluated in over 6,500 healthy children and 3,700 healthy adults. The results of completed pivotal studies are summarised in Table 1.

Table 1

Study	Population	Results
AV006	Children (15-71 months old)	Vaccine efficacy =93% (95% CI =88-96% against culture-confirmed influenza pneumonia; 98% efficacy against influenza associated otitis media
AV006	Children	Vaccine efficacy=87% (95% CI=78,93) against culture-

(second year)	(15-71 months old)	confirmed influenza following the first annual influenza revaccination.; 94% efficacy against influenza-associated otitis media
AV011	Children	Reduction in viral shedding of vaccine virus after intranasal challenge (efficacy=83%; 95% CI=60,93)
AV003	Adults	Vaccine efficacy = 85% (95% CI=28,100) against laboratory-confirmed influenza
AV009	Adults	19% (95% CI=7-29) reduction of severe febrile illnesses; 24% (95% CI=13,33) reduction in febrile upper respiratory illness; Reduction also seen for days of work lost, of health care provider Visits, use of prescription antibiotics, and use of over the Counter medication during the peak influenza period.

The ease of administration of CAIV-T by intranasal sprayer could lead to increased compliance and better public health control of influenza and therefore, a reduction in the impact of this disease.

As with any vaccine, CAIV-T may not protect 100% of individuals given the vaccine. The following are additional risks that may be associated with CAIV-T.

CAIV-T was generally well tolerated in clinical trials. In children in the 10 days following Dose One, the most common events were fever (5% over placebo), runny nose/nasal congestion (11% over placebo), and vomiting, muscle aches, headaches and decreased activity (each approximately 2% over placebo). However, following Dose Two and after annual re-vaccination, there were no significant differences between the vaccine and placebo group.

Currently, there have been no serious adverse experiences attributed to CAIV-T in completed clinical trials performed by Aviron, Inc. or Wyeth Lederle Vaccines. CAIV-T is contraindicated in individuals hypersensitive to any component of the vaccine. Intranasal influenza virus vaccine is propagated in eggs. Therefore, CAIV-T should not be administered to anyone with a history of hypersensitivity to eggs. The occurrence of a hypersensitivity reaction to the vaccine following vaccination with CAIV-T is a contraindication to further use of this product.

In February 2000, a multicentre, randomised, observer-blind study designed to demonstrate the equivalence of immunogenicity of the liquid and frozen formulations began in children living in the Republic of South Africa. Enrolment was completed in March 2000 with a total of 1394 children enrolled. 1310 children received a second dose. No vaccine related serious adverse events have been reported from this trial. In September 2000, a multicentre, randomised, double-blind study designed to evaluate the safety and efficacy of the liquid formulation began in children
living in China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, and Thailand. Enrolment was completed on November 11, 2000 with a total of 3175 children enrolled. This trial is continuing. In September 2000, a multicentre, randomised, double-blind study designed to evaluate the safety and efficacy of the liquid formulation began in children 6 to <36 months of age, and attending daycare in Finland, Belgium, Spain, UK and Israel.
Enrolment was completed on November 17, 2000 with a total of 1706 children enrolled. This trial is continuing.

In September 2000, a multicentre, open label study designed to evaluate the safety and efficacy of the liquid formulation began in children and adolescents aged 6 to 17 years living in Belgium, Finland, and Germany. Enrolment was completed on October 23, 2000 with a total of 498 children enrolled. No vaccine related serious adverse events

have been reported from this trial. This trial is continuing.

Comparison of Frozen and Liquid Formulations in Children

A direct comparison between the reactogenicity rates of the frozen formulation and the liquid formulations was made in clinical trial protocol D153P500. This was a randomised, observer-blind, controlled, multicentre clinical trial performed in South Africa from February 2000 to June 2000, to compare the safety and immunogenicity of the two formulations in children aged 12 months to 36 months of age. In total 1394 children were randomised on a 1:1 ratio to receive two doses one month apart of either the liquid or frozen formulations. Although the trial data with respect to individual treatment assignments remain blinded at this time, the preliminary reactogenicity data for all subjects are summarised in Table 2 for the two vaccine groups.

The data in Table 2 represent the cumulative total of subjects who experienced at least one episode of the symptom, irrespective of severity, during the 11 days of follow-up post-vaccination (Study Day 0 to Study Day 10) as obtained from worksheets completed by the parents or legal guardians. These are parental or legal guardian observations and did not involve pre-defined symptomatology.

No clinically pertinent differences can be observed between the rates of reactogenicity episodes in D153P500 for either study group and for either dose of the frozen or liquid formulations. The rates of respiratory symptoms following each dose were consistent between the two groups in D153P500, and importantly were also consistent with data summarised from Aviron clinical trials where approximately one-third of children aged 12 to 23 months experienced cough and 69% experienced runny nose or nasal congestion following receipt of CAIV-T [37]; and in previously published observations in the 2 month old to 18 month old age group, where at least one-third experienced cough and 57% experienced runny nose or nasal congestion following receipt of bivalent influenza A CAIV, compared with a rate of 50% in placebo recipients [39].

Table 2

Study D153P500 Reactogenicity events with onset Day 0 to 10 by Dose and Treatment Group (All data blinded)—Children 12-36 months of age

	Post-dose 1		Post-dose 2	
Events	**Group 1 (n=662)**	**Group 2 (n =658)**	**Group 1 (n=649)**	**Group 2 (n=649)**
Cough	341 (52)	313 (49)	289 (45)	265 (42)
Runny nose/ Nasal congestion	478 (73)	445 (69)	371 (58)	363 (57
Sore throat	72 (11)	58 (9)	35 (6)	43 (7)
Irritability	147 (23)	150 (24)	97 (15)	90 (14)
Headache	77 (12)	63 (10)	47 (7)	34 (5)
Chills	32 (5)	33 (5)	26 (4)	20 (3)
Vomiting	78 (12)	74 (11)	55 (9)	44 (7)
Muscle aches	34 (5)	21 (3)	16 (3)	5 (1)
Decreased Activity	88 (14)	49 (8)	44 (7)	38 (6)
Fever ≥37.5°C	67 (11)	61 (10)	65 (10)	66 (11)
Fever ≥38.5°C	28 (5)	24 (4)	33 (5)	37 (6)
Fever ≥40.0°C	1 (0.2)	2 (0.3)	4 (0.6)	5 (0.8)
Any reactogenic event	553 (84)	522 (81)	443 (70)	439 (70)

Groups 1 and 2 received either frozen or liquid versions of CAIV-T. The designation remains blinded at this time. The numbers in parentheses represent percentage of subjects who experienced an episode.

Good Clinical Practice and Regulatory Compliance

The study will be conducted in compliance with procedures outlined in this protocol, ICH harmonised tripartite guidelines for good clinical practice, the Declaration of Helsinki and with laws of Bangladesh.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

This is a phase III, randomised, partially-blinded, placebo-controlled, multicentre outpatient study to assess the safety, tolerability and immunogenicity of Influenza Virus Vaccine, trivalent, Types A & B, Live Cold-Adapted (CAIV-T) administered concomitantly with live, attenuated, orally administered poliovirus vaccine (OPV) to 2400 healthy children aged 6 to less than 36 months. Informed consent will be sought from all parent(s)/legal guardian(s) of children before any study-related procedures are performed.

Subjects will be prospectively randomised to one of three study groups in a 1:1:1 ratio as detailed below:

Study Group	No. of Subjects	Dose 1	Dose 2
1	800	CAIV-T (IN) OPV	CAIV-T (IN)
2	800	Placebo (IN) OPV	Placebo (IN)
3	800	CAIV-T (IN)	CAIV-T (IN)

CAIV-T = influenza virus vaccine, trivalent, types A and B, live, cold-adapted;
OPV= live, attenuated, trivalent, poliovirus vaccine, administered orally;
Placebo = placebo consisting of saline only
IN= intranasal

Each dose of intranasal CAIV-T or placebo will consist of approximately 0.2 ml in total volume administered as an intranasal spray using a spray applicator. Approximately 0.1 ml will be sprayed into each nostril. Details of the specific OPV to be used will be provided in the Investigator manual. OPV will be administered orally according to the manufacturer's instructions. Immediately following the vaccination each subject will be observed for 15 minutes for signs and symptoms of anaphylaxis and local reactions (e.g., nasal congestion/runny nose). The time interval between the assigned first dose and the assigned second dose will be 35 +/- 7 days. Prior to the second vaccination the subject will be assessed for continued eligibility.

A blood sample of approximately 5 millilitres will be collected from subjects on three occasions to evaluate immunogenicity using a serum hemagglutination inhibition assay for influenza virus types A/H1N1, A/H3N2 and B and a virus neutralisation assay for Polio types 1, 2, and 3. These blood samples will be collected prior to the first dose (study visit 1), prior to the second dose (study visit 2), and 35 +/- 7 days after the second dose (study visit 3). Specimen collection and processing guidelines will be provided separate from this document.
Following vaccination, field research assistants (FRAs) will visit each child at home for 11 consecutive days from the day of vaccination, Day 0 to Day 10, and collect data on axillary temperature, runny nose/nasal congestion, cough, vomiting, irritability, and decreases in appetite and activity level using a

standardised questionnaire. The FRA will then check the child's temperature with a digital thermometer supplied by WLV. If the child has fever, elevated respiratory rate (> 50/min) or danger signs (chest indrawing, lethargy, unwillingness to feed, convulsion, or cyanosis), then the FRA will immediately refer them to clinic. Information regarding any physician consultations and any other concomitant medications (excluding fluoride supplements and vitamins) will also be recorded for 11 days after each vaccination. These children are presently under weekly surveillance for disease incidence (dengue, ALRI, diarrhoea). After the daily visits for 11 consecutive days, routine weekly surveillance will be resumed and all study participants will be advised when to visit the field clinic for their scheduled blood draw on day 35± 7days post vaccination.

Adverse events will be monitored for 11 days following receipt of each dose of study vaccine. FRAs making daily home visits, as described above, will collect information on adverse events for all subjects. In addition, parent(s)/legal guardian(s) will be instructed to notify the Investigator should the subject develop any clinically significant illness or event, including but not limited to those requiring an unscheduled healthcare provider visit or prescription/non-prescription medications within 11 days (Days 0 to 10) of vaccination. All serious adverse events (SAEs) will be monitored from study enrolment to study completion. Details of the event, including concomitant medication(s) and treatment will be recorded on the SAE form provided.

If a subject terminates from the study due to an adverse event, the Investigator will report this to the Sponsor's pharmacovigilance group or designee, within 24 hours of learning of termination, by faxing the completed, signed and dated Subject Outcome page of the Case Report Form (CRF).

Table 3 summarises the study procedures for all subjects participating in the study. In order that study visits are scheduled within the correct timeframes, the day of study vaccination visit should be considered as Day 0.

