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BELLAGIO

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GENERAL

March 3, 1986

Dear George:

Thanks for your letter of February 20, 1986 and the research proposal entitled "The Active Immunization of the Fetus Against Tetanus, Diphtheria and Polio".

I believe the Task Force should support this research project. The topic is an important one, the research design and methodology are appropriate, the investigators experienced, and the budget reasonable. Unfortunately, I can provide no specific suggestions regarding likely sources of funding.

With kind regards,

Sincerely,

Anthony R. Measham
Health Adviser
Population, Health and Nutrition Department

Dr. George Rubin
Consultant, Research & Development
The Task Force for Child Survival
1989 North Williamsburg Drive
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The Task Force for Child Survival
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February 20, 1986

Dr. Anthony Measham
Health Adviser
Health, Population & Nutrition
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear Tony:

Please find enclosed a copy of a proposal entitled, "The Active Immunization of the Fetus Against Tetanus, Diphtheria and Polio" for your review. I would appreciate learning from you whether you

1. think The Task Force should support this effort; and

2. have any ideas on finding funding support for the study.

Many thanks for your assistance.

Sincerely,

George

Dr. George Rubin
Consultant, Research & Development

Enclosure

THE JOHNS HOPKINS UNIVERSITY
School of Hygiene and Public Health
Department of Health Policy and Management

April 9, 1985

Mr. William Watson
Task Force for Child Survival
1989 N. Williamburg Drive
Suite I
Decatur, GA 30033

Dear Bill:

Thank you for taking the time Monday to discuss the attached proposal "The Active Immunization of the Fetus Against Tetanus, Diphtheria and Polio". As I explained to you on the telephone, we are looking for funding for this is a protocol which has been developed by myself, Dr. Robert Yolken, of the Johns Hopkins School of Medicine, and Dr. Jacobson Dr. Kesaje and Dr. Stuery, who are currently working in Kenya. The work of Dr. Thomas Gill and his colleagues as well as theoretical and animal data that are in the literature indicate that such a mechanism of immunizing children is indeed feasible. As I point out to you on the phone, if a child were to be immunized in utero, then there is the potential for requiring only one dose of vaccine after the child is born because this dose would act as a booster and could protect the child throughout early childhood. The implications for future immunization programs and the saving of millions of lives among children who do not return for immunizations once they leave maternity centers or who are currently receiving only one or 2 dose of DTP or polio vaccine are very great.

From our discussion, I understand that there is no money within the current Task Force budget for such activities, but that you and Bill Foege are in contact with organizations like the Rockerfeller Foundation which are potential supporters of this protocol. I enclosed the protocol with a copy of the essential budget elements. You will note that I, Dr. Yolken and Dr. Jacobson are willing to work without compensation on this project. We do, however, need support for the Kenyan field staff and the General Preventive Medicine Resident who will be leading the project in Kenya. This General Preventive Medicine Resident is an excellent candidate, is eager to work on the project, and is available beginning July 1, 1985. The essential budget also includes funds to pay for the laboratory testing, transportation and a certain number of supplies. Because of our enthusiasm for seeing this project funded, if you or any of the contacts you have can only provide part of the budget, we would be quite

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willing to patch together contributions from several sources. I would be very happy to talk to you about this protocol and the financing of it at any time.

Because you mentioned Bill will be back next Monday, I am looking forward to a call from him at that time. Thanks again for your help.

Best wishes,

A. Marshall McBean, M.D., M.Sc.
Principal Investigator

Enclosure

cc: Mary Lou Thoms
Sonia Hutchins

ABSTRACT

Immunization programs in developing countires have been unable to provide the required number of three doses of polio vaccine and DTP needed to protect all infants against the major handicapping and killing diseases of paralytic polio, diphtheria, tetanus and pertussis. Discovery of a means of protecting the newborn child through infancy and the first three to four years of life with one dose of polio vaccine or DTP given at birth would save many millions of lives in the developing countries. Such a strategy would be possible using existing vaccines if the newborn were exposed to vaccine antigens in utero and developed active immunity by the time of birth.

We propose to assess the ability of the fetus to develop active immunity against three vaccine antigens given to the mother during pregnancy. This will be done in a randomized control trial in which we will provide one or more of the following vaccines: tetanus toxoid (TT), tetanus and diphtheria toxoid (Td) and inactivated polio vaccine (IPV) to pregnant women. The immune response of the fetus will be measured by determining 1) the presence or absence of IgM in cord blood at the time of delivery, and 2) the magnitude and speed of response to a "booster" given to the child during the first three days of life of the same antigens received by his pregnant mother. The presence of IgM specific for the antigens given and a more rapid and higher antibody response in these children compared with the response in children born to unimmunized mothers would confirm previous active immunity. We will also contrast the immunogenic effect of this new schedule with the immunization schedule for children currently recommended by the World Health Organization.

A. PROJECT GOALS AND OBJECTIVES

There are three major goals of the study: (1) to provide evidence for or against the ability of the fetus to develop active immunity against certain antigens (tetanus toxoid, diphtheria toxoid and inactivated polio vaccine) given to the mother during pregnancy, (2) if active immunity is produced, to provide evidence for or against the ability of a "booster" dose of the same antigen given within the first three days of life to produce an antibody response in a greater percentage of newborns and to a higher level than seen when these antigens are given to children whose mothers have not been immunized, and (3) to provide data to compare the immunizing effect of the vaccination schedules currently recommended by the World Health Organization for these antigens with a two-dose schedule for the offspring of mothers immunized during pregnancy consisting of an immunization at birth and one at 2 months of age.

Tetanus toxoid was chosen in order to confirm the work of Gill, et al., (1983) described in the next section. Diphtheria toxoid will be used because of its similarity to tetanus toxoid and the importance of the disease in children in certain countries such as India (Kim-Farley, 1984). IPV will be used because of the large burden of polio in the population under one year of age and the inability of most immunization programs to provide three doses of oral polio vaccine within the first six months (or even the first 12 months) of life.

B. PROJECT SIGNIFICANCE

Polio lameness surveys carried out in developing countries (Laforce, 1980; Bernier, 1984) have reemphasized the importance of polio as the major cause of paralysis. In many countries five to ten children per 1,000 are paralyzed due to polio contracted before the third birthday. Approximately 20 to 35% of the cases occur during the first year of life. It is, therefore, essential that children be successfully immunized as early as possible. Most countries recommend that an initial series of three doses of oral polio vaccine (OPV), or inactivated polio vaccine (IPV), separated by two months, be given to children beginning at 6 to 12 weeks of age. In the United States, where only two doses of OPV are recommended in infancy, over 90% of the children are protected (McBean, 1983; Hardy, 1970). In developing countries the response may be much poorer. After three doses of OPV, seroconversion has been reported as low as 42, 79 and 48 percent to types I, II and III, respectively (Bottiger, et al., 1978; Oduntan, et al., 1978). Coupled to these low seroconversion rates are very low immunization coverage rates which average between 10% and 36% for the different WHO regions. (See Table 1 below).

Table 1
Percentage of children immunized
by 12 months of age with indicated vaccine

WHO Region	3 doses of OPV	3 doses of DTP
Africa	17	19
(Maseno District, Kenya	13	12)
Americas	36	35
Southeast Asia	10	25
Eastern Mediterranean	28	24

Although diphtheria does not cause as much morbidity or mortality as polio in most developing countries, nonetheless, diphtheria toxoid is provided by the immunization programs in DTP vaccine. Unlike OPV there is no report of a decreased immunologic response to the toxoid, but there are very low coverage rates. (See Table 1).

One particularly disturbing fact related to the need to provide three doses of OPV and DTP has been the 10% and 75% difference in the percent of children receiving the first and third dose. Even between the second and third dose of DTP and OPV, the average dropout rate is between 25% and 30% (Martin, 1984).

The difficulty of providing the three doses of OPV and

DTP has led to efforts to reduce the number of doses of vaccine required. For example, we (McBean, et al., 1983) are currently evaluating a new more potent IPV which may reduce the number of required doses of IPV. The data indicate that 2 doses of IPV given at two and four months of age are sufficient to protect over 90% of the children during the first 18 months of life.

Reducing the number of required doses to one, and being able to give that dose at or near the time of birth, as is the case for BCG, would be even better. In addition to providing active immunity as soon as possible, it should also result in major improvements of immunization coverage. If active immunization of the fetus can be demonstrated, then one dose of IPV, diphtheria toxoid or tetanus toxoid given at birth could be sufficient to provide immunity through the three to four year period when the child is at highest risk to paralytic polio, diphtheria and tetanus. Possibly, a second dose of these antigens would be required during the first 6 months of life, but even that would be a significant reduction of visits required after leaving the maternity for immunization (one) and result in a tremendous increase in the number of children protected against these diseases.

Existing scientific knowledge concerning four elements critical to the proposed study: (1) the ability of the human fetus to develop active immunity, (2) the ability of the antigens used (tetanus toxoid, diphtheria toxoid, inactivated polio virus) to cross the placental barrier, (3) the ability of the newborn child to produce antibodies to the antigens used, and (4) the ability of the newborn child to produce antibodies in the presence of high levels of maternal antibody; plus a fifth issue, the question of immunologic tolerance are reviewed below.

The human fetus is capable of producing antibodies, and specifically IgM, soon after conception. Alford (cited in Solomon, 1971) detected antibodies 112 days post coitus and Gitlin and Biasucci (cited in Solomon, 1971) reported the appearance of IgM 74 days post coitus. Similar evidence from other authors leaves no doubt as to the immunologic competence of the fetus early in life and, certainly, prior to the time at which we plan to vaccinate the women.

Many molecules have been shown to cross the placental barrier, and it is necessary that they do. However, the placenta is selective. Digestive enzymes break down many harmful chemicals, although other teratogenic ones are allowed to pass (Solomon, 1971). The only data on the passage of tetanus toxoid comes from the work of Gill, et al., (1983) who gave a 5 Lf dose of tetanus toxoid to pregnant women during the fifth and eighth months of pregnancy. They demonstrated the presence of tetanus antitoxin specific IgM in the cord blood of 67% (16/24) of the babies born to these women. Babies born to unimmunized women had no antitetanus IgM. Because IgM does not cross from the maternal to the fetal circulation, the IgM must have been of fetal origin. Thus, the tetanus toxoid (molecular weight around 140,000) must have crossed the placental barrier. No similar data exist for diphtheria toxoid. Diphtheria toxoid has a molecular weight of around 64,000, and so it may be expected to behave similarly to tetanus toxoid. In fact, it may even pass more readily to the fetal circulation.

Numerous viruses and other organisms have been shown to pass from the mother to the fetus. Treponema pallidum, toxoplasmosis

gondii are classic examples of bacterial and parasitic infections of the fetus. Sever and White (1968) list 13 viruses which can infect the fetus, including poliovirus, although the frequency of the latter is not noted. Experimentally, bacteriophage have crossed from the maternal to fetal circulations in guinea pigs when the concentration of bacteriophage was very high (10 million particles/ml) (Uhr, et al., 1963). The poliovirus vaccine to be used in this study is a new high potency vaccine. This will maximize the concentration of virus particles available to us, although it will not approach the level used by Uhr, et al., in guinea pigs.

The ability of the newborn to respond to vaccines and produce antibodies has been clearly demonstrated, although this ability is influenced by the presence of maternal antibodies. BCG is recommended by the World Health Organization for administration at birth (WHO Study Group, 1980).

One dose of tetanus toxoid given to young chidren usually does not stimulate high, protective antitoxin levels nor keep the titer elevated in the protective range. Two doses of tetanus toxoid will protect 99 to 100 percent of the vaccine recipients. Numerous studies evaluating DTP have shown the effectiveness of the two or three dose schedule for tetanus toxoid even when the vaccine is given during the first week of life.
Diphtheria toxoid is not as potent an immunogen as tetanus toxoid. However, two or three doses of diphtheria toxoid will protect 75 to 100 percent of children who begin the immunization series during the first week of life (Di Sant Agnese, 1949; Barr, et al., 1955; and Barrett, et al., 1962).

Newborn infants are also able to respond to OPV during the first week of life. Studies reported by Halsey and Galazka (1984) and De-Xiang, et al., (1984) have shown 4% to 67% of children responding to OPV given at birth. As shown by Sabin (1983), many children who did not respond serologically may have been immunogically primed because of the rapid response to a challenge dose of IPV.

The ability of IPV to stimulate serum antibodies is reduced by the presence of maternal antibodies. However, one dose of IPV has resulted in seroconversion rates of 38%, 40% and 62% against polio virus types I, II and III, respectively, in two month old children who had measurable maternal antibodies (McBean, unpublished).

It is not known how well the newborns in this study will respond in the presence of high titers of maternal antibodies stimulated by the immunization of the mother. This can best be determined by looking at the response after one dose of each antigen. Unfortunately, Gill, et al. waited until after three doses of DTP were given before they measured tetanus antitoxin levels in the children. He reported no difference in serum IgG levels. This may have been caused by the infants born to unimmunized mothers "catching up" to the other children as a result of three doses of this potent antigen.

Immunologic tolerance, described elegantly by Owen (1945)

in dizygotic twin cattle, has been raised as an issue and argument against the early immunization of children or the fetus. As discussed earlier, however, humans become immunocompetent long before birth. The tolerance-responsive period closely follows the time when lymphocytopoiesis occurs. Lymphocytes appear in the peripheral circulation as early as seven to eight weeks of gestation (Solomon, 1971). Thus, this is not an issue in this study.