Table 3

SCHEDULE OF PROCEDURES

Study Visits	1			2			3
Visit Window (Days After Previous Visit)	(0)	(2-4)	(10-12)	(35±7) (0)	(2-4)	(10-12)	(35±7)
Informed Consent	X						
Subject Eligibility	X						
Demography	X						
Medical History	X			◆			◆
Physical Examination	X						
Blood Sample	X			X			X
Vaccination	X			X			
Assess Acute Reactions – 15 Minutes Post Vaccination	X			X			
Daily home visits for complications and SAEs		X	X		X	X	
Review of Morbidity Data				X			X
Record Concomitant Medication Use	X			X			X
*Adverse Event Collection	X	X	X	X	X	X	X
Serious Adverse Event Reporting	X	X	X	X	X	X	X

Randomisation Procedures

A randomisation schedule will be prepared and provided by WLV or by their designate. Study participants will be prospectively randomised in a 1:1:1 proportion among Study Group 1, Study Group 2, and Study Group 3. See group distributions in Section 3.1.3. Once a subject number and/or treatment is assigned to a particular subject, it will not be reused, even if the subjects drops out of the study prior to administration of the first study vaccination.

Designated representatives of WLV will have a masked randomisation codebreaker list of treatment assignments for vaccine administration. Holders of the codebreaker list will maintain a written log of the indications for all instances of unblinding. This log will be made available for review at study completion. Requests to unblind any given subject or subjects must be directed to WLV. The treatment will be unblinded only in the event of a medical emergency and only in cases where the unblinding is necessary for the immediate treatment of the subject.

Blinding and Vaccine Dispensing Procedures

To minimise bias in the reporting of post-vaccination reactions and other study events, neither the study subjects, their parent(s)/legal guardian(s) nor the clinical personnel will know whether intranasal CAIV-T or placebo is being administered for those subjects assigned to Study Groups 1 and 2.

All vaccines will be dispensed according to applicable local procedures, laws and regulations. Dispensing procedures will be provided to the Principal Investigator at each site and filed with all study-related documents. In addition, individuals with the responsibility of dispensing vaccines in this study will be listed on the Authorised Signature
Record/Investigator Delegation Log.

Study Vaccine

Liquid CAIV-T consists of three cold-adapted influenza virus reassortants that have been concentrated and purified by centrifugation from the allantoic fluid of specific pathogen-free (SPF) chicken eggs. The formulation contains sucrose-phosphate-glutamate, acid-hydrolysed porcine gelatin and arginine as stabilisers. The total volume of 0.2 ml is administered intranasally with a spray applicator (approximately 0.1 ml into each nostril). Each dose of CAIV-T used in this study will contain approximately $10^{7+0.5}$ $TCID_{50}$ of each of the three influenza virus strains. The placebo consists of physiological-normal saline. The total volume of 0.2 ml is administered intranasally with a spray applicator (approximately 0.1 ml into each nostril). The concomitant vaccine will be a live, attenuated, trivalent, poliovirus vaccine (OPV). OPV will be administered orally according to the manufacturer's instructions.

Each dose of CAIV-T or intranasal placebo contained in the spray applicator will be supplied as identically packaged, single-dose units. Study vaccine sprayers and outer packaging boxes will be labelled as investigational products in accordance with applicable local, legal and regulatory requirements. All supporting regulatory documentation as required by local regulatory agencies and the Sponsor will be in place and verified prior to shipment of vaccine to the clinical study centres.

Liquid (IN) CAIV-T and placebo will be shipped to each study centre upon request of the Sponsor. Receiving departments should be notified that rapid handling of the shipment is required. Upon receipt at study site, the liquid CAIV-T and placebo should be immediately transferred to a 2°C to 8° C refrigerator. Once the vaccine is stored in
refrigerated conditions it should not be frozen. OPV will be stored according to the instructions provided in the Investigator's Manual. The refrigerator must be secure and with limited access. We will monitor refrigerator temperature and maintain daily temperature logs. Receipt and storage of all study treatments will be documented on the Vaccine Accountability Record (or equivalent) provided by the Sponsor. Study vaccine will not be used after the specified expiration date.

Exact written records of receipt and storage of all study treatments, including date received, quantity received, and each administered dose with the identification of the subject, must be present. Any known discrepancies in the accountability of the study vaccine must be adequately documented. At the end of the trial by prior agreement with the Sponsor, the Investigator (or named designee) will return to the Sponsor (or designee) all unused vaccine. The Investigator will not use any study treatments in any other manner than that provided for in the protocol.

Subject Participation

Approximately 2,400 subjects will be enrolled at multiple centres (India, Malaysia, Thailand, Philippines, Mexico, turkey, and Bangladesh) beginning approximately September 1, 2001. We expect to enrol 350-400 participants at the Bangladesh study site (Kamalapur). The last subject is expected to be enrolled no later than October 15, 2001. The study duration for each participant will be approximately 3 months.

An Investigator and/or Sponsor may withdraw a subject from the study if deemed appropriate. Criteria for termination of a subject from the study may include, but are not limited to, request for withdrawal, loss of subject to follow-up or clinically significant adverse events that constitute contraindications to further vaccine administration.

It is the policy of the sponsor, Wyeth Lederle Vaccines, that study data must be verifiable from the source data, which necessitates access to all original recordings, laboratory reports, and subjects' records. The investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. The parent(s)/legal guardian(s) must also allow access to the subjects' medical records, and they will be informed of this and will be signing their agreement when giving informed consent. The subject diary card is considered to be a source document and relevant information regarding adverse events and concomitant medications from this document must be recorded onto the CRF.

The following selection criteria must be met in order for the subject to participate in the study.

Inclusion Criteria

Subject must fulfil all of the following conditions or characteristics in order to be considered for study enrolment and vaccination. Subjects must:

-- be at least 6 months of age and less than 36 months of age at the time of first vaccination

-- have received a full primary vaccination schedule consisting of three doses of OPV in the first year of life

-- be in good health as determined by medical history, physical examination and clinical judgement

-- have written informed consent of parent(s)/legal guardian(s)after the nature of the study has been explained

-- along with their parent(s)/legal guardian(s) be available for duration of the trial (3 months)

--- be reachable by study staff through home visit, clinic, or telephone for post-vaccination contacts.

Exclusion Criteria

Subjects with any of the following conditions or characteristics will be excluded from study enrolment:

--- parent(s)/legal guardian(s) are perceived to be unavailable or difficult to contact for evaluation or study visits during the study period

--- any serious chronic disease (e.g., with signs of cardiac or renal failure or severe malnutrition), including progressive neurological disease

--- Down's syndrome or other known cytogenetic disorders

--- known or suspected disease of the immune system or those receiving immunosuppressive therapy, including systemic corticosteroids (see corticosteroid section below)

--- received any blood products, including immunoglobulin, in the period from six months prior to vaccination through to the conclusion of the study

--- There is intent to administer any other investigational vaccine or agent from one month prior to enrolment through to the conclusion of the study
--- there is an immunosuppressed or an immunocompromised individual living in the same household
--- at any time prior to entry into this study, received a dose of any influenza vaccine (commercial or investigational)
--- a documented history of hypersensitivity to egg or egg protein or any other component of the assigned study vaccine
--- received aspirin (acetylsalicylic acid) or aspirin-containing products in the two weeks prior to vaccination or for which use is anticipated during the study
--- any medical conditions that in the opinion of the Investigator might interfere with interpretation of the study results.

If any of these criteria are met following enrolment, the subject will be excluded from subsequent vaccine dosing.

Definition of Corticosteroid Use

For the purposes of this clinical trial, corticosteroid use as defined by the committee of Infectious Diseases of the American Academy of Pediatrics, The Red Book [40], will meet the exclusion criterion. The Red Book text concerning this is as follows:

Children who receive corticosteroid therapy can become immunocompromised. The minimal amount of systemic corticosteroids and duration of administration sufficient to cause immunosuppression in an otherwise healthy child are not well defined. The frequency and route of administration of corticosteroids, the underlying disease, and concurrent other therapy are other factors affecting immunosuppression. Despite these uncertainties, sufficient experience exists to recommend empiric guidelines for administration of live-virus vaccines to previously healthy children receiving corticosteroid therapy for nonimmunocompromising conditions. Many clinicians consider a dosage equivalent to 2 mg/kg per day or greater of prednisone or equivalent to a total of 20 mg/day or greater for children who weigh more than 10 kg, particularly when given for more than 14 days, sufficient to raise concern about the safety of immunisation with live-virus vaccines. Accordingly, guidelines for administration of live-virus vaccines to recipients of corticosteroids are as follows:

Topical therapy or local injections of corticosteroids. Administration of topical corticosteroids, either on the skin or in the respiratory tract (i.e., by aerosol) or eyes, and intra-articular, bursal, or tendon injections of corticosteroids usually do not result in immunosuppression that would contraindicate administration of live-virus vaccines. However, live-virus vaccines should not be administered if clinical or laboratory evidence of systemic immusuppression results from prolonged application until corticosteroid therapy has been discontinued for at least 1 month.

Physiologic maintenance doses of corticosteroids. Children who are receiving only maintenance physiologic doses of corticosteroids can receive live-virus vaccines during corticosteroid treatment.

Low or moderate doses of systemic corticosteroids given daily or on alternate days. Children receiving less than 2 mg/kg per day of prednisone or its equivalent, or less than 20 mg/d if they weigh more than 10 kg, can receive live-virus vaccines during corticosteroid treatment.

High doses of systemic corticosteroids given daily or on alternate days for 14 days or more. Children receiving 2 mg/kg per day or more of prednisone or its equivalent, or 20 mg or more daily if they weigh more than 10 kg, should not receive live-virus vaccine until corticosteroids therapy has been discontinued for at least 1 month.

Criteria for Temporarily Delaying Vaccination Administration

In general, the subject must be in good health (by physical examination and medical history) at the time of each study vaccination. The following conditions are temporary or self-limiting and a subject may receive study vaccine once the condition(s) has/have resolved and no other exclusion criteria are met:

-- A febrile illness (axillary temperature > 37.5°C) or other acute illness within 36 hours prior to study vaccine administration.
-- A respiratory illness in the subject and/or household member within 72 hours prior to study vaccine administration. Study vaccination of the subject may occur if a subject is experiencing mild symptoms of the common cold (e.g., slight cough and a runny nose), which is not going to be medically treated, and if the investigator feels that the subject's condition is not a respiratory illness and does not require any special clinical management. If the symptoms require medical intervention, it should be considered a respiratory illness and the study vaccination should be delayed until the illness has resolved. Vaccination should be delayed if a subject is taking medication (other than an antibiotic—see below) to prevent a particular respiratory related symptom (e.g., runny nose). In addition, if nasal blockage exists, it must be minimal enough to not reduce the likelihood of successful administration of the vaccine.
-- Treatment of the subject with an antibiotic within 72 hours prior to study vaccine administration. Vaccination should be delayed if the subject requires any medical intervention with an antibiotic at the time of vaccination. If a subject is currently taking medicine (other than an antibiotic) at the time of vaccination for prophylaxis against a non-respiratory related illness, the subject may be vaccinated.
-- Administration of any live virus vaccine (other than assigned study vaccine) within one month prior to enrolment or expected to receive another live virus vaccine (other than assigned study vaccine) within one month of vaccination in this study.
-- Receipt of the third dose of the primary schedule of OPV within the 60 days prior to the first study vaccination.
-- Receipt of any subsequent dose of OPV (a fourth or later dose) within 60 days prior to the first study vaccination.
-- Receipt of a dose of any influenza treatment (commercial or investigational) in the two weeks prior to vaccination.
--- A clinically confirmed febrile respiratory illness with wheezing within two weeks prior to vaccination. For a non-complicated, non-febrile wheezing episode, a delay of 72 hours will suffice.