Immunologic tolerance caused by high levels of maternal antibody in the children of immunized mothers immediately after birth is another theoretical issue. However, tetanus toxoid is recommended for use in pregnant women in many countries, and no report of difficulty in their offspring responding to tetanus toxoid has been made. Further, Gill, et al., did not show any evidence of immunologic tolerance in the children born to women who were immunized during pregnancy.

C. PROJECT DESIGN & METHODS

1. Study Population and Study Groups

Participants for the study will be volunteers from among the women and children using the prenatal clinics and maternity services of the Tenwek (Kenya) Hospital and the outlying Maternal and Child Health clinic. This 120 bed hospital and affiliated clinic provide a full range of preventive and curative services for a population of approximately 400,000 people. The facilities provide prenatal care for approximately 1,600 women per year and deliver 2,000 children per year.

Women, 18 years of age or older, who appear for prenatal care and agree to participate in the study will be randomly assigned to Group A, B or C (See Figure A). These women will receive one or both of the following vaccines: diphtheria and tetanus toxoids (Td), or inactivated polio vaccine (IPV) according to the schedule shown in Figure A. Specifically:

women in Groups A and C will receive a dose of Td and a dose of IPV during the 6th and 8th months of their pregnancy;

women in Group B will receive a dose of Td during the 6th and the 8th months of their pregnancy; and

Group D will consist of women who come to the hospital at the time of delivery who have not received prenatal immunizations here or elsewhere.

Group E will consist of children who come to the hospital or clinic at 2 months of age in whom the mother has not received immunizations here or elsewhere.

2. Informed Consent and Enrollment

All women meeting the criteria indicated above who present for prenatal care (Groups A, B and C), delivery (Group D) or for immunizations for their children (Group E) will be offered the opportunity to participate in the study. The women will be informed of the benefits of receiving tetanus toxoid during pregnancy, of the potential benefits from participating in the study, and of the risks and inconvenience to her and her child due to their participation in the study. They will be told that their decision to participate or not participate in the study will not influence the treatment they receive at the hospital or the clinic. Those who indicate their willingness to participate will

have this information recorded in their clinic chart. They will indicate that they understand the study and are willing to participate by signing or placing a mark on the informed consent form. At that time demographic and other information indicated on Data Forms #1, 2 and 3 (See Appendices I, II and III) will also be collected. This will include the woman's name and age, the head of household's name, husband's name, village, expected date of confinement, or date of delivery, immunization history for TT, diphtheria toxoid and IPV during pregnancy, and clinic and hospital I.D. numbers.

3. Immunization Schedule (See Figure A and Figure A'. Figure A shows all of the immunizations which will be given which are relevant to the testing of hypotheses. Figure A' shows all of the immunizations which will be given to the children so that they are adequately protected against the three study diseases, plus pertussis, by 6 or 8 months of age depending on the group).

The schedule for the vaccines to be given to the women during pregnancy were described in Section A, 1, above.

Children in Group B will be given DT during the first three days of life. Children in Group C will be given DT and IPV during the first three days of life. Children in these groups will receive no further antigens for the purpose of the study until 6 months of age when Group B will receive DTP and Group C will receive DTP and IPV. They will, however, receive pertussis vaccine (Group C) or pertussis vaccine and IPV (Group B) at 2 and 4 months of age. At the end of the study (8 months of age) they will receive their third dose of tetanus diphtheria and polio antigens.

Children in Group D will receive DT and IPV at birth, DTP and IPV at 2 months of age, DTP at four months of age, a third dose of pertussis vaccine at 6 months of age and a third dose of IPV at the end of the study.

Children born to mothers in Groups A and E will receive their doses of DTP at 2, 4 and 6 months of age as is recommended by the World Health Organization. They will receive IPV at two and four months of age which is the schedule we have shown to be effective in inducing adequate antibody levels to polio virus in U.S. childrn (McBean, et al., 1984). However, a third dose of IPV will be given at the end of the study to meet the three dose recommendation of the World Health Organization for IPV.

4. Vaccines and Vaccine Doses

Tetanus and diphtheria toxoids, Adsorbed (For Adult Use) (Td):

Td containing 5 Lf of TT and 2.0 Lf of diphtheria toxoid per 0.5ml dose will be given intramuscularly.

Inactivated polio vaccine (IPV):

IPV prepared on human diploid cells by Connaught Laboratories, Ltd., containing 40±8 D-antigen units of Type I, 8±2 D-antigen units of Type II and 32±6 D-antigen units of Type III polio virus per 0.5ml dose will be given intramuscularly.

Diphtheria and Tetanus Toxoids, Adsorbed (DT)

DT containing 25 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid per 0.5 ml dose will be given intramuscularly.

Pertussis Vaccine

Pertussis vaccine containing 4 mouse protection units (mpu) per 0.5 ml dose will be given intramuscularly.

Diphtheria and Tetanus toxoids plus Pertussis vaccine, Adsorbed (DTP):

DTP containing 5 Lf of TT, 25 Lf of diphtheria toxoid and 4 mouse protection units (mpu) of pertussis vaccine per 0.5cc dose will be given intramuscularly.

Before obtaining the vaccine, vaccine potency for each lot used will be confirmed with the manufacturer. Also, only those vaccines with expiration dates beyond the completion date of the study will be used.

Vaccines will be sent directly to Kenya by the manufacturer via air freight in isothermic boxes with canned ice to maintain the proper temperature. Advance notice will be given to Customs Officials in Kenya to facilitate clearance into Kenya. Upon arrival in Kenya, the canned ice will be replenished and the vaccine will be taken directly to Tenwek Hospital four hours away by road. There it will be stored in a refrigerator at

+4 to +8oC which will be monitored for that temperature for the duration of the study. Isothermic boxes will be used to store the vaccine when it is taken to the clinics.

Upon completion of the study, three to five vials of each vaccine will be returned to the manufacturer for potency testing.

5. Vaccine Administration and Participant Follow-up:

Vaccines will be drawn up and administered by either the Research Scientist, or the Nurse Supervisor. Women will receive Td in the left deltoid area and IPV in the right deltoid area. Children will receive DT, DTP, or pertussis vaccine in the left anterior thigh and IPV in the right anterior thigh.

(Newborns weighing less than 2.5kg at birth or suffering with obvious congenital malformations will be excluded from the study.)

The Research Scientist and Nurse Supervisor will maintain a log of all patients enrolled in the study which will allow them to identify patients who are scheduled for return immunization visits. They will work closely with the Community Outreach Worker and the Community Health Workers (CHW) in each village to remind the women of their need to return for their second dose of vaccine during the eighth month of pregnancy and of the need to bring the child for the blood specimens and immunizations at the appropriate ages.

6. Specimen Collection and Handling

As indicated in Figure A, blood specimens will be taken at the time the woman is enrolled in the study, from the umbilical cord at the time of delivery and from the childen at one month or 2 months of age. Later specimens will be taken from Group B and C children at 6 months of age and from all children in Groups A, B, C and E at 8 months of age.

Five mililiters of blood will be drawn from the antecubital fossa of each woman using a red top Vacutainer (Becton-Dickenson, Rutherford N.J.) A similar amount of cord blood will also be collected in a red top Vacutainer at delivery. Two mililiters of blood will be obtained from the children by the heel or finger stick method using microtainer capillary blood collectors (Becton-Dickenson, Rutherford, N.J.)

In all cases, after the blood has been allowed to clot, it will be centrifuged and the serum drawn off into appropriately labeled vials.

Vials containing serum will be frozen at Tenwek Hospital usually within four hours and always within eight hours of

collection. They will be kept frozen there at -20oC and prepared for shipment. Dry ice will be obtained in Nairobi and packaged with the specimens for air shipment to Johns Hopkins University for testing.

7. Specimen Coding and Data Handling

At the time each woman is enrolled in the study, she will receive a study number. For women enrolled during pregnancy, (Groups A,B and C) that number will have previously been randomly assigned to one of the three study groups using random number tables. For women enrolled at the time of delivery of their child or when they appear when the child is 2 months of age assignment into Group D or E will take place at that time.

Self-stick labels (four for Group A, five for Groups B and C, and two for Groups D and E) which are to be used in sequence will be attached to the Data Form and pre-stamped with the study group number as well as one of the letters (A, B; or A, B, C or D; or A, B, C, D, E). These letters will have been randomly preassigned for each of the serum specimens. This will facilitate serum handling and "blind" the laboratory as to the sequence in which the sera were collected. In addition, each Data Form will have noted on it the order in which the self-adhering labels are to be used. For example for three subjects in Group A:

Specimen	Subject #1	Subject #2	Subject #3
	ID #0001	ID #0002	ID #0003
Pregnancy	0001 B	0002 D	0003 C
Cord Blood	0001 C	0002 B	0003 D
Child (1 month)	0001 A	0002 C	0003 A
Child (7 months)	0001 D	0002 A	0003 B

These lables will be attached to the tubes or vials throughout the process of serum separation and freezing.

The Data Forms, as mentioned earlier, has been designed for the collection of identifying information on each woman and child. We will also indicate the vaccines given in the study, when they were given, and the date blood specimens were taken. In addition to the copy retained by the study staff, a copy of this form will be included in the mother's and the child's clinic records.

8. Adverse Reaction Plan

Because of the safety and lack of contraindications to

Td, DT and IPV during pregnancy and early infancy, we will carry out active surveillance for adverse reactions during the time the newborns are in the hospital and passive surveillance for adverse reactions during pregnancy or following childhood immunizations given at, or after, 2 months of age. Active surveillance will consist of direct observation of the newborns 12, 24 and 48 hours after they receive their immunizations (See Appendix IV for the Adverse Reaction Form). In addition to taking the temperature, any inflammation, induration and pain will be recorded as well as whether or not the child has been fussy, spitting up, not sucking, crying excessively, having seizures, fainted or has had other problems. Any medications or other treatment will also be noted.

Women will be told to return for any severe local reactions or systemic reactions they or the children experience. In addition, at the time of each visit, each mother will be asked about reactions following immunizations she or her child received: such as convulsions, and/or prolonged fever of three to five days.

9. Laboratory Analysis

The level of IgG and IgM antibodies against tetanus and diphtheria toxin as well as the three types of polio virus will be measured in each serum specimen.

Analysis of all specimens will take place under the supervison of Dr. Robert Yolken using ELISA technology.

The ELISA method will consist of the following steps:

i. partially purified toxin or viral antigen will be absorbed to the solid phase,

ii. serum will be added at a predetermined dilution, e.g. 1:100,

iii. goat human IgG or IgM enzyme conjugate will be added,

iv. the test will be developed by adding the substrate to the enzyme and read in an automated micro-ELISA reader.

The ELISA results will be standardized using sera with known antibody levels which have been tested using traditional methods of antibody determination. For tetanus the traditional method will be toxin neutralization tests using the mouse paralysis model (Hardegree, et al, 1970). For diphtheria it will be toxin neutralization tests using the rabbit intradermal test procedure (Schubert and Cornell, 1958).

For polio virus the standard method will be poliovirus

neutralizing antibodies using the colorimetric (metabolic inhibition) neutralization test in microtiter trays (96-well flat-bottomed, Linbre-Flow Laboratories). The polio viruses used in the tests will be Strain Mahoney, MEF-1 and Saukett for Types I, II and III poliovirus, respectively. The sera will be diluted in two-fold steps starting at 1:4. The tissue culture medium and serum diluent will be Eagle minimal essential medium (EMEM) with Earle's balanced salt solution, 5% fetal bovine serum, 0.4% dextrose, 0.003% phenol Red, 0.15% $NaHCO_3$ and antibiotics. Sera will be diluted in microtiter trays using titertek multichannel pipette (Flow Laboratories). Each serum dilution will be tested in two wells for each virus. An equal volume of virus (0.025ml) will be added to each well and the serum-virus mixture will be incubated for 2 hours at room temperature. Then 0.05ml of Vero cell suspension (200,000 cells/ml) will be added to each well followed by 0.01 ml sterile mineral oil (Drakeol) and the trays incubated for 5 to 7 days at 37oC in an incubator. At the end of the incubation period, tests are read colorimetrically. A pH of 7.4 or higher indicates viral activity, while pH at 7.2 or lower is considered indicative of specific neutralization of virus. Endpoint titers will be calculated as the reciprocal of the serum dilution which neutralized CPE in 50% of the wells. A known serum prepared by the Office of Biologics of the United States Food and Drug Administration for each polio type will be tested with the experimental sera. A conversion factor will then be calculated to convert the observed, reciprocal of the serum dilution which neutralized CPE in 50% of the wells to International Units (IU).

10. Sample Size: (See Table 2, page 16)

Based on the work of Gill, et al. we expect approximately 70% of the cord blood specimens from the mothers in Groups A, B and C who received two doses of any vaccine to have measurable IgM levels specific for the antigen(s) they received. No cord blood specimens from unimmunized mothers should contain IgM to these specific antigens. (See Table 2A)

Expected seroconversion rates to polio virus or the expected percent of children with serum antitoxin levels $\geq$ 0.01 IU/ml to tetanus or diphtheria in neonates receiving their first dose or second ("booster") dose of each of the antigens are shown in Table 2.B. As seen from the table, the expected differences are estimated to be between 33 and 70% with the lower percent of subjects with antibodies between 20 and 45%. The "worse cases" from the perspective of sample size (that is, the greatest number of subjects needed) are for diphtheria antitoxin and for poliovirus type III. For diphtheria the difference in the proportion between the first dose and booster dose children is 32% and the smaller probability of success (or failure) is 12%. For polio type III, the difference is 33%, and the smaller probability of success (or failure) is 5%. Based on the exact

method of Casagrande, et al., (1978) an alpha of Ø.Ø5 and a beta of Ø.2 and using a one-tailed test of significance, the maximum number of children we would need is 37 for these two comparisons. In all other cases, the required number of subjects will be fewer.