All subjects must receive the first dose of study vaccine within the defined recruitment period and the second dose of study vaccine no later than 42 days following the first dose of study vaccine, for subject to be considered fully immunised according to protocol.

Withdrawal criteria

Participating subjects will be contraindicated to subsequent doses of study vaccine if the subject has a related Serious Adverse Event (SAE) or any other related alarming or unusual event, including anaphylaxis. Any AE which is not considered vaccine related, but that is of concern will be discussed with the Sponsor prior to the administration of the subsequent dose.

A subject can be withdrawn from the study if deemed appropriate. Criteria for withdrawal of a subject from the study include, but are not limited to, request for withdrawal, subject lost to follow-up, development of any condition specified in the exclusion criteria, clinically significant adverse events and events that constitute contraindications or precautions to further vaccine administration. Following enrolment, development of any condition specified in the initial exclusion criteria will constitute a

contraindication to subsequent dosing. However, the subject will be followed for safety and blood sample collection until the completion of the study, where possible. If an intervening illness does not resolve, the subject may be discontinued from the study at the discretion of the Investigator. Where possible the tests and evaluations listed for the next scheduled study visit will be performed. Information must be collected on any new/continuing adverse events and concurrent medications since the last study visit. Any serious adverse events that are continuing at the time of withdrawal from the study must be followed to resolution. An effort must be made to determine why a subject fails to return for the necessary visits or discontinued from the study. Information detailing the circumstances leading to the withdrawal of a subject from the study, as well as the date of withdrawal, will be recorded on the Study Outcome Case Report Form and reported to the Sponsor/designee within 24 hours. Additional subjects will not be enrolled to replace discontinued/withdrawn subjects.

Study procedures

The schedule of procedures for individual study participants is presented in Table 3. To ensure study visits are scheduled within the correct timeframes, the day of each vaccination visit should be considered as Day 0.

Study Screening Procedures

Prior to enrolment, the Investigator will review the subject's medical history to ensure that the subject is in good health and meets all of the inclusion criteria and none of the exclusion criteria.

Informed Consent

Informed written consent will be obtained in the privacy of study subject's home. The parent(s)/legal guardian(s) of subjects who fulfil all the study eligibility criteria will be informed of the purpose and conduct of the study and asked to read the information leaflet and consent form. Voluntary written study-specific informed consent will be obtained from the parent(s)/legal guardian(s) before any study-related procedures are performed. The parent(s)/legal guardian(s) must sign and date the consent form. [] The Investigator (or authorised designee listed on the Authorised Signature Record/Investigator Delegation Log) is responsible for obtaining written informed consent for each subject enrolled. Each signature on the informed consent form must be personally dated by the signatory. A copy of the signed and dated Informed Consent Form is given to the subject's parent(s)/ legal guardian(s). The subject's source documentation must reflect that informed consent was obtained prior to participation in the study. Following informed consent, baseline household demographic data will be updated and parent(s)/legal guardian(s) will be given a date and time to bring children to the field clinic for all procedures and vaccination.

Study Visit Procedures

Study Visit One, (Day 0)

-- Obtain and record medical history, including current medication usage and vaccination history (see section 6.2).

-- Perform physical examination, including axillary temperature, to determine that no acute illness is present.

If the subject continues to meet all of the inclusion criteria, *and* none of the exclusion criteria, assign the next sequentially-available subject identification number.

-- Collect approximately 5 ml of blood (before vaccination) for immunogenicity testing.

-- Administer a single dose of assigned study treatment see section 6. The appropriate study personnel must update the vaccine accountability records.

Note: The assigned oral study treatment should be administered first (if applicable), with the assigned intranasal study treatment administered no more than 30 minutes later.
-- After vaccination, observe each subject for a minimum of 60 minutes. Emergency management supplies (AMBU bag, adrenaline (epinephrine), and antihistamines) will remain available for initial treatment of an allergic reaction if needed. (All medical personnel will have been trained on treatment procedures regarding emergency intervention for anaphylaxis.) Record any local reactions or systemic events on adverse event pages in the CRF.
-- Beginning that afternoon and for the following 10 days, daily axillary temperature and reactogenicity events will be captured on a standardised questionnaire by the FRAs. They will also record any other adverse events, unscheduled physician visits, concomitant prescription and non-prescription medication used.
-- The parent(s)/ legal guardian(s) will be asked to contact their FRA or the field clinic immediately if any significant illness or hospitalisation occurs during the study period.
-- Any subject with a clinically significant event (e.g., high fever, convulsion, etc) will be evaluated immediately by a study physician.
-- Serious adverse events (SAEs) data, regardless of causality, will be collected up to study completion. Treatment for such events will be provided by the study, including hospitalisation, at no cost to the study subject.
-- The subject and parent(s)/legal guardian(s) will be given an appointment to return for their next study visit.
-- Record all information in the appropriate source documents, and complete the CRF.

Study Clinic Visit Two, (Day 0)

This visit occurs 35 (+/- 7) days after the first dose of assigned study vaccine. Surveillance staff will visit the home prior to the scheduled visit to remind the parent.
-- Review patient information from previous visit. Obtain and record interim medical history including all adverse events and concomitant medications between Day 0 and Day 10 following the first dose of assigned study treatment (see section 6.2).
-- Assess subject to ensure continued study eligibility. Record axillary temperature, to determine that no acute illness is present.
If the subject continues to meet the study eligibility criteria:
-- Collect approximately 5 ml of blood for immunogenicity testing.
-- Administer assigned intranasal study treatment. The appropriate study personnel must update vaccine accountability records.
-- After vaccination, observe each subject for a minimum of 60 minutes. Emergency management supplies (AMBU bag, adrenaline [epinephrine], and antihistamines) will remain available for initial treatment of an allergic reaction if needed. Record any local reactions or systemic events on adverse event pages in the CRF.
-- Initiate home visits by the FRA as described above, beginning with the afternoon of the immunisation day.
-- The parent(s)/legal guardian(s) are asked to contact the FRA or field clinic immediately if any significant illness or hospitalisation occurs during the study period.
-- Any subject with a clinically significant event (e.g., high fever, convulsion, etc) should be evaluated immediately by a study physician.
-- Serious adverse events (SAEs) data, regardless of causality, will be collected up to study completion. All treatment and associated costs will be provided by the study, as described above.
-- Record all information in the appropriate source documents, and complete the CRF.

Study Visit Three, Study Termination

This visit occurs 35 (+/- 7) days after the second dose of assigned study vaccine. Surveillance staff will contact the parent/guardian and arrange for this visit to the clinic or arrange for the visit with blood collection to occur at home.

--- Review subject data from the last visit.

--Obtain and record interim medical history since the last study visit (visit two). Obtain and record all adverse events and concomitant medications between Day 0 and Day 10 following second dose of assigned study treatment (see section 6.2).

-- Collect approximately 5 ml of blood for immunogenicity testing.

-- Serious adverse events (SAEs) data, regardless of causality, will be collected up to study completion. Any SAE ongoing at study termination must be followed until resolution.

-- Record all information in the appropriate source documents, and complete the CRF.

VACCINE ADMINISTRATION

Vaccine to be Administered

At study Visit 1, each enrolled subject will receive either intranasal CAIV-T, or saline placebo, and may concomitantly receive OPV, as assigned. At Study Visit 2, the subject will receive the same intranasal study treatment that he/she received at Visit 1, but no oral treatment. The time interval between Dose 1 and Dose 2 will be 35 (+/- 7) days.

Epinephrine 1:1000 (1 mg/ml) and resuscitative equipment should be available in the event of an anaphylactic reaction.

Handling of Study Treatments

The intranasal study treatments should be allowed to come to room temperature for 5 minutes just prior to use.

Details of the specific OPV to be used will be provided in the Investigator manual.

Administration of Study Treatments

-- OPV will be administered orally according to the manufacturer's instructions.

-- A single intranasal administration comprises delivery of approximately 0.1 ml CAIV-T or placebo into each nostril.

-- Each spray applicator of CAIV-T or placebo has an adapter that allows delivery of approximately half the contents to one nostril. Removal of the adapter allows delivery of the remaining vaccine to the other nostril.

-- CAIV-T or placebo will be sprayed as a fine mist into each nostril while the child is in an upright position.

--- After vaccination, all participants will be observed for a minimum of 15 minutes by the study staff. Emergency management supplies (for example: AMBU bag, adrenaline [epinephrine] and antihistamine) will remain available for initial treatment of an allergic reaction if needed. Local reactions or systemic events must be recorded on adverse
event pages in the CRF.

Accountability and Disposal of Used/Unused CAIV-T and Placebo

-- Used study treatment applicators will be placed in locked containers or sealed bags immediately after use. Used vaccine applicators will not be discarded until instructed to do so by the Sponsor (or designee). Instructions will be provided as to the correct disposal of applicators.

-- Unused CAIV-T and placebo will be maintained at 2°C to 8°C in a refrigerator and monitored daily until return or destruction of supplies is arranged. The sponsor (or designee) will provide written instruction for shipment conditions and procedures.

Concurrent Vaccinations and Other Treatments

-- Routine childhood vaccinations (excluding live viral vaccines) administered at the time of CAIV-T or placebo administration will be recorded.

-- Medication(s) the child is taking at the time of enrolment will be obtained from the parent(s)/legal guardian(s) in order to understand any risk of reactions.
-- During the Day 0 to Day 10 post-vaccination period, use of any non-prescription and prescription medications (including antipyretics, decongestant/antihistamines, analgesic preparations, and antibiotics) will be reported (exceptions: vitamins, iron, fluoride supplements). This includes any prescription or non-prescription medications or
treatments given as countermeasure therapy during an Adverse Event.

Allowable Concurrent Vaccines

CAIV-T may be administered concomitantly with routinely scheduled vaccines (excluding live viral vaccines). Any concomitantly administered vaccines will be recorded.

Restricted Use of Other Vaccines

A live virus vaccine must not be administered within one month prior to study vaccination or 1 month following receipt of study vaccination. A dose of OPV must not have been administered in the 60 days prior to study enrolment.

Other Restricted Treatments

-- Aspirin (acetylsalicylic acid) and aspirin-containing products must not be given to study participants during the trial as the use of salicylates in children with concurrent influenza illness has been associated with Reye's syndrome.
-- Anti-influenza antiviral therapy (e.g., neuraminidase inhibitors, amantidine, rimantidine) must not be given to study participants prophylactically during the trial as these may interfere with assessment of true vaccine take and illness incidence.

Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. **(TYPE WITHIN THE PROVIDED SPACE).**

Features of the Study Site Where the Visit Will Occur

Kamalapur is an urban slum located in the southeastern sector of the Capitol city, Dhaka approximately 30 – 40 minutes drive from ICDDR,B. The intervention area is spread over 4.0 sq Km (1.5 sq mile or 988 acres) There are 32,339 households in the community, all of which have been entered into an electronic database maintained at ICDDR,B. The total population as of 30 November 2000 was 118,654. The outmigration rate averages < 2%, however the population of the community has doubled since 1997, largely as a result of immigration from rural areas. The population is relatively young. In our 1998 census, the mean age of mean was 32.8 years, of women was 24.2 years, while 11.2% of the population was less than five years old.
There is a mixture of squatter settlements and formal permanent structures. The mean household size 4.0 but ranges from 1 – 20 persons per household. Population density is 29,663 per square kilometre (191 persons per acre or 77,048/sq mile). Educational levels in the community among adults are low, however the majority of children less than 12 years attend school. Mean level of schooling for men above 18 years old is 4.5 years, and for women is 3.1 years. Unemployment is relatively low. Most men less than 60 years are employed at least part time, resulting in total unemployment of only 1.6%. Among occupations, the most common for men are merchant (24.2%), office worker (21.6%), rickshaw puller (17.0%), and skilled labourers (12.3%). Day labourers and unskilled workers comprise only 7.7%. (See Figure 1 below.) The mean family income is TK 3,000 or about US $60/month.

Vaccine coverage for the community is inconsistent and varies by age and type of vaccine. Among the rates of coverage: BCG: 82.8% among children less than 12 months; DPT 1 among 2 month olds = 48.9%; However 81.3% have at least one DPT by 12 months of age; DPT 2 among 4 month olds = 25.2%;DPT 3 among 6 month olds = 65.3%;OPV 1 among 2 month olds = 55.9%;OPV 2 among 4 month olds = 54.4%;OPV 3 among 6 month olds = 97.5%;Measles coverage among children 9 – 12 months old = 45.2%.

Surveillance System

- Active surveillance system, i.e. we actively collect data using a standardised calendar questionnaire.
- Once weekly home visits by a field research assistant (FRA) to every household for data collection.

- The questionnaire asks about specific signs associated with disease for the past seven days since the last visit.
- Those with illness are referred to the field clinic.
- A field research officer (FRO) supervises the FRAs.
- The FRO sends daily field reports to our office as indicator of the system's performance. Quality assurance also maintained by repeat visits of a sub-sample of the home interviews and weekly staff meetings.

The Clinic

- Staff: 3 medical officers (MO), 3 nurses and 6 health workers.
- MO conducts a history and physical exam on all visitors using a standardised questionnaire to protect the uniformity of case detection.
- Perform appropriate lab tests on all patients meeting our standardised case definitions for diseases under study.
- Treat illnesses using standardised protocols. Follow-up all patients by 48 hours of starting therapy.
- Refer anyone with severe to ICDDR,B hospital or to one of our partner hospitals.

Research Activities

0. Pneumonia surveillance in children less than 2 years old: just completed. Study was designed to determine disease burden (incidence and prevalence) and provide primary disease prevention using pharmacological dose of zinc to reduce to the attack rate (lower the incidence). Results being analysed.
0. Dengue Emergency Response Surveillance: To determine disease burden in the community and conduct a nested case control analysis to determine risk factors dengue and dengue haemorrhagic fever for this population.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. **(TYPE WITHIN THE PROVIDED SPACE).**

Data from this multicentre trial will be analysed by WLV. Data collected specifically from this site in Bangladesh will also be analysed by the investigators at ICDDR,B. SPSS and/or SAS will be used to analyse the data. Given the short duration of this study, no interim analysis will be done. The code will be opened at the conclusion of the study (when 2400 patients have completed participation in the multi-centre study).

The multidimensional comparison of primary interest is (1) to evaluate non-inferiority of the serum antibody response to OPV following concomitant administration with CAIV-T relative to the response to OPV administered separately temporally (at least 1 month apart) from CAIV-T and (2) to evaluate non-inferiority of the serum antibody response to CAIV-T following concomitant administration with OPV relative to the immune response of CAIV-T administered separately temporally (at least 1 month apart) from OPV. The response criterion for each viral strain of CAIV-T is a four-fold increase from baseline titre in the hemagglutination inhibition assay (HAI) for influenza virus strains A/H3N2, A/H1N1, and B. The response criterion for each antigen component of OPV is a post-vaccination titre of 1:10 for Poliovirus types 1, 2, and 3 by virus neutralisation assay. The primary analysis interval for influenza strains A/H1N1, A/H3N2, and B is one month following the second intranasal vaccination. The primary analysis interval for poliovirus types 1, 2, and 3 is one month following the single dose of OPV. The primary analysis endpoint will be achieved if lower limits of six independent 95% one-sided confidence intervals for differences in response rates are each greater than -10%.

It is expected that approximately 2,400 subjects will be enrolled in at multiple study sites. Determination of the appropriate sample for this study is dependent on the following assumptions:

-- Loss to follow-up is not greater than 15%.
-- Post-dose 2 influenza antibody response rates, measured as a four-fold or greater increase from baseline serum hemagglutination assay (HAI) will be similar to those observed in earlier studies of CAIV- T, ranging from 48% to 68% for the three strains □ Immune response rates for OPV measured at the end of the study by 1:10 or greater
virus neutralisation assay titres for Poliovirus types 1, 2, and 3 will be similar to those observed in earlier studies of OPV and may be as low as 75%.[32,36]
-- The co-administration of CAIV-T with OPV will be demonstrated not to interfere with immune response to poliovirus and co-administration of OPV with CAIV-T will be demonstrated not to interfere with immune response to CAIV-T if each lower bound of 95% one-sided confidence intervals for the Poliovirus type 1, Poliovirus type 2, and
Poliovirus type 3 response rates compared between Study Group 1 and Study Group 2 AND each lower bound of 95% one-sided confidence intervals for the A/H1N1, A/H3N2, and B response rates after 2 doses compared between Study Group 1 and Study Group 3 is greater than -10%. A study with at least 680 subjects completed in each treatment group would provide 98% power to demonstrate that a treatment with a true response rate of 55%, is non-inferior to a reference treatment with a true response rate of 55%, on a 10% criterion for non-inferiority. The simultaneous evaluation of six independent comparisons, each with 98% probability of success, provides an overall probability of success greater than 90%. The planned enrolment will provide at least 90% power to demonstrate non-inferiority of co-administration compared to separate administrations (at least one month apart) of liquid CAIV-T and OPV based on response criteria for antibody levels to three polio antigens and three influenza virus strains.
The proportion of responders for concomitant administration of CAIV-T and OPV
(Group 1) will be compared with the immune response to polio antigens in Group 2 and the immune response to influenza antigens in Group 3. The non-inferiority evaluation will be based on exact 90% two-sided confidence intervals for the six differences in proportions . If the lower limit of the confidence interval ** of _co-admin- _reference is _-10% for polio antigen Types 1, 2, and 3 and for influenza strains A/H1N1, A/H3N2 and B, then the null hypothesis of inferiority with respect to a 10% criterion will be rejected at =0.05. StatXact will be used to determine the exact confidence interval. In a secondary analysis the comparison between co-administration and separate administration regimens will be based on the antibody titre (polio) or the titre ratio to baseline (influenza) expressed on a logarithmic scale. The t-test of the mean difference (in log) will be used to form the 90% confidence interval. The estimated difference and the confidence interval will then be exponentiated to obtain the GMT (geometric mean titre, polio) or GMR (geometric mean ratio, influenza) ratio (co-admin./reference) and its 90% confidence interval. If the lower limit of each confidence interval is _ 0.5, the null hypothesis of inferiority with respect to a two-fold criterion will be rejected at =0.05.

Each of the six immune responses will be evaluated at level of 0.05. The overall level for the six tests remains <0.05 as the null hypotheses for the six tests are required to be rejected simultaneously in order to demonstrate the acceptability of responses of co-administration.

Subjects who were immunised per protocol with blood samples drawn per protocol will be included in the immunogenicity analysis. Specifically, subjects must meet the following criteria to be included in the immunogenicity
analysis:
-- The first blood draw (Pre Dose 1) must have occurred at the day of the first dose but prior to the first dose.
-- Time interval between the first and second doses must be 35 + 7 days.

-- The second blood draw (Post Dose 1) must have occurred at the day of the second dose but prior to the second dose.
- Time interval between the second dose and the third blood draw (Post Dose 2) must be 35 + 7 days.

Influenza Seronegative Baseline Population – defined for each influenza strain: Those subjects of the immunogenicity evaluable population who had baseline titres for serum A/H1N1, A/H3N2, or B HAI less than or equal to 1:4.

Immunogenicity All Available Population: Subjects who received at least one dose of the assigned treatment and had a pre-dose and post-dose evaluation of serum antibodies.

Safety Population: Subjects who received at least one dose of the assigned treatment.

The demographic data, including gender, and age at each dose, of the immunogenicity and safety analysis populations will be summarised. Baseline serum antibody levels will be reported and the subject definition for seronegative baseline will be applied as a grouping criterion for some immunogenicity outcome summaries.

The primary measure of immunogenicity will be:

--- Poliovirus types 1, 2, and 3 by virus neutralisation assay;
-- Influenza virus strains A/H3N2, A/H1N1, and B by hemagglutination inhibition assay (HAI). OPV immune response for each poliovirus type is measured at the end of study by 1:10 or greater virus neutralisation assay titre.
CAIV-T immune response for each virus strain is measured at the end of study by an increase from baseline HAI of four-fold or greater. The primary endpoint for immunogenicity is the proportion of subjects achieving a post-vaccination serum antibody response (as defined above) for each antigen component of OPV and CAIV-T. The primary analysis interval for influenza strains A/H1N1, A/H3N2, and B is one month following the second intranasal vaccination. The primary analysis interval for poliovirus types 1, 2, and 3 is one month following the single dose of OPV.

The secondary endpoint for immunogenicity is the titre of serum antibody for each antigen component of OPV and the titre ratio to baseline of serum antibody to each virus strain of CAIV-T obtained 1 month after vaccination.

The primary analysis interval for influenza strains A/H1N1, A/H3N2, and B is one month following the second intranasal vaccination. The primary analysis interval for poliovirus types 1, 2, and 3 is one month following the single dose of OPV.

The safety objective is to assess the safety and tolerability of CAIV-T in healthy children aged 6 to less than 36 months.

The reactogenicity adverse events are:
Fever (axillary temperature > 37.5°C); Cough; Runny nose or nasal congestion; Irritability; Vomiting; Decreased activity; and Decreased appetite.

The proportion of subjects with any reactogenicity event reported and with other adverse events on any day during the 11-day period following each dose of CAIV-T or placebo will be evaluated. Serious adverse events occurring within 42 days of the first or second vaccination will be listed and summarised.