At eight months of age, the percent of children with serum antibodies in Group E will represent the expected levels following the currently recommended immunization schedule. (See Table 2.C.) At least 95% of the children should have antibodies to Tetanus and Diphtheria antitoxin at a level of $\geq$ Ø.Ø1 IU/ml., and between 93 and 99% of the children will have antibodies to the three poliovirus types. In order to be recommended for adoption, the immunization schedules represented by Groups B and C will have to perform equally well. By "equally well", we mean within 15% of the expected levels found in Group E. Applying the same standards as for the serum taken at one month of age,(an alpha of Ø.Ø5, a beta of Ø.2, and using a one-tailed test of significance), we would need 55 children in each of the groups. In this calculation of sample size we have used the method of Gail and Gart (1973) which according to Schlesselman (1982) is the preferred method for calculation of sample size when the probability of success in one group is very high ($p \geq .90$ or .95) as will be the case at 8 months of age.

In order to have 55 children finish the study, we will enroll 11Ø women in Groups A, B, C and E. In groups A, B and C, we expect to lose 15% of the subjects between the time of enrollment and delivery, and 3Ø to 35% more prior to the last visit. A good rate of return is expected because of the planned contact between the mothers, the Community Outreach Workers and the study personnel. Although fewer visits are expected and the time is shorter, we will also enroll 11Ø women in Group E because they will not have come for prenatal care. Therefore, we assume that more of them will drop-out during the period of immunizing the child than the women in Groups A, B and C. Thus, we should have about the same number of children in each group at the end of the study.

For the purposes of the study, only 37 children are needed in Group D at the end of the study, therefore, only 65 will be enrolled in that group.

TABLE 2

Expected Percent of Antibodies Used to Determine Sample Size

2A -

Expected Percent of Cord Blood specimens with IgM

Vaccinated Groups	70%
Unvaccinated Groups	0%

2B - Expected Percent of 1 Month Old Children With Seroconversion to Polio Virus Types and/or Tetanus or Diphtheria Antitoxin Levels ≥ 0.01 IU/ml

Children who Received	POLIO Type I	POLIO Type II	POLIO Type III	Tetanus Antitoxin ≥ 0.01 IU/ml	Diphtheria Antitoxin ≥ 0.01 IU/ml (range)
First Dose	39	40	62	20	45 (8-56)
"Booster"	93	99	95	90	94 (88-100)
Expected Difference (Booster minus First Dose)	54	59	33	70	49 (worse case is 88-56 = 32%)

2C - Expected Percent of 8 Month Old Children with Seroconversion to Polio Virus Types and/or Tetanus or Diphtheria Antitoxin Levels ≥ 0.01 IU/ml

Type I	Type II	Type III	Tetanus Antitoxin ≥ 0.01 IU/ml	Diphtheria Antitoxin ≥ 0.01 IU/ml
93	99	95	≥ 95%	≥ 95%

11. Data Management and Analysis

Data entry and analysis will occur at the Johns Hopkins School of Hygiene and Public Health. Comparisons will be made between study groups for IgG, IgM and total antibodies to tetanus and diphtheria toxins and polio virus types I, II and III for each of the four serum specimens. These comparisons will be based on the percent of mothers, or children, with antibodies and the reciprocal geometric mean titers of these antibodies. The evaluation of the difference between proportions will be done using Chi Square. Reciprocal geometric mean titers will be compared using the t-test. We will also look at the changes in titer within each study group. Changes in titers in the same individuals will be compared using the McNemar test of change.

Specific comparisons and the reason for making them are as follows:

a. Within Group comparisons:

i. Six months versus cord blood: Antibody levels against all three antigens used will be compared in Groups A, B and C at six months of pregnancy and at time of delivery
Purpose: to assure potency and immungenicity of all vaccines.

ii. Cord blood versus serum taken at one month of age:
Purpose: look for rapid booster effect of the tetanus and diphtheria toxoids in Groups B and C; look for booster rapid effect of IPV in Group C. Group A will show the natural decline of antibodies to the three antigens in the offspring of immunized women. Group D will show the effect of the 3 antigens given to newborns of mothers who were not given these vaccines.

iii. Four week serum versus serum taken at 6 (Groups B and C) or 8 months of age (Groups A and D):
Purpose: Look for the long term effect of the first dose of tetanus and diphtheria toxoids in Group B and C; look for the long term effect of the first dose of IPV in Group C. Look for the effect of WHO recommended schedule of childhood immunizations in the offspring of women who received all the study antigens during pregnancy in Group A. Look for the effect of the WHO recommended

schedule of childhood immunizations in Group E.

iv. Six month versus 8 month serum (Groups B and C, only): Look for the effect of a second dose of tetanus and diphtheira toxoids given to the children in Group B and C; look for the effect of a second dose of IPV given to the children in Group C.

b. Between group comparisons

i. Sixth month of pregnancy: comparisons will be made to confirm the similarity of Groups A, B and C at baseline and the success of the randomization process.

ii. Cord Blood: Group D's cord bloods are the controls for IgM and IgG determinations against all three antigens in groups A, B, and C. In addition, Group B is a control for the response to polio antigen in Groups A and C.

iii. One month old children: Tetanus and diphtheria antitoxin response in Groups B and C will be compared with Group A and D. Group A will provide data on the level of antibodies in offspring of recently immunized mothers where the offspring do not receive a "booster" dose at birth. Group D will reflect the antibody levels in children not immunologically "primed" in utero. Similarly, the polio antibody response in Group C will be compared with Groups B and D (no exposure to polio antigen in utero) and Group A (no booster dose).

iv. Serum taken at 6 and 8 months of age: Group E is the standard for long term protection against which all other groups will be measured. Of primary importance are the comparisons with Group B (Tetanus and Diphtheria) and Group C (Tetanus, Diphtheria and Polio). The Group E titers will be compared with both the 6 and 8 month titers in Group B and C to evaluate the long term effect of one dose of the 3 antigens given to the "primed" children at birth and to see if, a schedule of a vaccine dose at birth and one at 6 months of age in primed children is superior to the currently recommended schedule. Group A will provide information on the long term effect of high levels of maternal antibody at birth. In this case we will see if there is any harmful effect of

receiving the antigens during pregnancy, not being immunized at birth for some social reason, e.g. didn't get to hospital, and then receiving childhood immunizations at the recommended times.

12. Project Timetable (See Figure B)

The total length of the project will be 24 months. The first month will be spent preparing materials, procurring supplies and in final negotiation of the collaborative agreement with Tenwek Hospital. During the second month we will hire and train new study personnel and conduct the necessary preliminary visits to surrounding villages. The principal activities during the remainder of the first two years will occur in Kenya.

With 1,600 women receiving prenatal care per year, there will be approximately 130 women available per month for enrollment in Groups A, B and C. Assuming 50% of them agree to participate in the study, it will take approximately six months to enroll the required number of pregnant women.

With approximately 50 women coming for delivery without prenatal care each month, it will take less than six months to enroll the 65 women required for Group D, even if only 25% agree to participate.

Because many women who have not received prenatal care bring their children to clinic we should have no trouble enrolling the 110 children needed for Group E in 6 months. Also because we have 5 months less follow-up time for Group E participants, the available enrollment period is 11 months. This will give more than ample time to enroll the children needed.

Serum specimens will be sent to Johns Hopkins for laboratory analysis 12 months after the start of enrollment and at the end of the study. Data analysis and preparation of the final report will be the principal activities of the last four months.

13. PROJECT MANAGEMENT

This project will require the collaboration of three institutions: Tenwek Hospital (Tenwek, Kenya), the Johns Hopkins School of Hygiene and Public Health and the Johns Hopkins School of Medicine (Baltimore, Maryland). Each of these institutions is represented by a senior member of the research team (Drs. Steury, McBean and Yolken). The details of this relationship for the purpose of implementing this project are shown below:

Project Consultants
Dr. Kaseje
Dr. Jacobson

Principal Investigator
Dr. McBean

Co-Principal Investigator
Dr. Yolken

Project Coordinator
Dr. Thoms

Field Supervisor
Dr. Steury

Laboratory Technician

Computer Programmer

Secretary

Research Scientist
(Dr. Hutchins)

Worker

Nurse Supervisor

Community Outreach Worker

The JHSH&PH and the JHSM are Divisions of the University and their faculty frequently collaborate on research projects.

An agreement will be established between the JHSH&PH and Tenwek Hospital in order to facilitate the hiring and supervision of the nurse supervisor, nurse, Community Outreach Worker and the clinic aids.

The 120 bed Tenwek Hospital and outlying clinic operate a full range of preventive and curative services for a population of approximately 400,000 people. It is currently undergoing renovations which will increase its bed-size to 190 by May 1985. Facilities are available for proper storage of vaccine and serum specimens.

Dr. McBean, the Principal Investigator, has had extensive experience over the past 13 years conducting vaccine field trials

Dr. McBean, the Principal Investigator, has had extensive experience over the past 13 years conducting vaccine field trials in Africa and the United States (See Attached Biographical Sketch.) Currently, he and a staff of six are involved in three vaccine trails which involve all of the steps required in the proposed study. That is to say, they have expertise in study implementation and logistics, including obtaining protocol approval, informed consent, form design and data analysis. In this project he will be responsible for overall guidance and implementation.

Dr. McBean is also Director of the General Preventive Medicine (GPM) Residency Program which has supervised GPM Residents in research projects in several developing countries. Dr. Mark Jacobson, a graduate of the program, is currently the Field Director of a four-year project for the training of Community Health workers (CHW) in which the JHSH&PH and the Christian Organizations Research Advisory Trust (CORAT, Africa), are working together. Dr. Jacobson is on the faculty and teaches at the University of Nairobi, as is Dr. Daniel Kaseje. They and Dr. Steury have worked together on the CHW project. Thus, there are both personal and organizational ties which will insure the proper coordination and support for the field portion of the project.

Dr. Steury, as Medical Superintendent of the Tenwek Hospital, will have overall responsibility for all field activities. He will supervise the Research Scientist and Nurse Supervisor and insure that appropriate hospital and clinic staff and facilities are available to support the project. The Research Scientist, Dr. Sonia Hutchins is currently a General Preventive Medicine Resident at the JHSH&PH. She will be granted the M.P.H. degree in May 1985. She has worked previously in Kenya and is participating in a special tutorial given by Dr. McBean on vaccines. Dr. Hutchins is fluent in Swahili.

The Nurse Supervisor and Community Outreach Worker will be hired from existing staff of the Tenwek Hospital or recent graduates from their training programs.

Dr. Robert Yolken will be responsible for the laboratory analysis of the sera. He has had extensive experience in developing and carrying out serum antibody determinations using the ELISA method. He will supervise the laboratory technician.

D. INSTITUTIONAL CAPABILITY

Two principle abilities will be needed to successfully complete the proposed study: 1) An ability to work effectively in developing countries like Kenya, and 2) an ability to direct large scale vaccine field trials. The Principle Investigator, Dr. McBean, has demonstrated that he has both of these skills. In Africa, he was the person in charge of two studies which resulted in the following publications. McBean, et al., (1972) Comparison of Intradermal and subcutaneous Routes of Cholera vaccine Administration, Lancet, 1, 527-29 and McBean, et al., (1978) Simultaneous Administration of Live Attenuated Measles Vaccine with DTP Vaccine, Pediatrics, 70:288-293.

These studies focussed on practical vaccination program questions. The first shows the superiority of the subcutaneous administration of cholera vaccine over the intradermal route. This study was carried out soon after the current Eltor cholera pandemic reached Africa. The second, in the area of multiple antigen administration, showed that live measles vaccine could be successfully administered simultaneously with DTP. He has successfully collaborated with Gateff and others in other trials of the simultaneous administration of multiple vaccine antigens, as well as other attempts at innovative methods of vaccine administration. These resulted in five publications:

Gateff C., P. Ravisse, D. Monchicourt, M. McBean et R. Labusquiere (1973) Vaccination BCG par Ped-O-Jet muni de bague de recul, Bull Soc Path Exot, 66:.

Gateff C., E. Relyveld, G. Legonidec, J. Vincent, R. Labusquiere, M. McBean, D. Monchicourt et L. Chambon (1973) Etude d`une nouvelle association vaccinale quintuple, Ann Microbiol 124B, 387-409.

Gateff C., M. McBean, D. Monchicourt et R. Labusquiere (1973) Contribution a l`etude de la vaccination BCG par la technique de piqures multiples a l`aiguille bifurquee, Bul Un Int Tub 1973, XLVII suppl. 29-38.

Gateff C., M. McBean et B. Durand (1974) Vaccination BCG a l`aiguille bifurquee OMS - Association combineeau vaccin antivariolique, Med Trop, 34, 37-58.

Gateff C., E. H. Relyveld, G. Legonidec, J. Vincent, M. McBean, B. Durand et L. Chambon (1974) Vaccination antitetanique simplifiee associee a des vaccins viraux vivant, Med Trop, 34:.