The overall incidence of reactogenicity events will be compared between the individual CAIV-T groups and the combined Placebo groups using two-sided Fisher's Exact Test. Exact 95% confidence intervals about reactogenicity adverse event frequency differences will be reported. The frequency of other adverse events will be separately compared between subjects randomised to CAIV-T or Placebo using two-sided Fisher's Exact Test.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

This trial will be performed in accordance with the principles of the Declaration of Helsinki/Somerset West, Republic of South Africa, October 1996.

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s), the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and ethical principles.
The Informed Consent Form describes that participation is voluntary and can be terminated at any time without reason. In addition, the parent(s)/legal guardian(s) will receive information on the study vaccine(s) to be used in the study. The scope of the trial will be explained. By signing the Informed Consent Form, the parent(s)/legal guardian(s)
confirms the child's voluntary participation and their intention to follow the study protocol and the instructions of the Investigator. The Investigator is responsible to obtain written informed consent for each subject enrolled. The Informed Consent Form must be signed and dated by the parent(s)/legal guardian(s) prior to study enrolment. Each parent/legal guardian will receive a copy of the signed Informed Consent Form.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

Animals will not be used in the conduct of this trial.

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

1 Maassab HF, Francis, Jr T, Davenport FJ, Hennessy AV, Minuse E, Andern G. 1969. Laboratory and clinical characteristics of attenuated strains of influenza virus. Bull WHO 41:589-592.

2 Maassab HF, Herlocher ML. 1999. Live influenza virus vaccine. In: Plotkin SA and Orenstein W (eds) Vaccines, 3 rd Edition WB Saunders Co, Philadelphia, pp. 909-927.

3 Glezen WP. 1982. Serious morbidity and mortality associated with influenza epidemics. Epidemiol Rev 4:25-44.

4 Couch RB, Kasel JA, Glezen WP, et al. 1986. Influenza: Its control in persons and populations. J Infect Dis 153:431-440.

5 Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. 1997. Influenza virus infections in infants. Ped Infect Dis J 16:1065-1068.

6 Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, Black S, Shinefield H, Fukuda K. NEJM 342, 2000: 232-239.

7 Neuzil KM, Mellen BG, Wright PF, Edward FM, Griffin MR. NEJM 342, 2000: 225-231.

8 Dong-Lu Z, Zi-Jing Z, Zhi-Liang W, et al. 1988. Surveillance of acute respiratory infections in three kindergartens in Beijing. Chinese Med J 101:787-792.

9 Ruutu P, Halonen P, Meurman O, et al. 1990. Viral lower respiratory tract infections in Filipino children. J Infect Dis 161:175-179.

10 Huq F, Rahman M, Nahar N, et al. 1990. Acute lower respiratory tract infection due to virus among hospitalised children in Dhaka, Bangladesh. Rev Infect Dis 12:S982-S987.

11 Doraisingham S, Goh KT, Ling AE, Yu M. 1988. Influenza surveillance in Singapore: 1972-86. Bull WHO 66:57-63.

12 Chew FT, Doraisingham S, Ling AE, et al. 1998. Seasonal trends of viral respiratory tract infections in the tropics. Epidemiol Infect 121:121-128.

13 Joosting AC, Harwin RM, Orchard M, Martin E, Gear JH. Respiratory viruses in hospital patients on the Witwatersrand. A 7-year study. S Afr Med J. 1979; 55:403-408.

14 Schoub BD, Johnson S, McAnerney JM, Martin E, dos Santos IL. Laboratory studies of the 1984 influenza epidemic on the Witwatersrand. S Afr Med J. 1986; 70:815-818

McAnerney JM, Johnson S, Schoub BD. Surveillance of respiratory viruses. A 10-year laboratory-based study. S Afr Med J. 1994; 84:473-477.

16 Schoub BD, Johnson S, McAnerney J, Blackburn NK. Benefits and limitations of the Witwatersrand influenza and acute respiratory infections surveillance programme. S Afr Med J. 1994; 84:674-678.

17 Avila M, Salomon H, Carballal G, Ebekian B, Woyskovsky N, Cerqueiro MC, Weissenbacher M. Isolation and identification of viral agents in Argentinian children with acute lower respiratory tract infection. Rev Infect Dis. 1990; 12(Suppl 8):S974-S981.

18 Weissenbacher M, Carballal G, Avila M, Salomon H, Harisiadi J. Catalano M, Cerqueiro MC, Murtagh P. Etiologic and clinical evaluation of acute lower respiratory tract infections in young Argentinian children: an overview. Rev Infect Diseases. 1990; 12(Suppl 8):S889-S898.
19 do Nascimento JP, Chaves JR, Ferreira V, Siqueira MM, Krawczuk MM, Deane G de M, Sutmoller F. Influenza surveillance in Rio de Janeiro between 1980-1981: a virological and serological study. Memorias do Instituto Oswaldo Cruz. 1984; 79:169-173.
20 de Arruda E, Hayden FG, McAuliffe JF, *et al.* Acute respiratory viral infections in ambulatory children of urban northeast Brazil. J Infect Dis. 1991; 164:252-258.
21 Nascimento JP, Siqueira MM, Sutmoller F, Krawczuk MM, de Farias V, Ferreira V, Rodrigues MJ. Longitudinal study of acute respiratory diseases in Rio de Janeiro: occurrence of respiratory viruses during four consecutive years. Revista do Instituto de Medicina Tropical de Sao Paulo. 1991; 33:287-296.
22 Sutmoller F, Ferro ZP, Asensi MD, Ferreira V, Mazzei IS, Cunha BL. Aetiology of acute respiratory tract infections among children in a combined community and hospital study in Rio de Janeiro. Clin Infect Dis. 1995; 20:854-860.
23 Ceruti E, Diaz A, Vicente M, *et al.* Aetiology of lower respiratory infections in hospitalised infants. Revista Chilena de Pediatria. 1991; 62:155-166.
24 Fleming DM. Cohen JM. Experience of European collaboration in influenza surveillance in the winter of 1993-1994. Journal of Public Health Medicine. 1996; 18:133-142.
25 Lina B. Valette M. Foray S. Luciani J. Stagnara J. See DM. Aymard M. Surveillance of community-acquired viral infections due to respiratory viruses in Rhone-Alpes (France) during winter 1994 to 1995. Journal of Clinical Microbiology. 1996; 34:3007-3011.
26 Carlsen KH, Orstavik I, Halvorsen. 1983. Viral infections of the respiratory tract in hospitalised children. A study from Oslo during a 90 months period. Acta Paediatr Scand 72:53-58.
27 Winter GF, Inglis JM. Respiratory viruses in children admitted to hospital in Edinburgh 1972-1985. 1987. J Infect 15:103-107.
28 Stanek J. Heinz F. Berankova M. Pennigerova S. Tumova B. Kunzova D. Fedova D. Hruskova J. Clinical diagnosis and laboratory study of acute respiratory diseases of viral origin in children. Ceskoslovenska Pediatrie. 1990; 45:715-718.
29 Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. Rev Infec Dis. 1991; 13:926-939.
30 World Health Organization Collaborative Study Group on Oral Poliovirus Vaccine. Factors affecting the immunogenicity of oral poliovirus vaccine: a prospective evaluation in Brazil and the Gambia. J. Infect Dis. 1995; 171:1097-1106.
31 John TJ. Antibody response of infants in tropics to five doses of oral polio vaccine. Br Med J. 1976;__:812.
32 Moriniere BJ, van Loon FPL, Rhodes PH, *et al.* Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet. 1993; 341:1545-50.
33 Sutter RW, Suleiman AJM, Malankar P, *et al.* Trial of a supplemental dose of four poliovirus vaccines. N. Engl J Med. 2000; 343:767-773.
34 Simasathien S, Migasena S, Beuvery C, *et al.* Comparison of enhanced potency inactivated poliovirus vaccine (EIPV) versus standard oral poliovirus vaccine (OPV) in Thai infants. Scand J Infect Dis. 1994; 26: 731-738.

35 Richardson G, Linkins RW, Eames MA, *et al.* Immunogenicity of oral poliovirus vaccine administered in mass campaigns versus routine immunisation programmes. Bull WHO 1995; 73:769-777.
36 Reichler MR, Kharabsheh S, Rhodes P, *et al.* Increased immunogenicity of oral poliovirus vaccine administered in mass vaccination campaigns compared with the routine vaccination program in Jordan. J Infec Dis. 1997; 175 (Suppl): S198-204.
37 Belshe RB. Mendelman PM. Treanor J. King J. Gruber WC. Piedra P. Bernstein DI. Hayden FG. Kotloff K. Zangwill K. Iacuzio D. Wolff M. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med. 1998; 338:1405-1412.
38 Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, Glezen WP, Wittes J. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomised controlled trial. JAMA. 1999; 282:137-144.
39 Gruber WC, Darden PM, Still JG *et al.* Evaluation of bivalent live attenuated influenza A vaccines in children 2 months to 3 years of age: safety, immunogenicity and dose response. *Vaccine.* 1997; 15:1379-1384.
40 American Academy of Pediatrics. Corticosteroids. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases. 25 th ed. Elk Grove Village, IL: American Academy of Pediatrics 2000: 61-62.

Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

It is anticipated that the findings of the multi-center study will be published with participation of ICDDR,B lead investigators. Leadership for publishing the results of the multi-center study will be the responsibility of WLV. Specific and notable findings from the component of the study involving participation of Bangladeshi subjects will be published in an appropriate journal focused on vaccines and/or influenza and/or prevention of poliomyelitis.

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. **(DO NOT EXCEED ONE PAGE)**

This study will be a multi-center collaborative study with WLV serving as the sponsor and leader of the conduct of the collaboration. Other collaborating institutions will be from countries within Asia (including India, Thailand, Malaysia, Philippines), the Americas (Mexico) and Europe (Turkey). WLV is the sponsor of this trial and will provide necessary fiscal support to conduct the trial.

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

Name	Position	Date of Birth
Robert F. Breiman, M.D.	Head, Programme on Infectious Diseases and Vaccine Sciences	November 17, 1953

Academic Qualifications (Begin with baccalaureate or other initial professional education)

Institution and Location	Degree	Year	Field of Study
University of Arizona	**B.A.**	**1975**	**Political Science**
University of Arizona	**M.D.**	**1979**	**Medicine**
UCLA Affiliated Hospitals	**Residency**	**1979-1983**	**Internal Medicine**
UCLA	**Fellowship**	**1984-1987**	**Infectious Diseases**
CDC	**Fellowship**	**1987-1989**	**EIS Program**

Research and Professional Experience

Concluding with the present position, list, in chronological order, previous positions held, experience, and honours. Indicate current membership on any professional societies or public committees. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **(DO NOT EXCEED TWO PAGES, USE CONTINUATION SHEETS).**

1. Investigator on molecular biology of *Legionella pneumophila* in the laboratory of Dr. Marcus Horwitz, 1984-7, Los Angeles, CA
2. Epidemiologic Research in Respiratory Diseases, CDC, 1987-2000
3. Chief, Respiratory Disease Branch, Epidemiology Section, CDC; 1989-1997
4. Director, U.S. National Vaccine Program Office. 1995-2000
5. Head, Programme on Infectious Diseases and Vaccine Sciences, ICDDR,B;2000-present

Bibliography (past three years only)

1: Breiman RF. Vaccines as tools for advancing more than public health: perspectives of a former director of the National Vaccine Program office.
Clin Infect Dis. 2001 Jan 15;32(2):283-8.