All of the studies involved the enrollment of children, motivation of parents or other participants to return for follow-up visits and the obtaining of blood specimens from children.

He was able to work with citizens of different African cultures as well as Europeans and Americans who were providing education or health services to the local population.

In the first two studies described, he was responsible for developing the study study design, study implementation and management, data analysis and the preparation of the final publications. (All biologics were maintained properly as were the specimens.) In the other studies he was assisted by Dr. Gateff in all phases of the project.

Over the past 4 1/2 years ye has been the Principle Investigator of large studies in Maryland which are currently in progress. The first "Re-evaluation of Polio Vaccine in U.S. Children" has already resulted in the interim publication "A Comparison of the Serologic Response to Oral and Injectable Polio Vaccines" (Rev. Infect. Dis. 6: S552-S555, as well as presentations of data at several national and international meetings. This study compares the serologic response to two new high potency inactivated polio vaccines (IPV) made by two manufacturers with the currently licensed oral polio vaccine (OPV). It has involved the enrollment of over 1200 children who are being followed for 18 months. during that time, they return four times for eithr vaccines or the taking of blood specimens. The field portion of the study will be successfully completed in April 1985.

Dr. McBean has effectively headed a team of eight full and part-time employees in order to successfully implement this project. Four collaborating organizations have been involved in the study and Dr. McBean has been responsible for the smooth inter-organizational relationships. He has been very ably assisted by Dr. Thoms who is the Project Coordinator on this and the two studies in progress described next.

The study "An Evaluation of Immunization Schedules for Inactivated Polio Vaccine Grown on Human Diploid Cells" will evaluate the serologic effectiveness of the new high potency IPV grown on human diploid cells, as well as a new immunization schedule of IPV using only one primary dose instead of the currently recommended two doses and is currently involving some of the same and additional sites and personnel, as the above study. Enrollment of 500 needed children will soon be completed. In this case, Dr. McBean designed and has had full responsibility for the study which has progressed without problems.

A recent addition to the "Re-evaluation of IPV in U.S. Children" study mentioned above is a extension to compare the effectiveness of IPV and OPV preventing the fecal and oral shedding of virus following a challange dose of monovalent OPV (polio shedding study). This portion of the study has just begun, and has involved the negotiating of new agreements with the cooperating site. We have also recontacted participants in the previus study who

appear eager to assist in the new study which is taken as a sign of satisfaction with the way the first trial was run.

In addition to carrying out the vaccine studies mentioned above in two Sub-saharan African countries, Dr. McBean lived in Cameroun for over 2 1/2 years and has lived and/or worked extensively in three others. He has worked for short periods of time or consulted in six others. He has, therefore, a good understanding of what can be reasonably to be accomplished in this type of country and can anticipate problems which might jeopardize a study. Few investigators combine this expertice with a proven ability to carry out large vaccine field studies in the United States. Because of the current domestic vaccine activities, he and his staff will be able to provide appropriate support for those people working in the field. Having been in that position, himself, he will be particularly skillful in anticipating their needs.

Co-Principal Investigator, Robert H. Yolken, M.D., will lead the laboratory portion of the study and supervise the development, standardization, and application of the assay systems. Dr. Yolken has extensive experience in the development of immunoassay systems as described in the enclosed biographical sketch. In addition, he has numerous collaborative relationships with investigators in the fields of immunology, microbiology, molecular biology, and biochemistry. He is thus able to call on the skills of these investigators to develop a wide range of rapid diagnostic techniques. Dr. McBean and a faculty member in the Division of Infectious Diseases of the Department of Pediatrics, which is headed by Dr. Yolken, are currently collaborating on the "polio shedding" study described above.

The following paragraphs indicate the pre-existing relationships between the Principle Investigator and other major participants in the study who are not mentioned above. This close professional relationship will help guarantee the success of the study.

Dr. McBean is Director of the General Preventive Medicine (GPM) Residency Program at the Johns Hopkins School of Hygiene and Public Health. The Program has supervised GPM Residents in research projects in several developing countires. Dr. Mark Jacobson is one of them. A graduate of the program, he is currently the Field Director of a four year project funded by the U.S. Agency for International Development for the training of Community Health Workers (CHW) in which the JHSH&PH and the Christian Organizations Research Advisory Trust (CORAT, Africa), are working together. Dr. Jacobson is on the faculty and teaches at the University of Nairobi as is Dr. Daniel Kaseje. They and Dr. Steury have worked together on the CHW training project. Thus, there are both personal and organizational ties which will insure the proper coordination and support for the field portion of the project.

Dr. Steury, as Medical Superintendent of the Tenwek Hospital, will have overall responsibility for all field activities. He will provide daily supervision of the Research Scientist and have ultimate responsibility for the performance of the Nurse Supervisor, Nurse, and Community Outreach Worker. He will also insure that appropriate hospital and clinic staff and facilities are available to support the project.

Dr. Sonja Hutchins, the Research Scientist, is currently a General Preventive Medicine Resident at the Johns Hopkins School of Hygiene and Public Health. She will be granted the M.P.H. degree in May 1985. She has had international health experience in Kenya. She is participating in a special tutorial given by Dr. McBean on vaccines, in addition to her other M.P.H. courses. Dr. Hutchins is fluent in Swahili which will facilitate communication with study participants.

E. **HUMAN SUBJECTS** (See Appendix V for the Informed Consent Forms)

The study population will consist of 505 women 18 years of age, or older and their subsequently delivered offspring residing in the Kericho District of Kenya. These women will be users of the health services provided by the Tenwek Hospital who come to the hospital or one of its outlying clinics for prenatal care during the sixth month of pregnancy (330), or failing that, come to these facilities at the time of delivery (185). The women will be in normal health. Women enrolled during pregnancy will receive two or three of the following antigens: Tetanus toxoid, adsorbed; Tetanus and Diphtheria toxoids, adsorbed; or Inactivated Polio Vaccine (IPV). The children will receive IPV, and either DTP or DT and pertussis vaccine. Pregnant women and children must be used in the study because of the hypothesis we are testing. Active immunization of the fetus can only be done by giving vaccine to pregnant women. The documentation of this phenomenon and of the "booster" effect in children of women given the antigens during pregnancy requires that children be included in the study and given vaccine.

Identifying information to allow us to contact women to remind them of the need for return visits will be obtained directly from the women. These data will be kept in a locked area in Kenya during the study and in a locked filing cabinet in Baltimore. This information must be retained throughout the study so that we can inform the children who are inadequately protected at seven months of age to return for additional immunications. No data sufficient to identify an individual will be entered into the computer during data analysis. Immunization histories during pregnancy and questions about side effects to the vaccine will be asked. All information will be obtained specifically for research purposes. At the completion of the study all data which could be used to identify an individual will be destroyed in the Johns Hopkins shredder.

Usual techniques will be used to obtain blood specimens from the women (venous blood drawn from the antecubital fossa) and children (heel or finger stick). Cord blood will be taken at the time of the severing of the umbilical cord. This is not known to cause any inconvenience or discomfort to the mother or the newborn. All of these specimens will be obtained specifically for research purposes.

Women who voluntarily come to the prenatal clinics or who come for delivery will be told of the immunization study by the providers staffing the clinics. She will be approached by the Nurse or the Nurse Supervsisor who will be from the same region of Kenya and, in most cases, of the same ethnic group. The purpose of the study will be explained in a language understood by the woman using animated drawings. She will be informed

of benefits of immunizations for herself and the infant, as well as the possible known complications to the vaccines in children. She will also be told of the need to return to the clinic or hospital for normally recommended, as well as extra visits, during her participation in the study. She will be told that by not participating in the study, she will not jeopardize any of the services she or the child would normally receive. She will be asked to indicate by signing on the informed consent form, or by placing a mark, that she understands.

Potential risks to the pregnant woman are essentially nil. The U.S. Advisory Committee on Immunization Practices, the "Red Book" of the American Academy of Pediatrics, and the American College of Physicians indicate that inactivated vaccines may be given during pregnancy. Further, the World Health Organization recommends that tetanus toxoid be given to pregnant women to prevent neonatal tetanus. Finally, the Td, adsorbed vaccine to be used in the study is licensed in Canada where it is manufactured for use in pregnant women.

The risks of taking blood from the pregnant woman and the cord blood are also essentially nil. There will be slight discomfort to the child at the time of drawing blood. there will be no discomfort after the child leaves the clinic and no risk of excessive loss of blood, infection or other problems.

With the exception of the vaccines given at birth, and the Group D children who receive a fourth dose of DTP at seven months of age, all vaccines given to the children are given at times that are recommended by the World Health Organization for IPV or DTP. Immunization during the newborn period has not been shown to be more dangerous for these antigens than at two months of age. The fourth dose of DTP could be dangerous if severe reactions occurred after the previous dose. We will not give additional DTP doses to any child who experiences major reactions to DTP. Thus, the risks are no different than for children receiving routine immunizations.

The benefit to the women and the newborn will be related to our encouragement that the woman return for and receive the second dose of Tetanus toxoid or Td during pregnancy. These children will be protected against neonatal tetanus.

The benefits to the children come from the facts that only 5 to 10% of the children in this population are currently properly immunized and there are cases (exact incidence unknown) of paralytic polio, neonatal tetanus, diphtheria and pertussis in the area. Participation in the study will greatly increase the likelihood that a child will be given the recommended vaccines at the appropriate age.

The potential for the harmful effect of having a lower

than expected or inadequate immune response when measured at seven months of age exists. One way of addressing this is by providing third doses of IPV to all children and third doses of DTP to children in groups B, C and D at the seven month visit. Thus, children in the Groups B, C and D would be receiving an adequate number of doses of diphtheria and tetanus toxoids to have normal levels of protection. Based on the work of Wilkens, et al. (1971) the response to the pertussis antigen should also be adequate. Further, once the analysis of the serum taken at seven months is completed, we will know if any children are unprotected against these diseases. Any susceptible child will be identified to Tenwek Hospital staff and called in for an additional immunization.

In order to minimize the inconvenience and cost of returning for the required visits and to compensate for lost time for other activities, $5.00 U.S. will be paid to each mother to reimburse her for her costs and effort for each visit other than the six month prenatal and delivery visits.

If any child experiences the major reported side effects due to DTP vaccine (convulsions, extended screaming or collapsing) no further DTP will be given. If such reactions or severe local reactions take place, treatment will be provided by the staff of Tenwek Hospital.

Because the risks are so small there will be a much greater benefit than risk from participating in this study. The women who receive two doses of tetanus toxoid will have their children protected against neonatal tetanus, and will only need one booster dose during their later pregnancies. The children in Groups B, C and D will be well protected against all of the diseases for which antigen will be given by the time they leave the study at seven months. Those in Groups A and E will essentially be receiving the currently recommended vaccination schedule.

We feel that there is a potential for a tremendous amount of knowledge to be gained for other children in Kenya and other developing countries. For the practical reason noted in section 2C, it is important to know if the fetus can be actively immunized with safe antigens such as tetanus toxoid, diphtheria toxoid and IPV. Then, if the study documents that giving only one dose of antigen at birth, or a dose at birth plus one a few months later which would give the same immune status as the currently recommended schedule would allow a tremendous improvement in vaccination coverage in developing countries and a large reduction in unnecessary deaths in infants.

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BUDGET

	Year I	Year II
Personnel		
JHSH&PH General Preventive Medicine Resident - Sonia Hutchins, M.D., M.P.H.	$14,040	$14,720
Consultants		
Dr. David Kaseje - Faculty of Medicine University of Nairobi	1,500	1,500
Dr. Mark Jacobson, CORAT, Africa	1,000	1,000
TOTAL PERSONNEL COSTS	$16,540	$17,220
Operating Expenses		
Supplies for blood collection	860	-
Vaccines - No cost, they will be provided by the manufacturer	-	-
Photocopying	200	200
Data Forms	300	-
Shipment of specimens	350	350
Telephone	250	100
Laboratory Analysis - 3,035 specimens @ $6.00/test - 750 in Year I 2,285 in Year II	4,500	13,710
Travel		
3 round trips - Baltimore to Nairobi/Tenwek Two in Year I and one in year II	4,196	2,098
Per diem in Kenya - at average cost of $50/day 20 days in Year I 10 days in Year II	1,000	500
In-country Kenya - 7,000 km at 20 cents/km	1,400	1,400
Data Entry and Analysis	-	1,000
Contractual Costs (*See Footnote)	11,825	10,625
TOTAL OPERATING EXPENSES	$24,881	$29,983
TOTAL COSTS	$41,421	$47,203
TOTAL COST FOR 2 YEARS		$88,624

Footnote - Contractual Costs

A contract will be negotiated with Tenwek Hospital in Kenya to provide clinical and community outreach staff as well as the vehicle for use by the Community Outreach Worker. The cost of the Subcontract is as follows:

Personnel in Kenya	Year I		Year II	
	% Effort	Salary & Benefits	% Effort	Salary & Benefits
Dr. J. Stuery - Medical Superintendent of Hospital	5%	-	-	-
Nurse Supervisor	75%	4,725	75%*	4,725
Community Outreach Worker	75%	4,500	75%	4,500

*Full Time for 9 months

Vehicle purchase & service & travel		
Motorcycle	1,500	
Repairs	100	400
Travel - 5,000 km/year at 20 cents/km	1,000	1,000

Figure A

Schedule of Immunizations and Collection of Serum Specimens showing those Immunizations Essential to the Study Protocol

Group and Sample Size	Month of Pregnancy				Age of Child (in Months)					
	6th	7th	8th	9th	0	1	2	4	6	8
Group A 110	Td IPV Serum (55)*		Td IPV		Serum from cord blood (37)**	Serum (37)	DTP IPV	DTP IPV	DTP	Serum (55)
Group B 110	Td Serum (55)		Td		DT Serum from cord blood (37)	Serum (37)			DTP*** Serum (55)	Serum (55)
Group C 110	Td IPV Serum (55)		Td IPV		DT IPV Serum from cord blood (37)	Serum (37)			DTP*** IPV Serum (55)	Serum (55)
Group D 65	Not Seen in Clinic				Serum from cord blood DT IPV (37)	Serum (37)				
Group E 110	Not Seen in Clinic						DTP IPV Serum (55)	DTP IPV	DTP	Serum (55)

DTP = Diphtheria and Tetanus Toxoid plus Pertussis Vaccine
IPV = Inactivated Polio Vaccine
Td = Tetanus and Diphtheria Toxoids, Adsorbed (for Adult use)
DT = Diphtheria and Tetanus Toxoids, Adsorbed

* Number in parentheses is the number of sera to be taken from complete sets of 4 sera (Groups A, B and C), or 2 sera (Group D and E) which will be analized

** The 37 specimens to be analized from the cord blood and 1 month of age specimens will be selected by omitting every 3rd one collected from laboratory analysis.

*** The use of the pertussis component of DTP is not essential for the study, but DTP is preferred over the use of DT and P separately which would require one more injection.

Figure A'

Revised Schedule of Immunizations and Collection of Serum Specimens Showing all of the Immunizations which will be given to the Participants. The vaccines in boxes for example, [P], are given to provide the best possible protection and safety to the children given the recommendations of the W.H.O and the needs of the study.

Group and Sample Size	Month of Pregnancy				Age of Child (in Months)					
	6th	7th	8th	9th	0	1	2	4	6	8
Group A 110	Td IPV Serum (55)*		Td IPV		Serum from cord blood (37)**	Serum (37)	DTP IPV	DTP IPV	DTP	[IPV] Serum (55)
Group B 110	Td Serum (55)		Td		DT Serum from cord blood (37)	Serum (37)	[P IPV]	[P IPV]	DTP Serum (55)	[DT IPV] Serum (55)
Group C 110	Td IPV Serum (55)		Td IPV		DT IPV Serum from cord blood (37)	Serum (37)	[P]	[P]	DTP IPV Serum (55)	[DT IPV] Serum (55)
Group D 65	Not Seen in Clinic				DT IPV Serum from cord blood (37)	Serum (37)	[DTP IPV]	[DTP]	[P]	[IPV]
Group E 110	Not Seen in Clinic						DTP IPV Serum (55)	DTP IPV	DTP	[IPV] Serum (55)

DTP = Diphtheria and Tetanus Toxoid plus Pertussis Vaccine
IPV = Inactivated Polio Vaccine
Td = Tetanus and Diphtheria Toxoids, Adsorbed (for Adult use)
DT = Diphtheria and Tetanus Toxoids, Adsorbed
P = Pertussis Vaccine

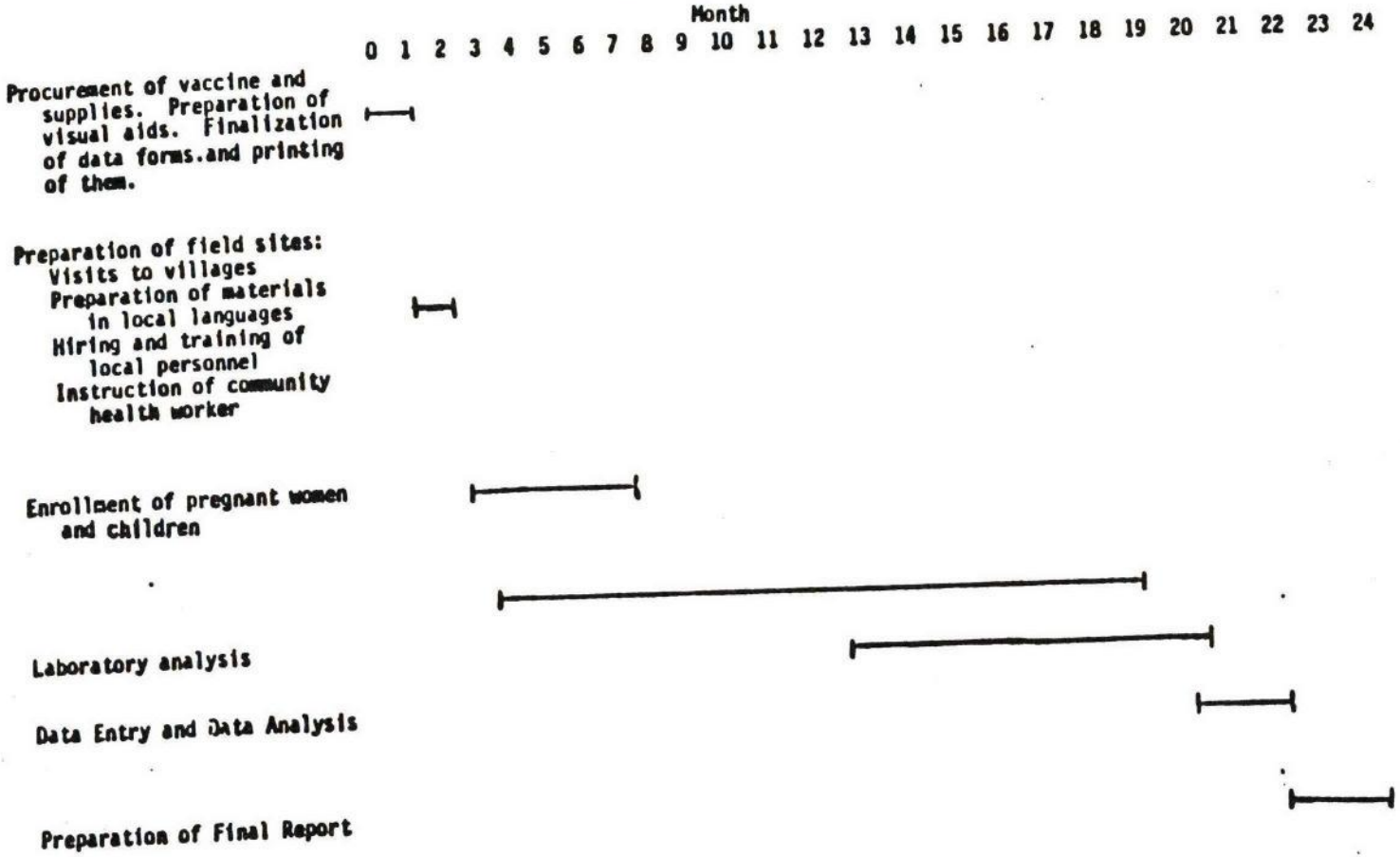
* Number in parentheses is the number of sera to be taken from complete sets of 4 sera, (Groups A, B and C), or 2 sera (Groups D and E), which will be analized.

** The 37 specimens to be analized from the cord blood and 1 month of age specimens will be selected by omitting every 3rd one collected from laboratory analysis.

*** The use of the pertussis component of DTP is not essential for the study, but DTP is preferred over the use of DT and P separately which would require one more injection.

Figure B

Time Schedule



Appendix 1
Active Immunization of the Fetus to Tetanus, Diphtheria and Polio
DATA FORM #1

Women Enrolled During Pregnancy
Mother

Name_____ Study Number_____

Clinic ID#_____ Age_____ Study Group_____

Hospital ID#_____ Order for use of labels ___,___,___,___

Name of Head of Household_____ Name of the Community Health Worker

Name of Husband_____ _____

Village_____

Expected Date of Confinement ___/___/___

History of Immunization:

Indicate any immunizations given to the mother during this pregnancy prior to enrollment:

	Yes	No		Yes	No
Tetanus Toxoid	☐	☐	IPV	☐	☐
Diphtheria Toxoid	☐	☐	Other _____	☐	☐

	Visit #1	Visit #2	Visit #3
	__ Month of Pregnancy	__ Month of Pregnancy	Delivery
Date of Visit	___/___/___	___/___/___	___/___/___ (Date of Birth)

Type of Vaccine Given to Mother	Visit #1 Yes	Visit #1 No	Visit #2 Yes	Visit #2 No	Visit #3
Td	☐	☐	☐	☐	XXXXX
IPV	☐	☐	☐	☐	XXXXX

Side Effects	Visit #1	Visit #2 Yes	Visit #2 No	Visit #3 Yes	Visit #3 No
	XXXXXX	Urticaria	☐ ☐	Urticaria	☐ ☐
	XXXXXX	Convulsions	☐ ☐	Convulsions	☐ ☐
	XXXXXX	Prolonged fever	☐ ☐	Prolonged fever	☐ ☐
	XXXXXX	Other	☐ ☐	Other	☐ ☐

Blood Specimen Taken	Visit #1 Yes	Visit #1 No	Visit #2	Visit #3 Yes	Visit #3 No
	☐	☐	XXXXX	☐	☐

Appendix I (continued)
DATA FORM #1 (continued)

Child

Name_____ Sex_____ Date of Birth __/__/__ Birth Weight_____ gms

Mother/Child Study Number_____ Study Group_____

Congenital Malformations noted Yes ☐ No ☐

If yes, describe_____

	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7	Visit #8
	Delivery	4 weeks of age	2 months of age	4 months of age	6 months of age	8 months of age
Date of visit	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Blood Specimen Taken	XXXXX	Yes ☐ No ☐	XXXXX	XXXXX	Yes ☐ No ☐	Yes ☐ No ☐
Type of Vaccine Given	Yes No DTP ☐ ☐ IPV ☐ ☐	XXXXXX XXXXXX	Yes No DTP ☐ ☐ IPV ☐ ☐ DT ☐ ☐ P ☐ ☐	Yes No DTP ☐ ☐ IPV ☐ ☐ DT ☐ ☐	Yes No DTP ☐ ☐ IPV ☐ ☐	Yes No XXXXX IPV ☐ ☐ DT ☐ ☐
Side Effects	XXXXX XXXXX XXXXX	Prolonged fever Yes ☐ No ☐ Convulsions ☐ ☐ Other ☐ ☐	Prolonged fever Yes ☐ No ☐ Convulsions ☐ ☐ Other ☐ ☐	Prolonged fever Yes ☐ No ☐ Convulsions ☐ ☐ Other ☐ ☐	Prolonged fever Yes ☐ No ☐ Convulsions ☐ ☐ Other ☐ ☐	Prolonged fever Yes ☐ No ☐ Convulsions ☐ ☐ Other ☐ ☐

Date Mother or Child Left Study __/__/__

Reason for Leaving _____

Appendix II
Active Immunization of the Fetus to Tetanus, Diphtheria and Polio
DATA FORM #2

Group D Women Enrolled at the Time of Delivery
Mother

Name_____ Study Number_____

Clinic ID#_____ Age _____ Study Group _____

Hospital ID#_____ Order for use of labels ___.___.___

Name of Head of Household_____ Name of the Community Health Worker

Name of Husband_____ _____

Village_____

Date of Delivery __/__/__ Cord Blood Speciman taken Yes ☐ No ☐ Birth weight_____gms.

History of Immunization:

Indicate any immunization given to the mother during this pregnancy prior to enrollment:

	Yes	No		Yes	No
Tetanus Toxoid	☐	☐	IPV	☐	☐
Diphtheria Toxoid	☐	☐	Other_____	☐	☐

Appendix II (Continued)
DATA FORM #2

Child

Name_____ Sex_____ Date of Birth __/__/__

Mother/Child Study Number_____ Study Group_____

	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6
	Delivery	4 weeks of age	2 months of age	4 months of age	6 months of age	8 months of age
Date of visit	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Blood Specimen Taken	XXXXX	Yes ☐ No ☐	XXXXX	XXXXX	XXXXX	XXXXX

Congenital Malformations: Yes ☐ No ☐ : If yes, describe _____

_____

_____.

Appendix II (continued)
DATA FORM #2

Child

	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6
Type of Vaccine Given	Yes No DTP ☐ ☐ IPV ☐ ☐	XXXXXX XXXXXX	Yes No DTP ☐ ☐ IPV ☐ ☐	Yes No DTP ☐ ☐	Yes No P ☐ ☐	Yes No IPV ☐ ☐
Side Effects	XXXXX Prolonged fever Yes No ☐ ☐ Convulsions ☐ ☐		Prolonged fever Yes No ☐ ☐ Convulsions ☐ ☐	Prolonged fever Yes No ☐ ☐ Convulsions ☐ ☐	Prolonged fever Yes No ☐ ☐ Convulsions ☐ ☐	Prolonged fever Yes No ☐ ☐ Convulsions ☐ ☐

Date Mother or Child Left Study ___/___/___

Reason for leaving study _____

Appendix III

Active Immunization of the Fetus to Tetanus, Diphtheria and Polio
DATA FORM #3
Group E Children Enrolled at the time of 2 month Immunization Visit
Mother

Name_____ Study Number_____

Clinic ID#_____ Age_____ Study Group_____

Hospital ID#_____ Order for use of labels ___.___.___.