2: Benkel DH, McClure EM, Woolard D, Rullan JV, Miller GB Jr, Jenkins SR, Hershey JH, Benson RF, Pruckler JM, Brown EW, Kolczak MS, Hackler RL, Rouse BS, Breiman RF.
Outbreak of Legionnaires' disease associated with a display whirlpool spa.
Int J Epidemiol. 2000 Dec;29(6):1092-8.

3: Breiman RF, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D, Farley MM, Schuchat A, Reingold AL.
Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients.
Arch Intern Med. 2000 Sep 25;160(17):2633-8.

Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, Miller MA, Shinefield HR.

4:
Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children.
JAMA. 2000 Mar 15;283(11):1460-8.

Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, Breiman RF.

5:
Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia.
Clin Infect Dis. 2000 Mar;30(3):520-8.

Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, Breiman RF.

6:
Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team.
N Engl J Med. 2000 Mar 9;342(10):681-9.

Tan MJ, Tan JS, Hamor RH, File TM Jr, Breiman RF.

7:
The radiologic manifestations of Legionnaire's disease. The Ohio Community-Based Pneumonia Incidence Study Group.
Chest. 2000 Feb;117(2):398-403.

Fiore AE, Moroney JF, Farley MM, Harrison LH, Patterson JE, Jorgensen JH, Cetron M, Kolczak MS, Breiman RF, Schuchat A.

8:
Clinical outcomes of meningitis caused by *Streptococcus pneumoniae* in the era of antibiotic resistance.
Clin Infect Dis. 2000 Jan;30(1):71-7.

Peter G, des Vignes-Kendrick M, Eickhoff TC, Fine A, Galvin V, Levine MM, Maldonado YA, Marcuse EK, Monath TP, Osborn JE, Plotkin S, Poland GA, Quinlisk MP, Smith DR, Sokol M, Soland DB, Whitley-Williams PN, Williamson DE, Breiman RF.

9:
Lessons learned from a review of the development of selected vaccines. National Vaccine Advisory Committee.
Pediatrics. 1999 Oct;104(4 Pt 1):942-50. Review.

File TM Jr, Plouffe JF Jr, Breiman RF, Skelton SK.

10:

Clinical characteristics *of Chlamydia pneumoniae* infection as the sole cause of community-acquired pneumonia. Clin Infect Dis. 1999 Aug;29(2):426-8.

Marx A, Gary HE Jr, Marston BJ, Erdman DD, Breiman RF, Torok TJ, Plouffe JF, File TM Jr, Anderson LJ.

11:

Parainfluenza virus infection among adults hospitalised for lower respiratory tract infection. Clin Infect Dis. 1999 Jul;29(1):134-40.

Brown CM, Nuorti PJ, Breiman RF, Hathcock AL, Fields BS, Lipman HB, Llewellyn GC, Hofmann J, Cetron M.

12:

A community outbreak of Legionnaires' disease linked to hospital cooling towers: an epidemiological method to calculate dose of exposure. Int J Epidemiol. 1999 Apr;28(2):353-9.

Guevara RE, Butler JC, Marston BJ, Plouffe JF, File TM Jr, Breiman RF.

13:

Accuracy of ICD-9-CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. Am J Epidemiol. 1999 Feb 1;149(3):282-9.

Robinson DA, Turner JS, Facklam RR, Parkinson AJ, Breiman RF, Gratten M, Steinhoff MC, Hollingshead SK, Briles DE, Crain MJ.

14:

Molecular characterization of a globally distributed lineage of serotype 12F Streptococcus pneumoniae causing invasive disease.J Infect Dis. 1999 Feb;179(2):414-22.

Kool JL, Fiore AE, Kioski CM, Brown EW, Benson RF, Pruckler JM, Glasby C, Butler JC, Cage GD, Carpenter JC, Mandel RM, England B, Breiman RF.

15:

More than 10 years of unrecognized nosocomial transmission of legionnaires' disease among transplant patients. Infect Control Hosp Epidemiol. 1998 Dec;19(12):898-904.

Chen FM, Breiman RF, Farley M, Plikaytis B, Deaver K, Cetron MS. Geocoding and linking data from population-based surveillance and the US Census to evaluate the impact of median household income on the epidemiology of invasive Streptococcus pneumoniae infections. Am J Epidemiol. 1998 Dec 15;148(12):1212-8.

16:

Butler JC, Dowell SF, Breiman RF.

17:

Epidemiology of emerging pneumococcal drug resistance: implications for treatment and prevention.
Vaccine. 1998 Nov;16(18):1693-7. Review.

Fiore AE, Iverson C, Messmer T, Erdman D, Lett SM, Talkington DF, Anderson LJ, Fields B, Carlone GM, Breiman RF, Cetron MS.

18:
Outbreak of pneumonia in a long-term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia.J Am Geriatr Soc. 1998 Sep;46(9):1112-7.

Tharpe JA, Russell H, Leinonen M, Plikaytis BD, Breiman RF, Carlone GM, Ades EW, Sampson JS.

19:
Comparison of a pneumococcal common protein (PsaA) antibody ELISA and a PsaA immune complex ELISA for detection of pneumococcal serum antibody. Pathobiology. 1998;66(2):77-83.

Breiman RF, Butler JC.

20:
Legionnaires' disease: clinical, epidemiological, and public health perspectives.
Semin Respir Infect. 1998 Jun;13(2):84-9. Review.
: Bartlett JG, Breiman RF, Mandell LA, File TM Jr.
Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America.
Clin Infect Dis. 1998 Apr;26(4):811-38.

Breiman RF.

22:
Prevention of pneumococcal disease--a new romance begins.
Clin Infect Dis. 1998 May;26(5):1124-6. No abstract available.

Breiman RF, Zanca JA.

23:
Of floors and ceilings--defining, assuring, and communicating vaccine safety.
Am J Public Health. 1997 Dec;87(12):1919-20. Review. No abstract available.

Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, Kolczak MS, Breiman RF.

24:
Incidence of community-acquired pneumonia requiring hospitalisation. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group.
Arch Intern Med. 1997 Aug 11-25;157(15):1709-18.

POSITION TITLE
Health & Child Survival Advisor, Health & Child Survival Fellows Program, International Centre for Diarrhoeal Disease Research, Bangladesh
Research Associate , Department of International Health, Johns Hopkins University School of Hygiene and Public Health

EDUCATION

Institution/Location	Degree	Year Conferred	Field of Study
Stanford University	MD	1991	Medicine
The New York Hospital / Cornell Medical Centre	Diploma	1994	Pediatrics
Johns Hopkins University	MPH	1995	International Health
Johns Hopkins University	Diploma	1996	Preventive Medicine

EXPERIENCE AND APPOINTMENTS

Year	Activity
1985-1986	Principal Investigator: Identification of heat-shock proteins in *F.hepatica*, Stanford University
1986	Investigator: Isolation of *L. major* attachment proteins, National Institutes of Health
1990	Epidemiology Intelligence Service Medical Student Clerkship, Enteric Branch, Centres for Disease Control and Prevention
1992	Investigator: Community-based dysentery intervention urban slum children, Salvador, Bahia, Brazil
1995	Multicentre Study on Lower Osmolar ORS, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)
1994 – 1997	Paediatric On-Call Physician, Kennedy-Krieger Institute, Johns Hopkins
1995 – 1997	Paediatric consultant: Urban school-based clinics for Baltimore County
1995 – 1997	Paediatric Emergency Room Attending, St. Joseph's Hospital, Baltimore
1996	Epidemiologist: Consultants in Epidemiology and Occupational Health, Washington, DC
1996	EPI-Technical Advisor: National measles vaccination campaign children 12 - 59 months, PAHO, EPI/SVI, Georgetown, Guyana
1996 – 1997	Chief Resident Preventive Medicine Program, Johns Hopkins University
1997 – Present	Paediatric Consultant, US Embassy, Dhaka
1997 – Present	Regional Medical Consultant: AEA International, Singapore
1997 – Present	Principal Investigator: Hospital-based study to test efficacy zinc in acute watery diarrhoea in children less than 6 months old
1998 – Present	Principal Investigator: Community-based study to prevent pneumonia/diarrhoea with zinc in children less than 2 years old
1999 – Present	Principal Investigator: Hospital-based study of efficacy zinc as adjuvant therapy in management severe pneumonia, hospitalised children < 2 y/o

PROTOCALS UNDER DEVELOPMENT

Projected Start Date	Intervention	Stage of Development
2000	Identification of Primary Bacterial and Non-bacterial Pathogens of Pneumonia and Their Patterns of Antimicrobial Resistance Among Urban Slum Children 2 – 59 Months of Age Through Community-based Active Surveillance	Proposal, possible donor
2000	Comparison of antimicrobial outpatient management regimens for pneumonia and their effects on antimicrobial resistance among urban slum children < 5 y/o	Proposal, possible donor

PUBLICATIONS RELATED TO PRESENT WORK

Brooks WA, Fuchs G. Recent advances in research on zinc and child health in developing countries. J Ind Pediatr 1998;35:1173-76.

APPENDIX

International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form

Title of the Research Project: A prospective, randomised, partially-blinded, placebo-controlled, Phase III, multicentre trial to assess safety, tolerability and imunogenicity of liquid influenza virus vaccine, trivalent, types A & B, live cold-adapted (liquid CAIV-T) administered concomitantly with live, attenuated, poliovirus vaccine in healthy children

Principal Investigator: RF Breiman, M.D.

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

PATIENT INFORMATION AND CONSENT FORM

Title: **A Prospective, Randomised, Partially-Blinded, Placebo-Controlled, Phase III, Multicentre Trial to Assess Safety, Tolerability and Immunogenicity of Liquid Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold Adapted (Liquid CAIV-T) Administered Concomitantly with Live, Attenuated, Poliovirus Vaccine in Healthy Children**

Protocol No: **D153-P511**

Sponsor: **Wyeth-Lederle Vaccines, Pearl River, NY USA**

Principal Investigator: **Robert F. Breiman, M.D.**
ICDDR,B
988-1761

Co-Principal Investigator: **Abdullah Brooks, M.D., M.P.H.**
ICDDR,B
988-1761

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You will receive a copy of this consent form for your records.

Introduction

You are being asked to permit your child to participate in a medical research study to evaluate the safety and usefulness of a new investigational vaccine that may prevent acute respiratory illness caused by influenza virus in children. An investigational vaccine is one that has not been licensed by any regulatory agency (including the US Food and Drug Administration and Bangladesh regulatory authorities).

Influenza is a virus (germ) that causes fever, muscle aches, a non-productive cough, headache, sore throat, stuffy nose, and a lack of energy. The infection is spread as droplets of virus from one person to another by sneezing, coughing or touching. Although complete recovery from influenza is common, the virus can cause viral pneumonia (a condition that affects the lungs) and other serious conditions that may cause death in the very young.

Clinical trials have been sponsored by the National Institutes of Health, Aviron, Inc., and Wyeth-Ayerst Research to examine new influenza vaccines developed to be given as a spray in the nose. These investigational vaccines have been tested in trials since 1975 with over 8,000 subjects ranging from 2 months of age to over 80 years. The safety of these investigational vaccines has been shown with over 17,000 doses given in over 90 clinical trials.

Both a frozen form and a liquid form of the investigational vaccines have been developed and produced by Aviron, Inc. and Wyeth-Lederle Vaccines. The frozen form of the investigational vaccine has been previously tested in clinical trials and, to date, 6500 children and over 3700 healthy adults have been vaccinated. The liquid form has been tested in clinical trials and, to date, 900 children age 6 to 36 months, 700 children 12 to 36 months, 490 children age 6 to 17 years, and 209 healthy adults have been vaccinated. Both forms of the vaccine appear to be safe and without many side effects.

The investigational vaccine is made from three live virus types that have been weakened so they don't grow well in the human body. In addition to the three live virus types, other ingredients are added to make the vaccine stable including arginine, acid- hydrolysed porcine gelatin, and sucrose/phosphate/glutamate. The liquid form of the investigational vaccine was developed to allow convenient storage and to make administration of the vaccine easier. The liquid form of the vaccine will be used in this study.

Alternate Vaccines

The current licensed injectable influenza vaccines are recommended for the prevention of influenza in adults and children with poor health conditions and in healthy adults at the age of 65 years or older in the United States. These recommendations, however, do not include healthy children who are also at risk of influenza infection and are largely responsible for its spread. There are no recommendations for influenza vaccine use in Bangladesh.

Purpose

The purpose of this trial is to:

- study if there is any effect on the body's immune response to oral poliovirus vaccine (OPV) and liquid form of the investigational vaccine (CAIV-T) when given at the same time.
- assess whether CAIV-T is safe and well-tolerated (few side effects).

Eligibility

Your child is being asked to take part in this study because he/she is at least 6 months of age and no older than 36 months of age (have not reached their Third Birthday). He/she has received three separate doses of OPV during his/her first year of life. Your child must be in good health as determined by a medical history, physical examination, and your doctor's judgement. You (parent/guardian) and your child must be available for the three-month duration of the study. You (parent/guardian) must be able to be contacted by the study staff for post vaccination interviews.

Your child may not participate in the study if he/she is acutely ill, has a condition or taking medication that affects the body's ability to fight disease, has any medical condition that would make participation dangerous or interfere with the study, or if any member of your household has a condition or is taking medication that affects their body's ability to fight infection. Your child may not take other study vaccines or medicines containing aspirin during the study, except as explained by the study doctor. Additionally, your child does not have an allergy to any ingredient of the investigational vaccine (CAIV-T), including eggs.

Procedures

If you want your child to be in the study, this is what will happen:

Study Visit 1

1. If you agree to allow your child to enter this study and you have signed and dated this consent form, your child will be enrolled into this study.

2. Your child's medical history will be discussed with you, including past and current illnesses and previous vaccines.

3. A physical examination will be done, including a temperature reading.

4. **If your child is well and can be immunised at this visit, approximately 1 teaspoon (5 ml) of blood will be collected from your child to test for antibodies (germ fighters).**

5. Your child will be randomly assigned to receive either CAIV-T or placebo. A placebo is a nose spray containing saline without the virus. In addition, your child may be randomly assigned to receive a dose of OPV.

6. Randomly assigned means assignment by chance, like drawing a card or flipping a coin.

7. You will be told whether your child was assigned to receive a dose of OPV. However, neither you nor your study doctor will know whether your child received CAIV-T or placebo. That information is available to the study doctor if needed in an emergency.

8. CAIV-T or placebo is administered intranasally (a spray into each nostril). OPV is administered into your child's mouth.

9. Your child will be observed for 15 minutes after the vaccination.

10. For today and for 10 days after this visit, you will be asked to take your child's afternoon or evening temperature using the thermometer provided to you by the study staff. You will keep a simple diary card of your child's symptoms (for example: temperature, cough, runny or stuffy nose, irritability, vomiting, activity level and appetite). You will also be required to record any unscheduled physician visits and any other medications used. Please contact the investigator immediately if any significant illness or hospitalisation occurs during the study period.

11. Study staff will contact you by home visit twice during the 10 day period to inquire about your child's general health and to answer any questions about how to complete the diary card. The first contact will be approximately 2 to 4 days after Study Visit 1. The second contact will be on approximately 10 to 12 days after Study Visit 1.

Study Visit 2

1. **A second visit will take place 28 to 42 days after Study Visit 1.**

2. **Your diary card will be collected and reviewed with you by the study staff. Your child's medical history since the last study visit will be discussed.**

3. **A brief physical examination will be performed, including a temperature reading.**

4. **If your child is well and can be immunised at this visit, approximately 1 teaspoon (5 ml) of blood will be collected from your child to test for antibodies (germ fighters).**

5. **Your child will receive either CAIV-T or placebo, as assigned at Study Visit 1. No children will receive OPV at this visit.**

6. **Neither you nor your study doctor will know whether your child received CAIV-T or placebo, however, that information is available to the study doctor if needed in an emergency.**

7. CAIV-T or placebo is administered intranasally (a spray into each nostril).

8. Your child will be observed for 15 minutes after the vaccination.

9. For today and for 10 days after this visit, you will be asked to take your child's afternoon or evening temperature using the thermometer provided to you by the study staff. You will be asked to record the same symptom information as you did before onto a simple diary card. You will also be required to record any unscheduled physician visits and any other medications used. Please contact the investigator immediately if any significant illness or hospitalisation occurs during the study period.

10. Study staff will contact you by home visit twice during the 10 day period to inquire about your child's general health and to answer any questions about how to complete the diary card. The first contact will be approximately 2 to 4 days after Study Visit 2. The second contact will be on approximately 10 to 12 days after Study Visit 2.

Study Visit 3

1. **A third visit will take place 28 to 42 days after Study Visit 2.**

2. **Your diary card will be collected and reviewed with you by the study staff. Your child's medical history since the last study visit will be discussed.**

3. **Approximately 1 teaspoon (5 ml) of blood will be collected from your child to test for antibodies (germ fighters).**

Blood Samples

As part of your child's participation in this trial, he/she will provide three blood samples. Blood samples that are collected during this trial on Study Visit 1, 2, and 3 will be stored indefinitely and may be used for future testing. These samples may be tested for antibodies (germ fighters) to influenza virus, poliovirus, and other germs (virus, bacteria, etc.) associated with respiratory infection.

At no time will genetic testing be performed on the blood samples collected from your child. The samples collected as part of this study will always be confidential, and your child's name will not be associated with the samples.

Duration of Participation

There are a total of 2,400 children participating in this study at multiple study sites. You and your child's participation will last for up to approximately three months.

Risks

1. CAIV-T: Possible side effects associated with CAIV-T vaccine include mild 'flu like symptoms such as fever, runny nose, stuffy nose, cough, sore throat, headache, chills, vomiting, muscle aches, tiredness, and stomach ache. All of these side effects seem to occur less often after receiving the second dose of CAIV-T.

2. Oral Polio Vaccine (OPV): For a while after your child has been immunised there is a very small chance that members of your family who have not received OPV or who have an immune deficiency condition may develop polio from being near your child. This vaccine-associated polio occurs more often after the first dose of OPV. The chance of vaccine-associated polio is one person in 6.2 million OPV doses administered. As part of this study, your child will be receiving his/her fourth dose of OPV.

3. Blood Sample: blood collection may be uncomfortable, and may be associated with local pain or bruising. On very rare occasions, infections may occur at the site where blood was collected.

As with any medicine, this investigational vaccine may involve other risks, which are not known at this time.

You will be informed immediately of any new information regarding study vaccine, which might affect your willingness to continue your child's participation in the study.

Benefits

Your child's participation will help in the development of effective vaccines to prevent influenza virus. Such vaccines may be of future benefit to babies and children throughout the world. As the vaccine is given as a spray in the nose and not an injection it may also be acceptable as a future method of protection against flu.

Alternative Treatment

There is no alternative treatment except to not participate in the study.

Alternatives to Participation

If you do not choose to have your child participate in this study, your child will receive all routine childhood immunisation according to the standard schedule recommended by your doctor.

Voluntary Participation/Withdrawal

Your and your child's participation in this study is entirely voluntary. If you agree to participate, you are free to withdraw your child at any time. Your decision not to participate or to withdraw from the study will not affect the care your child received or your relationship with your doctor. Your doctor retains the right to withdraw your child from the study if it is considered to be in your child's best interest. The sponsor may also terminate the study if they choose.

Compensation for Injury

You will be reimbursed for any reasonable and necessary medical treatment by the Sponsor for any injury that is a direct result of the vaccine or study procedures.

If you think your child has suffered a research-related injury, contact

There is no payment for you to be in this study. However, we will provide reimbursement for expenses you have incurred to travel to the clinic for each visit.

Costs

There is no cost to you or your child for being in this study.

Confidentiality

All information obtained during the course of this study is strictly confidential. Data may be reported in scientific journals and will not include any information that identifies your child as a subject in this study.

People who work for the Sponsor Company (Wyeth Lederle Vaccines), Ethics Committee members and national and international regulatory authorities (US Food and Drug Administration) may be able to review your child's medical and study records. Any information given to these organizations remains confidential and your child will not be identified in publications of the study results.

Therefore, you hereby authorize your child's Investigator to release your medical records to Wyeth Lederle Vaccines, it's employees or agents, national and international regulatory health authorities, and the ICDDR,B Ethical Review Committee. You understand that they will utilize these records only in connection with carrying out their obligations relating to this clinical study.

Who to Contact with Questions

If you have any questions regarding this study, now or at any time in the future, you may call Dr. Abdullah Brooks or Dr. Aliya Naheed at 988-1761.

If you have questions about your child's rights as a research subject, you may call Mr. Bejoy Saha at 881-0117

Informed Consent

I hereby confirm that I have been informed about the nature, conduct, benefits and risks of the clinical study. I have also received, read, and understood the above written information (Patient Information Leaflet and Informed Consent) regarding the clinical study.

I am aware that the results of the study, including my child's sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.

I may, at any stage, without prejudice, withdraw my consent for my child's participation in the study.

I have had sufficient opportunity to ask questions and agree to my child's participation in the study.