Name of Head of Household_____ Name of Community Health Worker

Name of Husband_____ _____

Village_____

Date of Birth ___/___/___

History of Immunization:

Indicate any immunizations given to the mother during this pregnancy.

	Yes	No		Yes	No
Tetanus Toxoid	☐	☐	IPV	☐	☐
Diphtheria Toxoid	☐	☐	Other _____	☐	☐

Child

Name_____ Sex_____ Date of Birth ___/___/___

Mother/Child Study Number_____ Study Group_____

	Visit #1	Visit #2	Visit #3	Visit #4
	2 months of age	4 months of age	6 months of age	8 months of age
Date of visit	___/___/___	___/___/___	___/___/___	___/___/___
Blood Specimen Taken	Yes ☐ No ☐	XXXXX	XXXXX	Yes ☐ No ☐
Type of Vaccine Given	Yes No DTP ☐ ☐ IPV ☐ ☐	Yes No DTP ☐ ☐ IPV ☐ ☐	Yes No DTP ☐ ☐ XXXXX	XXXXX Yes No IPV ☐ ☐

Appendix III
DATA FORM #3 (continued)

Child

	Visit #1	Visit #2	Visit #3	Visit #4
Side Effects	XXXXX	Prolonged fever Yes ☐ No ☐	Prolonged fever Yes ☐ No ☐	Prolonged fever Yes ☐ No ☐
		Convulsions ☐☐	Convulsions ☐☐	Convulsions ☐☐
		Other_____ ☐☐	Other_____ ☐☐	Other_____ ☐☐

Date Mother or Child Left Study ___/___/___

Reason for leaving study _____

Appendix IV
Active Immunization of the Fetus Against Tetanus, Diphtheria and Polio
Adverse Reaction Reporting Form
Groups A, B and C

Name_____ Mother's name_____

Study Number __ __ __ __ Hospital Number_____ Hospital Ward_____ Bed Number_____

Study Number ___ Date of Injection __ __-__ __-__ __ Time of Injection_____

Date of Birth __ __-__ __-__ __

Temperature and Problems where shot was given:

	12 hours after injection	24 hours after injection	48 hours after injection
1. Temperature (Fahrenheit)	__ __ __.__	__ __ __.__	__ __ __.__
2. Inflamation Redness at Injection Site (Yes=1 No=2) arm	__	__	__
2. Inflamation Redness at Injection Site (Yes=1 No=2) leg	__	__	__
3. Induration Hardness of Injection Site (Size in mm) arm	__ __	__ __	__ __
3. Induration Hardness of Injection Site (Size in mm) leg	__ __	__ __	__ __
4. Pain at Injection Site (Yes=1 No=2) arm	__	__	__
4. Pain at Injection Site (Yes=1 No=2) leg	__	__	__
5. Other Problems			
Fussy	__	__	__
Spitting up	__	__	__
Not sucking	__	__	__
Crying	__	__	__
Seizures	__	__	__
Fainting	__	__	__
Other (specify)	_____	_____	_____
	__	__	__
6. Medication given and number of times given since child last seen.			
Asprin	__	__	__
Acetaminophens	__	__	__
Other (specify)	____ __	____ __	____ __
7. Treatment given and number of times given			
Cold Compress	__	__	__
Cool Bath	__	__	__
Other (specify)	____ __	____ __	____ __

ACTIVE IMMUNIZATION OF THE FETUS AGAINST TETANUS, DIPHTHERIA AND POLIO

Appendix V

Informed Consent

The following Informed Consent Form will be discussed by the nurse supervisor with each pregnant woman attending the Tenwek Hospital or outlying prenatal or immunization clinics.

The study will be explained in the language understood by each woman and a book containing animated drawings which will illustrate the major points of the study - purpose, procedures, risks, benefits, etc. - will be used to guide the discussion.

Separate Informed Consent Forms for use with potential enrollees for Groups A, B, C, Group D and Group E are attached.

ACTIVE IMMUNIZATION OF THE FETUS AGAINST TETANUS, DIPHTHERIA AND POLIO

Appendix Va

INFORMED CONSENT
For Groups A, B and C

The Johns Hopkins University School of Hygiene and Public Health and the School of Medicine in the United States of America and the Tenwek Hospital in Kenya are conducting a study to determine whether tetanus, diphtheria and inactivated polio immunizations given to women during pregnancy and infants at birth will protect the infants against tetanus, diphtheria and polio through active immunity to these diseases. If this is possible we could greatly improve our ability to protect many children in Kenya and other countries from the disabilty and death that these diseases cause.

Neonatal tetanus occurs commonly when mothers have not received 2 doses of tetanus toxoid either before or during pregnancy and the delivery of the baby takes place in unsterile conditions. Children become infected at birth and become very sick usually within a week, and are unable to nurse. In some areas more than half of these sick children die in spite of medical treatment. Thus, prevention through immunization of mothers is very important.

Tetanus also occurs in older children and adults who do not receive protection through immunization of themselves. Unimmunized people who have deep cuts or other injuries which become infected with the bacterium can develop tetanus. These cases can be very severe and many will die in spite of medical care. Prevention of the disease through immunization of children is very important.

Diphtheria is a disease which is not frequently reported in Kenya, probably due to mild skin infections which protect children against this severe respiratory disease. Those children who do get diphtheria have high fevers, difficulty swallowing and may develop severe complications. Immunization early in a child's life has been shown to be very effective in preventing the disease if the three recommended injections are given.

Polio is caused by an organism which infects almost all children in countries like Kenya. It can cause permanent lameness or other paralysis in some people who get it. There is no way of determining beforehand which children will be paralyzed. Also, about 25 to 30% of the cases of paralysis will occur before the child is one year of age. Therefore, it is very important that children be immunized at the recommended times early in their first year of life.

In Kenya, tetanus toxoid is already routinely given to women during their 6th and 8th month of pregnancy to prevent neonatal tetanus. Although diphtheria and inactivated polio vaccines are not routinely given to women during pregnancy, medical authorities indicate that there are no known risks to the mother or child in giving inactivated vaccines during pregnancy. The combined tetanus and diphtheria vaccine to be used in this study is licensed in Canada for use in pregnant women.

With the exception of the vaccines given at birth, all other vaccines which will be given to your infant are given at times recommended or approved by the World Health Organization.

Eligibility and Participation

If you are in your sixth month of pregnancy you are eligible to participate in this study. If you agree to participate you will be assigned to one of three study groups.

The first group will receive tetanus and diphtheria toxoids and inactivated polio vaccines during the 6th and 8th month of pregnancy. Their children will receive diphtheria, tetanus toxoids and pertussis (DTP) vaccine at 2, 4 and 6 months of age and inactivated polio vaccine (IPV) at 2, 4 and 8 months of age.

The second group will receive tetanus and diphtheria vaccines (Td) when they are in their 6th and 8th month of pregnancy. Their children will receive DT at birth and DTP at 6 months of age, pertussis vaccine at 2 and 4 months of age, IPV at 2, 4 and 8 months of age, and DT at 8 months of age.

The third group will receive Td and IPV vaccines when they are in their 6th and 8th month of pregnancy. Their children will receive DT and IPV at birth, DTP and IPV at 6 months of age, plus pertussis vaccine at 2 and 4 months of age and DT and IPV at 8 months of age.

Children in each of the groups will have received the recommended number of doses of each of the antigens by the time they are 8 months of age.

In addition we will take a small blood sample when you are in your sixth month of pregnancy. When your baby is born we will take a sample of blood from the umbilical cord. If you are in the first group we will ask you to bring your child back to the clinic when one month of age and when eight months of age so we can take a small blood sample from the finger or heel. If you are in the second or third groups we will ask you to bring your child back to the clinic when one month of age, six months of age and eight months of age so we can take

a sample of blood from the finger or heel.

The risks in this study are no different than for children receiving routine immunizations. No major side effects or adverse reactions are expected, however, some minor local reactions may occur, such as redness and/or swelling at the site of injection.

The risks of taking blood from you during pregnancy, from the umbilical cord at birth or from the infant are essentially nil.

There will be slight discomfort when giving the immunizations or drawing the blood but there will be no discomfort after leaving the clinic and no risk of excess blood loss, infection or other problems.

The benefits include the protection of yourself and your child against these diseases. Also, if the analysis of the blood taken at 8 months of age shows that your child is not protected against all three of these diseases, he/she will be asked back for a further immunization, if appropriate.

Participation in the study is entirely voluntary. If you agree to participate you are free to withdraw at any time. You will continue to receive the services of the clinic and hospital as usual.

If you should have any reactions to the immunizations contact the Community Health Worker or Nurse Supervisor. They will see that you receive proper medical care.

A copy of the information received about you and your child during the program will become part of your medical record. No information will be taken from the medical records. Information gained during this program will be held in confidence and analysis of the data will be done only after your name has been removed from the data forms.

The Johns Hopkins University does not have a program to provide compensation for persons participating in studies who may experience an injury which is not due to the fault of the investigator or the staff associated with the research.

_____ _____

Witness Signed by participant

ACTIVE IMMUNIZATION OF THE FETUS AGAINST TETANUS, DIPHTHERIA AND POLIO

Appendix Vb

INFORMED CONSENT
For Group D

The Johns Hopkins University School of Hygiene and Public Health and the School of Medicine in the United States of America and the Tenwek Hospital in Kenya are conducting a study to determine whether tetanus, diphtheria and inactivated polio immunizations given to women during pregnancy and infants at birth will protect the infants against tetanus, diphtheria and polio through active immunity to these diseases. If this is possible we could greatly improve our ability to protect many children in Kenya and other countries from the disabilty and death that these diseases cause.

Tetanus occurs in older children and adults who do not receive protection through immunization of themselves. Unimmunized people who have deep cuts or other injuries which become infected with the bacterium can develop tetanus. These cases can be very severe and many will die in spite of medical care. Prevention of the disease through immunization of children is very important.

Diphtheria is a disease which is not frequently reported in Kenya, probably due to mild skin infections which protect children against this severe respiratory disease. Those children who do get diphtheria have high fevers, difficulty swallowing and may develop severe complications. Immunization early in a child's life has been shown to be very effective in preventing the disease if the recommended number of injections (3) are given.

Polio is caused by an organism which infects almost all children in countries like Kenya. It can cause permanent lameness or other paralysis in some people who get it. There is no way of determining beforehand which children will be paralyzed. Also, about 25 to 30% of the cases of paralysis will occur before the child is one year of age. Therefore, it is very important that children be immunized at the recommended times early in their first year of life.

A number of women who are coming to the hospital or clinic when they are six months pregnant have volunteered to receive immunizations for tetanus, diphtheria and polio during their pregnancy and for their child to receive immunizations at birth and specified times during the child's first eight months of life.

We also need to follow some children from birth to eight

months of age whose mothers did not receive vaccines during pregnancy to see if these children react differently to vaccines given after birth than the children whose mothers received vaccines during pregnancy.

With the exception of the vaccines given at birth, all other vaccines which will be given to your infant are given at times recommended or approved by the World Health Organization.

Eligibility and Participation

If you are about to deliver a child and have not received any immunizations during your last pregnancy to tetanus, diphtheria or polio you and your child may participate in the study.

Children participating in the study will receive injectable immunizations against tetanus, diphtheria and polio while in the hospital. They will receive tetanus and diphtheria toxoid plus pertussis vaccine at 2 and 4 months of age, inactivated polio vaccine at 2 and 8 months of age and pertussis vaccine at 6 months of age.

In addition we will take a sample of blood from the umbilical cord when your child is born. We will also ask that when you bring your child back to the clinic at 1 month of age for immunizations that we be permitted to take a small blood sample from his/her finger or heel.

Children in each of the groups will have received the recommended number of doses of each of the antigens by the time they are 8 months of age.

The risks in this study are no different than for children receiving routine immunizations. No major side effects or adverse reactions are expected, however, some minor local reactions may occur, such as redness and/or swelling at the site of injection.

The risks of taking blood from the umbilical cord at birth or from the infant are essentially nil.

There will be slight discomfort when giving the immunizations or drawing the blood but there will be no discomfort after leaving the clinic and no risk of excess blood loss, infection or other problems.

The benefits include the protection of your child against these diseases.

Participation in the study is entirely voluntary. If you agree to participate you are free to withdraw at any time. You will continue to receive the services of the clinic and hospital as usual.

If you should have any reactions to the immunizations contact the Community Health Worker or Nurse Supervisor. They will see that you receive proper medical care.

A copy of the information received about you and your child during the program will become part of your medical record. No information will be taken from the medical records. Information gained during this program will be held in confidence and analysis of the data will be done only after your name has been removed from the data forms.

The Johns Hopkins University does not have a program to provide compensation for persons participating in studies who may experience an injury which is not due to the fault of the investigator or the staff associated with the research.

_____ _____

Witness Signed by participant

ACTIVE IMMUNIZATION OF THE FETUS AGAINST TETANUS, DIPHTHERIA AND POLIO

Appendix Vc

INFORMED CONSENT
For Group E

The Johns Hopkins University School of Hygiene and Public Health and the School of Medicine in the United States of America and the Tenwek Hospital in Kenya are conducting a study to determine whether tetanus, diphtheria and inactivated polio immunizations given to women during pregnancy and infants at birth will protect the infants against tetanus, diphtheria and polio through active immunity to these diseases. If this is possible we could greatly improve our ability to protect many children in Kenya and other countries from the disabilty and death that these diseases cause.