Child's Name_____

Please print

Relationship of Parent or Legal Guardian to Child:_____

Name of Parent or Legal Guardian _____

Please print

Signature of Parent or Legal Guardian _____

Date

Name of Witness to Consent Procedure * _____

Please print

Signature of Witness to Consent Procedure* _____

Date

Investigator's Name _____

Please print

Investigator's Signature _____

Date

***As applicable by guidelines of the Institution or Ethics Committee or illiteracy of the parent/guardian**

_____

Signature of Investigator/ or agents
Date:

_____

Signature of Subject/ Guardian
Date:

Budget per Year — **1st Year**

Name	Pay Level	No. of Staff	% Effort	Mo'ly Rate	Man/ month	Subtotal
Personnel						
Dr Robert Breiman	Co-Inv	1	0.20	0	6.0	0
Dr. W. Abdullah Brooks		1	0.25	12,529	6.0	18,794
Dr Aliya Naheed	No-B	1	0.50	796	6.0	2,388
Medical Officer	No-A	4	1.00	656	6.0	15,744
Nurse	GS5	4	1.00	362	6.0	8,688
Field Research Officer	GS5	1	0.50	362	6.0	1,086
Field Research Assistant	GS3	10	1.00	233	6.0	13,980
Project/Office Manager	No-A	1	0.25	656	6.0	984
Senior Attendant	GS-2	1	0.30	275	6.0	495
Health workers		4	1.00	78	6.0	1,872
Subtotal						**64,031**
Travel						
Domestic						5,000
Subtotal						**5,000**
Supplies and Materials						
Shipping						1,200
Non-stock drugs						1,200
Consumable equip/suppl/mt						4,800
Subtotal						**7,200**
Lab. test and other						
Centrifuge, Aliquot sera						300
Subtotal						**300**
Other Contractual Services						
Photocopying						300
Training Workshop, Seminars						500
Subtotal						**800**
Interdepartmental Services						
Misc						1,000
Subtotal						**1,000**
Other Capital Expenditures						
Refrigerator						1,500
Subtotal						**1,500**
Total Direct						**79,831**
Total Indirect (25%)						**19,958**
Total Costs						**99,788**
Grand Total						

06-May-2001

Shamima Moin
Controller, Budget & Costing

International Centre for Diarrhoeal Disease Research, Bangladesh
Mohakhali, Dhaka-1212

Detailed Budget for New Proposal

~~Project Title: : A prospective, randomised, partially-blinded, placebo-controlled, Phase III, multicentre trial to assess~~ **safety, tolerability and imunogenicity of liquid influenza virus vaccine, trivalent, types A & B, live cold-adapted (liquid CAIV-T) administered concomitantly with live, attenuated, poliovirus vaccine in healthy children**

Name of PI: Robert F. Breiman, M.D

Protocol Number: Name of Division: PIDVS

Funding Source: Wyeth Lederle Vaccines Amount Funded (direct): Total:
Overhead (%)

Starting Date: September 1, 2001 Closing Date: January 31, 2002

Strategic Plan Priority Code(s):

Budget per Year **1st Year**

Name	Pay Level	No. of Staff	% Effort	Mo'ly Rate	Man/ month	Subtotal
Personnel						
Dr Robert Breiman	Co-Inv	1	0.20	0	6.0	0
Dr. W. Abdullah Brooks		1	0.25	12,529	6.0	18,794
Dr Aliya Naheed	No-B	1	0.50	796	6.0	2,388
Medical Officer	No-A	4	1.00	656	6.0	15,744
Nurse	GS5	4	1.00	362	6.0	8,688
Field Research Officer	GS5	1	0.50	362	6.0	1,086
Field Research Assistant	GS3	10	1.00	233	6.0	13,980
Project/Office Manager	No-A	1	0.25	656	6.0	984
Senior Attendant	GS-2	1	0.30	275	6.0	495
Health workers		4	1.00	78	6.0	1,872
Subtotal						**64,031**
Travel						
Domestic						5,000
Subtotal						**5,000**
Supplies and Materials						
Shipping						1,200
Non-stock drugs						1,200
Consumable equip/suppl/mt						4,800
Subtotal						**7,200**
Lab. test and other						
Centrifuge, Aliquot sera						300
Subtotal						**300**
Other Contractual Services						
Photocopying						300
Training Workshop, Seminars						500
Subtotal						**800**
Interdepartmental Services						
Misc						1,000
Subtotal						**1,000**
Other Capital Expenditures						
Refrigerator						1,500
Subtotal						**1,500**
Total Direct						**79,831**

Total Indirect (25%)	**19,958**
Total Costs	**99,788**
Grand Total	
TOTAL DIRECT COST	**$99,788**

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

Budget Justification

Personnel

- **Dr Robert Breiman** will lead the investigation as a vaccinologist and the senior epidemiologist.
- **Dr W. Abdullah Brooks** will co-lead the investigation as the field epidemiologist and paediatrician. The time input will average 2 hours per day of a five-day workweek or 25% time.
- **Dr Aliya Naheed** will provide tactical and logistical management and supervision on a daily basis to field operations. For the duration of the study, this will involve average four hours/day of a five-day workweek or 50% time.
- **Medical Officers:** There are two on-going studies. The medical officers will have to provide intense input for screening for eligibility to enrol, perform physical exams and administer vaccine, as well as draw blood and provide follow-up to all 400 enrolees. Each enrolee will require 2 hours of physician time per visit (one hour for medical history review, physical exam, blood drawing, and vaccination and completion of forms; and one hour for observation post vaccination) for three visits, or a total of 6 hours. There will be 400 patients, thus patient use of physician time is 400 patients X 6 hours of physician time/patient = 2,400 of physician time. Allowing for a 48 hour work week, the number of physicians required over a three month (allowing 4.2 weeks/month) period becomes **2,400 physicians hours/12.6 weeks/48 hours/week = 4 physicians**. Thus, the study should have **4 full-time physicians** for the three-month period.
- **Nurses:** The functional unit of the clinic is a triad of physician/nurse/health worker. Thus, if there are four physicians, we require four nurses.
- **Health Workers:** The same applies to the health workers as does the physicians and nurses.
- **Field Research Officer:** This officer must supervise, monitor and co-ordinate the data collection activities of the field research assistants (FRAs). The FRO must also compile and submit daily and monthly summary reports on the performance of the field surveillance activities to the senior project staff as a component of monitoring and quality assurance.
- **Field Research Assistants:** The duties of the FRAs will be to consent and enrol the study participants, to obtain background demographic data, arrange for and ensure clinic visits of the patients, and conduct daily home visits to obtain data on adverse events, reactogenicity, obtain axillary temperature, and make referrals to clinic as needed for the duration of the study (total time 6 months). Consent and enrolment *may* take up to **4 hours** per individual, including identification, repeat visits, written consent, obtaining a witness, baseline data collection and travel time between residences. Daily home visits to submit questionnaires and take axillary temperature will average 30 minutes/visit, including travel time between homes. However, constraints in the field require that all routine visits be conducted between 0900 and 1400 (5 hours), otherwise respondents will object. Thus, the effective data collection workweek is 25 hours/FRA. The remainder of FRA time is devoted to follow-up visits of sick children and completing/cross-checking the questionnaires. Thus, the number of FRAs required is 70 patients/week X 4 hours/patient X 1 FRA/25 hour workweek = **11 FRAs for enrolment**. Post vaccination visits will take 400 patients/0.5 hours/week X 1 FRA/25 hour workweek = **8 FRAs for follow-up**. Thus, **10 FRAs** should be adequate for both enrolment and follow-up.
- **Project Manager:** A part-time manager will be required to receive phone calls, process requests, maintain a filing system including photocopies of all documents, co-ordinate shipments, and monitor expenses. This should average 2 hours/day or 10 hours/week = 10hours/40 hours/work week = **25% of workweek.**
- **Senior Attendant:** This individual will assist with procurements, logistical placement of materials in the field including retrieval of vaccines from storage and conveying them to the field in timely manner, bringing lab samples from the field to the lab for processing, bring medicines and other supplies to the field

office and bring reports from the field to the Centre. This will average 2.5 hours/day or 12.5 hours/week/40 hours/work-week = **30% workweek**.

Travel

- **Domestic:** This includes transport of materials to and from the field (twice daily 5X/week), the use of Centre transport (driver and petrol) twice daily 5days/week X 2 weeks/month for Quintiles monitoring, and transport of study personnel between field and office for six month period. Average Tk2,000/day X 5 days/week X 4.2 week/month X 6 month = $4,754.72 or **US $5,000**.

Supplies and Material

- **Refrigerator:** The unit cost of a 2° C – 8° C refrigerator is approximately US $500 - $800 in the local market. Thus, two (one main one backup) could be purchased for approximately **US $1,500**.
- **Shipping:** This is to cover the cost of shipping of CAIV-T vaccine and other study related materials, such as blood collection tubes, serum storage tubes, thermometers etc from offices in Singapore and India to Bangladesh, as well as transport of unused materials and blood products to the company headquarters or its designee.
- **Non-stock Drugs:** The monthly cost of providing medicine, including antibiotics, anti-scabies and anti-fungal drugs to the population served by the field clinic averages US $0.50 per person per month. The cost of providing such treatment to 400 study = 400 X $0.50/month = $200/month X 6 months = **US $1,200**.
- **Consumable Equipment:** The monthly cost of consumable equipment (tongue blades, gloves, tubes, syringes, needles, spirit etc) per patient and their family members = US $2.00/month. Thus 400 patients X US $2.00 = US $800/month X 6 months = **US $4,800**.

Laboratory Tests and Others

- **Centrifugation:** The cost of centrifugation and serum separation will be no more than **US $300**.

Contractual Services

- **Photocopying:** The cost of photocopying is approximately TK 1.5/page. The consent form will be a maximum of 7 pages, daily follow-up sheets and CRF forms will be provided by the company. The baseline questionnaires and calendars will need to be printed locally. The baseline questionnaire is 5 pages X 400 patients X TK 1.5 X US $1/TK 54 = US $60 for the baseline questionnaires. However, there will be other miscellaneous copying requirements. The figure of US **$300** is an approximation only, but reflects a realistic study-associated operating cost of US $50/month.
- **Training and Workshop:** All study personnel will require training. The training focuses on the consent and data collection activities for the field staff, including practice sessions and standardisation exercises to ensure both accuracy (correct method) and precision (reproducibility and close inter-observer agreement). The medical officers and nurses will require training on the history and physical exam for the study, as well as emergency resuscitation methods for anaphylaxis. The cost of training, including the printing of materials, production of overhead transparencies, test materials, pens, paper etc = $50/day X 10 days training (average for training and standardisation exercises) = **US $500**.

Other Support

Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration. (DO NOT EXCEED ONE PAGE FOR EACH INVESTIGATOR)

Not applicable

Check List

After completing the protocol, please check that the following selected items have been included.

1. **Face Sheet Included** ☐
2. **Approval of the Division Director on Face Sheet** ☐
3. **Certification and Signature of PI on Face Sheet, #9 and #10** ☐
4. **Table on Contents** ☐
5. **Project Summary** ☐
6. **Literature Cited** ☐
7. **Biography of Investigators** ☐
8. **Ethical Assurance** ☐
9. **Consent Forms** ☐
10. **Detailed Budget** ☐

To :

Date:

From :