Tetanus occurs in older children and adults who do not receive protection through immunization of themselves. Unimmunized people who have deep cuts or other injuries which become infected with the bacterium can develop tetanus. These cases can be very severe and many will die in spite of medical care. Prevention of the disease through immunization of children is very important.

Diphtheria is a disease which is not frequently reported in Kenya, probably due to mild skin infections which protect children against this severe respiratory disease. Those children who do get diphtheria have high fevers, difficulty swallowing and may develop severe complications. Immunization early in a child's life has been shown to be very effective in preventing the disease if the recommended number of injections (3) are given.

Polio is caused by an organism which infects almost all children in countries like Kenya. It can cause permanent lameness or other paralysis in some people who get it. There is no way of determining beforehand which children will be paralyzed. Also, about 25 to 30% of the cases of paralysis will occur before the child is one year of age. Therefore, it is very important that children be immunized at the recommended times early in their first year of life.

A number of women who are coming to the hospital or clinic when they are six months pregnant have volunteered to receive immunizations for tetanus, diphtheria and polio during their pregnancy and for their child to receive immunizations at birth and specified times during the childs first eight months of life.

We also need to follow some children from 2 months of age to 8 months of age whose mothers did not receive vaccines during pregnancy to see if these children react differently to vaccines

given after birth than the children whose mothers received vaccines during pregnancy.

All vaccines which will be given to your infant are given at times recommended or approved by the World Health Organization.

Eligibility and Participation

If your child is 2 months of age and has not received any immunizations and you did not receive any immunizations during your pregnancy to tetanus, diphtheria or polio, your child is eligible to participate in the study.

Children participating in the study will receive injectable immunizations against tetanus, diphtheria and pertussis at 2, 4 and 6 months of age and against polio at 2, 4 and 8 months of age.

In addition, we will take a small sample of blood from your child's finger or heel when he/she comes to the clinic for the 2 month and 8 month visit.

Children in each of the groups will have received the recommended number of doses of each of the antigens by the time they are 8 months of age.

The risks in this study are no different than for children receiving routine immunizations. No major side effects or adverse reactions are expected, however, some minor local reactions may occur, such as redness and/or swelling at the site of injection.

The risks of taking blood from your child are essentially nil.

There will be slight discomfort when giving the immunizations or drawing the blood but there will be no discomfort after leaving the clinic and no risk of excess blood loss, infection or other problems.

The benefits include the protection of your child against these diseases. Also, if the analysis of the blood taken at 8 months of age shows that your child is not protected against all three of these diseases, he/she will be asked back for a further immunization, if appropriate.

Participation in the study is entirely voluntary. If you agree to participate you are free to withdraw at any time. You will continue to receive the services of the clinic and hospital as usual.

If you should have any reactions to the immunizations contact the Community Health Worker or Nurse Supervisor. They will see that you receive proper medical care.

A copy of the information received about you and your child during the program will become part of your medical record. No information will be taken from the medical records. Information gained during this program will be held in confidence and analysis of the data will be done only after your name has been removed from the data forms.

The Johns Hopkins University does not have a program to provide compensation for persons participating in studies who may experience an injury which is not due to the fault of the investigator or the staff associated with the research.

_____ _____

Witness Signed by participant

FORM NO. 75
(6–83)

THE WORLD BANK/IFC

Eric Bellagio

ROUTING SLIP	DATE: 11-6-85

NAME	ROOM NO.
① for own copy	
~~Nancy Birdsall~~	~~N 452~~
~~Tony Measham~~	~~N 440~~
② Measham	

	APPROPRIATE DISPOSITION		NOTE AND RETURN
	APPROVAL		NOTE AND SEND ON
	CLEARANCE		PER OUR CONVERSATION
	COMMENT		PER YOUR REQUEST
	FOR ACTION		PREPARE REPLY
	INFORMATION		RECOMMENDATION
	INITIAL		SIGNATURE
	NOTE AND FILE		**URGENT**

MARKS:

In case you
missed this in the Times.

FROM: Alan	ROOM NO.:	EXTENSION:

Experts Predict Almost Every Child on Earth Will Be Vaccinated by 1990

By ERIK ECKHOLM

The campaign to vaccinate all the world's children against six deadly diseases by 1990 has made dramatic gains in recent months and, for the first time, many health officials say they believe the goal will be virtually accomplished.

"We'll have solid data showing massive declines around 1990 in deaths from measles and tetanus, and in lameness from polio, from all corners of the globe," said Stephen C. Joseph, coordinator for child health with the United Nations Children's Fund, or Unicef.

The target diseases — measles, tetanus, whooping cough, polio, diphtheria and tuberculosis — now take the lives of [illegible] and a half million children each year and cripple hundreds of thousands more, according to the World Health Organization, a specialized United Nations agency that set the vaccination goal in 1974.

All the diseasees can be prevented with vaccines, but most children in Africa, Asia and Latin America have not yet been protected. In developed countries nearly all children have received the vaccines.

"We'll get very close," said Kenneth S. Warren, director of health sciences at the Rockefeller Foundation, a major sponsor of medical research. "We won't reach every single child by 1990, but if recent momentum is maintained, we can reach 80 to 90 percent in nearly all countries." At that level of immunization, epidemics of these diseases will be prevented, health experts say.

New Approach Gets Results

Officials attribute their newly found optimism not to any technological breakthroughs but to a new approach of "political and social mobilization" in which government leaders, the media, schools, churches and groups like the Rotarians, the Red Cross and the Boy Scouts are joining in concerted national vaccination campaigns. With this approach, scores of millions of children in more than 20 countries have been immunized just in the last 18 months.

"We've developed the ability to transform public health programs into social movements," Dr. Joseph said.

The goal of immunizing all children by 1990 was established in 1974 by governments at a meeting of the World Health Organization. Officials set the distant objective while they were flush with their imminent success in eradicating smallpox. At the time, fewer than 4 percent of people living in developing countries had been vaccinated against the other six threats.

UNICEF/Maggie Mu

Children being vaccinated in Senegal under the auspices of the United Nations.

The ensuing decade saw considerable progress in the spread of immunizations. Still, according to W.H.O. estimates reported last week at an international meeting on immunization in Cartagena, Colombia, the proportion of infants in developing countries receiving vaccines against diphtheria, whooping cough, tetanus or polio remains under 40 percent, and the percentage vaccinated against measles, the greatest single killer among the six, is only half that.

Inspired by Other Countries

But intense, highly effective vaccination campaigns last year in Colombia, Brazil, Sri Lanka and other countries, officials said, inspired governments around the world and showed the value of the approach that mobilizes efforts across a broad spectrum of society.

"This last winter, it became apparent that the goal of universal immunization set back in 1974 just might be doable," James P. Grant, executive director of Unicef, said in an interview. He said the governing boards of Unicef and W.H.O. decided jointly in January "to give it a serious try."

Some health experts, including many involved in the current effort, worry that intense, media-oriented campaigns for immunization might not bring lasting benefits; that the necessary month-by-month and year-by-year follow-ups will not occur. They say this will be a particular problem in Africa, where vaccine coverage is lowest and medical facilities are scarce.

Supporters of the vaccination campaign say they recognize these dangers but argue that quick successes can stimulate the development of institutions to provide future immunizations and other basic health services.

"Crash campaigns are useful for getting a program going," said Dr. Warren of the Rockefeller Foundation. "But we've got to move beyond that phase and develop this a regular aspect of health care."

Colombia's Campaign Is Model

Colombia's success in the summer of 1984 in raising its proportion of vaccinated children from 40 to 80 percent has served as a model for other countries. The nation's president led the crusade, with support from the opposition newspaper and the close involvement of many other groups. Now, at baptisms priests routinely ask mothers if their babies have been vaccinated.

Worldwide, the campaign has produced some remarkable scenes. In El Salvador, weapons were idled for a day in each of three successive months last spring to permit the vaccination of more than 300,000 children. Sri Lanka reached millions with the message "Immunize Your Child Today" by painting it in giant white letters in three languages across the green field of the Sri Lanka-India cricket matches, which were televised throughout the subcontinent.

Observers say the stage for the recent surge in vaccinations was set by two key developments. In the 1970's the World Health Organization, under the leadership its director Halfdan Mahler, encouraged developing countries to begin a wrenching transition from an emphasis on expensive urban hospitals toward low-cost "primary health care" for the neglected poor.

Promoting Primary Care

In addition, experts say, for the last several years Mr. Grant of Unicef has, through tireless, peripatetic proselytizing, stimulated official concern for child health in many countries and promoted the technique of social mobilization that is proving so effective in the vaccination effort.

"I see immunization strictly as a means to a broader end, the promotion of primary health care and child survival," Mr. Grant said.

More countries are constantly joining the crusade. This year or next, from 20 to 40 countries, including China, India, Bangladesh and Indonesia, plan major campaigns.

China, where close to half the children are already immunized, has just set a target of reaching 85 percent by 1988. Prime Minister Rajiv Gandhi of India says he hopes all children will be immunized in the next five years as a "living memorial" to his assassinated mother.

Last May, the director of the Pan American Health Organization announced the goal of completely eradicating polio from the Americas by 1990, which other experts agree is now entirely feasible.

And last month in Turkey the President and the army chief of staff opened a Colombia-style crusade that observers say will immunize more than 80 percent of the nation's children before this winter's first snows.

In the case of immunization, at least, financing seems to be the least of involved officials' worries. Unicef estimates a total cost of $5 billion for vaccination programs over the next five years, $1.5 billion of that to be provided as international aid. Officials say these funds, which would entail a tripling of current expenditures, will come from many sources. The government of Italy recently made a special donation of $100 million to Unicef for immunizations and related activities in Africa; Rotary International, a private group, pledged $120 million to fight polio.

'At present, no committed country with a realistic plan will be constrained by a lack of funds or supplies," Ralph H. Henderson, director of immunization for W.H.O., told the conference in Cartagena last week.

The goal of protecting children has provided a rare topic of agreement at this month's United Nations meetings in New York. Secretary General Javier Pérez de Cuéllar recently wrote all heads of state to urge their personal support for the vaccination campaign, and many leaders are highlighting their immunization achievements or plans in their addresses to the General Assembly. Governments will consider a formal resolution endorsing the 1990 goal when the world body marks its 40th anniversary Thursday. The next day Unicef will host a conference on the subject with hundreds of the private groups involved in the campaign.

Extra Benefits Are Seen

Beyond the direct benefits, experts also hope that the current campaigns will create conduits for reaching children with new vaccines they expect will soon be available against many more diseases.

A malaria vaccine, for example, is to be tested in humans in the coming year, and improved protection against other major killers including diarrhea and hepatitis B is also in the offing. Genetic engineers expect to plant vaccines against numerous diseases on a single virus, permitting one-shot protection where multiple injections spread over months are now required.

"Now, without doubt we are on the threshold of another major revolution" in development of vaccines, an Australian scientist, Gustav Nossal, told a conference last year. He added that "vaccines are history's most cost-effective public health tool."

(2)

The Targets: 6 Diseases That Threaten Children

MEASLES: Without vaccination, virtually all young children in developing countries catch measles. About 3 percent of those, more than 2 million a year, die from the viral disease or its complications, which include pneumonia, blindness, deafness and malnutrition. Mortality rates from measles among children already malnourished can rise to 10 percent or higher.

TETANUS: Caused by a bacterial toxin, tetanus can strike at any age but takes its greatest toll among rural newborns who are exposed by the unsterile cutting of the umbilical cord or the use of contaminated mud, ashes or dung as a poultice on the umbilical stump. Infected newborns become unable to suck, swallow or breathe and 85 percent of untreated patients die. Neonatal tetanus kills nearly one million infants every year.

PERTUSSIS: This bacterial infection of the respiratory tract strikes 80 percent of unprotected children. Also called whooping cough or the "hundred-day cough," pertussis kills, either directly or by precipitating pneumonia or malnutrition, about 1.5 percent of children in developing countries who catch it, more than half a million annually.

POLIOMYELITIS: More a crippler than a killer, the polio virus spreads mainly through contact with food and water contaminated with excreta. Only a small fraction of those infected develop paralysis, but several hundred thousand children in poor countries are still lamed annually. Polio can spread more viciously as sanitation improves and fewer children are infected in infancy, when they are partly protected by maternal antibodies; epidemics of paralyzing polio can then strike unvaccinated older children.

DIPHTHERIA: Although its prevalence is poorly documented, diphtheria, a bacterial infection that can kill by damaging the cardiovascular and nervous systems, is an increasing threat in some developing countries. Mild skin infections with the bacteria were once common, creating immunity, but with improved living conditions the frequency of mild cases is declining, permitting serious epidemics.

TUBERCULOSIS: The disease is most common among adolescents and adults, but tuberculosis, especially the form known as TB meningitis, also kills tens of thousands of children each year.

THE VACCINES: DPT is a combined vaccine against diphtheria, pertussis and tetanus. BCG vaccine protects against tuberculosis, measles and polio; according to the World Health Organization, measles vaccines and polio vaccines are sometimes administered independently instead. Tetanus toxoid is given to adults, especially women of childbearing age since this also protects their newborns during their vulnerable first weeks, the health agency says. The DPT and oral polio vaccines are usually administered 3 times at monthly intervals in the early months of life. The measles vaccine is given at about the age of 9 months; before then the infant's natural immunity renders it ineffective.

Thanks

Mr. J. Norga

1/31

ARO

John:

Mark will be pleased to know that generally positive comments on the Bresse paper have now been received from MOH & UNICEF, Colombia. In addition, Bresse's WHO ideas were re-endorsed at a recent 2-day PAHO/UNICEF meeting attended by H. Barnum.

Larry

PAHO/WHO INTEROFFICE MEMORANDUM

Date: 10.I.86

From: Dr. José María Paganini, CR Colombia

To: Dra. Elsa Moreno, HPM

Our Ref: COL/RP-041-86

Attention: Dr. Ciro de Quadros, HPM/EPI

Your Ref:

Subject: comentarios al documento "Efectividad d los costos de los programas de Inmunización en Colombia."

Originator:

cc to HB

Adjunto al presente me permito hacer llegar a usted copia de la comunicación que hemos recibido del Dr. Luis A. VAlero, Jefe de la Oficina de Planeación del Ministerio de Salud, con la cual hace comentarios al documento "Efectividad de los costos de los programas de Inmunización en Colombia.

Cordialmente,

Anexo

PAHO/WHO INTEROFFICE MEMORANDUM

Date: 10.I.86

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To: Dra. Elsa Moreno, HPM

Our Ref: COL/RP-041-86

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Cordialmente,

Anexo

REPUBLICA DE COLOMBIA

MINISTERIO DE SALUD

Calle 16 Número 7-39

BOGOTA, D. E.

TELEGRAMAS Y CABLES: "MINSALUD"

Al contestar esta nota mencione el número y la sección de procedencia e indique su dirección.

DIVISION:

NUMERO 006883

SECCION: OFICINA DE PLANEACION

10 ENE 1986

Bogotá, D.E. 9 de Enero de 1986

Doctor
JOSE MARIA PAGANINI
Representante OPS/OMS
Presente

Apreciado Doctor Paganini :

Atentamente me permito remitirle algunos comentarios relacionados con el Documento " Efectividad de los costos de los programas de Inmunización en Colombia " enviado a la Doctora Magnolia Giraldo y al suscrito.

El estudio realizado por los Doctores Andrew L. Creese y María Alicia Dominguez Ugá es muy interesante, sinembargo hay resultados que dejan grandes interrogantes, posiblemente debido a limitaciones técnicas, ya que en Colombia no se tiene una metodología establecida de cálculo de costos, por lo tanto algunos de los resultados observados no pueden ser muy confiables.

En Organismos de Salud con condiciones y recursos similares y dentro de una misma regional donde las características de la prestación de servicios es muy - homogénea, se observan diferencias muy amplias, por ejemplo : en la Regional de Facatativá los costos promedio por inmunización son : En Faca $60.4 y en Albán $964.0 o sea 14.8 veces más costoso en Albán que en Faca.

Teniendo en cuenta los niveles de desarrollo de las diferentes regiones del país, tal vez no es muy aconsejable inferir a todo el País, el resultado de los costos observados en 10 Organismos de Salud.

En las Tablas 7 y 8 se observa que el costo promedio por inmunización en las Jornadas Nacionales de Vacunación es bajo en algunos de los Organismos como en Garcés Navas, Ismael Perdomo, Campoalegre y Ribera, sinembargo el costo

./.

REPUBLICA DE COLOMBIA
MINISTERIO DE SALUD
Calle 16 Número 7-39
BOGOTA, D. E.
TELEGRAMAS Y CABLES: "MINSALUD"

Al contestar esta nota mencione el número y la sección de procedencia e indique su dirección.

DIVISION: OFICINA DE PLANEACION NUMERO

SECCION:

09-01-86

Dr. José María Paganini

promedio por niño totalmente inmunizado se incrementa considerablemente en las JNV lo que demuestra que el indicador " Niños vacunados con tercera dosis de DPT " no es el más apropiado para calcular el costo de niños totalmente inmunizados; pero sin duda, dada la poca disponibilidad de tiempo y de otros elementos, no habría otra alternativa.

Es importante como dicen los autores de este estudio profundizar en las características y costos de las estrategias utilizadas en este país e identificar su repercusión en la comunidad.

Varios de los aspectos de este valioso estudio fueron tenidos en cuenta para el desarrollo de la Evaluación de las Jornadas de Vacunación correspondientes al año 1985.

Finalmente, doy mis mas sinceros agradecimientos por haberme facilitado oportunamente este excelente documento; si es posible, sería muy importante conocer el Anexo No. 1 para identificar los componentes del costo.

Cordial Saludo,

LUIS ANTONIO VALERO RUEDA
Jefe Oficina de Planeación.

UNICEF
FONDO DE LAS NACIONES UNIDAS PARA LA INFANCIA
OFICINA REGIONAL PARA
AMERICA LATINA Y EL CARIBE
CALLE 76 No. 10-02 BOGOTA - COLOMBIA
TEL. CONMUTADOR
212 9111

REF: 5- 02

2 de Enero de 1986

Estimado señor Paganini:

Acuso recibo de su atenta carta de fecha 26 de Diciembre/85 junto con la cual me envía copia del Estudio Costo-Eficiencia de las Jornadas de Vacunación, realizado por los Doctores Andrew Creese y María Alicia Domínguez-Ugá, sobre el cual solicita mis comentarios.

Al respecto, deseo manifestarle que asistiré a la reunión que tendrá lugar en Washington para discutir los procesos de Evaluación de las Jornadas Nacionales de Vacunación y, por lo tanto, tendré la oportunidad de expresar allí mis comentarios sobre dicho Estudio.

Al agradecer su gentil envío, me suscribo de usted,

Atentamente,

Eduardo Busteio
Asesor Regional
Planeación y Evaluación

Sr. José María Paganini
Representante OPS/OMS
Apartado Aéreo 29668
Bogotá

1945-1985
40 años de las
Naciones Unidas

EVALUATION OF IMMUNIZATION PROGRAMS

MEETING OF PAHO, UNICEF, AND THE WORLD BANK
WASHINGTON D.C., 22-24 JANUARY 1986

PARTICIPANTS:

Steve Joseph, UNICEF*
Twig Johnson, UNICEF
Eduardo Bustelo, UNICEF
Frances Stuart, UNICEF*
Howard Barnum, WORLD BANK
Philip Musgrove, PAHO
Ciro de Quadros, PAHO
Jean-Marc Olivé, PAHO
Peter Carrasco, PAHO

The meeting was held to discuss the following evaluation topics: EPI costing methodologies; rapid assessment, program reviews, and coverage surveys. The purpose of the meeting was to coordinate efforts among the organizations and standardize the approaches. What follows is a summary of the conclusions.

EVALUATION

The participants agreed that the there was overlap between the two methodologies being used by PAHO and UNICEF in their approaches in evaluation of immunization efforts.

Therefore, the discussants agreed that the evaluation methodology currently being used by PAHO, (draft document "Methodology for Multidisciplinary Evaluation," February 1984.) should serve as a basis for proceeding with joint PAHO/UNICEF evaluations. However, additional chapters building on the issues addressed in the UNICEF document titled "Rapid Assessment of High Priority GOBI Interventions", concerning the acceleration of immunization programs in relation to political and social mobilization and costs should be added.

In certain instances, evaluations may be followed by special case studies to further explore and illuminate certain issues raised but not resolved by the evaluation.

In addition, provision should be made to obtain coverage data through either cluster sampling techniques, quality control methodologies, or via the existing national immunization information system.

---

*Attended first day only

PLANNING AND IMPLEMENTATION:

Evaluation activities in the region should be jointly planned and implemented between PAHO and UNICEF. In addition, all other donor agencies should be invited to participate.

In view of the acceleration efforts in the region, the evaluation of immunization programs and accelerated efforts should be planned so that the results are made available no later than 3 months after the activity has been completed.

REPORTS:

In order to share the experiences and lessons learned with the international audience, a second report may be produced based on the original evaluation report. In such cases, this second report should be written by members from the original evaluation team.

FUTURE ACTIVITIES:

To standardize and field test the proposed approach, the group agreed to select a country among those countries that have recently completed or will soon undertake accelerated immunization activities,i.e. Peru, Ecuador,Belize,and Guatemala. The selection of the country should be jointly agreed to in the next UNICEF/PAHO meeting to be held in Bogota, Colombia in February 1986.

The joint collaboration between the organizations using the standardized methodology will permit counties to efficiently and effectively improve program performance. Moreover, this approach will allow all evaluative information to be rapidly and easily disseminated to all audiences both within and outside the region.

It was agreed that, after the first or second implementation of the proposed approach, a second meeting be held to review the experience, key issues and problems in order to adapt or change the approach.

COSTING METHODOLOGY:

The participants agreed that the WHO costing guide lines (document EPI/GEN/79/5.) constitutes the basis for determining cost associated with immunization programs , as well as for costing accelerated immunization efforts including geographic variations and alternative strategies of delivery. The costing guidelines should include a methodology for arriving at the promotional costs of the program.

Capital costs: The group agreed that the costing guidelines needed more information on the analysis of capital costs. This will permit the users to include or exclude these costs in their analysis depending upon the conditions, assumptions and difficulties in estimating capital costs in the country of interest.

There should be greater discussion on the presentation of costing data,and the discussants recommended that a standardized format be followed which will allow for the identification of the different types of costs such as:

*Total Cost (including incremental costs and existing).

*Incremental Costs in both:
-national monies.
-foreign monies.

*Existing finanical resources (devoted to the program before expansion).

*Social Costs (non-monetary).

To facilitate comparisons across studies, social costs ,as defined here, do not include costs absorbed by the consumer of the immunization services but rather those costs that the government's immunization program must incur and would have had to pay for if it were not donated or volunteered.

A standardized presentation should allow for comparisons of costs among different countries. Therefore, the current document should include a suggested format for analysis and presentation of data.

Where appropriate the results of the cost evaluation should form part of the overall report of the entire evaluation.

The comments made therein should be forwarded immediately to Dr. A. Creese (the author of the existing costing guidelines) so that he can respond to them. It is also suggested that those individuals that have applied this methodology be consulted to obtain further information on their applicability.

Twig Johnson

Ciro de Quadros

Eduardo Bustelo

Peter Carrasco

December 9, 1985

Via Federal Express

Mr. Alfred Link
Vice President
Manufacturing and Operations
Merck Sharp and Dohme
Sumneytown Pike, Building W36-2
West Point, Pennsylvania 19486

Dear Mr. Link:

After conversations with people at UNICEF and WHO, we have concluded that operational field trials with the Ezeject are indicated to anticipate the difficulties to be encountered in wide-scale use. We will develop a unified protocol to be used by approximately 10 different countries as soon as we can get delivery of the Ezeject.

We would like the lowest possible price quote for 100,000 Ezeject syringes with measles vaccine. We require the licensed international measles vaccine stablized and adjusted for international tropical distribution. The central issue after field trials will be whether or not the unit price will permit very large quantity purchases by WHO and UNICEF.

In addition, we would like 5,000 empty Ezeject syringes, which we plan to use with DTP and tetanus toxoid to secure FDA approval.

Final specifications for the Ezeject syringe are being developed at this time based on the Guatemala experience and should be available within 10 days.

It is extremely urgent that we get the manufactured product at the earliest possible time. Please advise.

Thank you for your assistance.

Sincerely,

William H. Foege, M.D.
Executive Director

cc: Dr. Maurice R. Hilleman

bcc: Ken Warren
Tim Rothermel
Tony Measham
Steve Joseph
Rafe Henderson

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033
(404) 325-2452 • Telex 8107518512
Administratively Affiliated with Emory University

December 3, 1985

TO: See Distribution Below

FROM: William H. Foege

SUBJ: Ezeject

In further reference to my memorandum of November 27, 1985 concerning the Ezeject project, we would appreciate receiving any ideas which you might have for protocol development, as mentioned in paragraph 4.C. We would appreciate receiving your suggestions by December 20, inasmuch as we hope to have the protocol developed and ready to send out for comments by early January.

Sincerely,

Bill Foege

William H. Foege, M.D.
Executive Director

cc: Newton Bowles
Joe Giordano
Billy Griggs
D.A. Henderson
Rafe Henderson
Maurice Hilleman
Alan Hinman
Don Hopkins
Steve Joseph
Tony Measham
John North
Ciro de Quadros
Tim Rothermel
Ken Warren

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033 (404) 325-2452 • Telex 8107518512
Administratively Affiliated with Emory University

November 27, 1985

TO: See Distribution Below

FROM: William H. Foege

SUBJ: Update - Ezeject

1. Merck hired an outside group to examine the possibility of Ezeject production, either alone or in collaboration with Merck. On November 12, I discussed their report with Dr. Maurice Hilleman. He said they had convinced him that Ezeject production is not a labor intensive operation as he had anticipated, but rather a demanding machine intensive high technology procedure. It is likely that technical barriers can be overcome, but a major capital investment will be required to begin production.

   Until that capital investment is made, Merck is still willing to provide Ezejects at the previously quoted price of between $1.70 and $1.80 each. An ultimate price estimate is not yet available for when Ezejects are mass produced, but it should be noted that Merck halted an earlier negotiation with a company that could produce at $.17 per Ezeject because it was too expensive. Therefore, we are still hopeful that the price will be competitive with current procedures which use disposable needles and syringes.

2. In conversations with Jim Grant and Steve Joseph on the night of November 19, it was decided that we should proceed with ordering 100,000 Ezejects for operational trials. In broad outline, we could provide about 10,000 to each of 10 countries to follow similar protocols for the fastest possible identification of operational difficulties encountered with daily use in large volumes. For example, limited use in Guatemala has already suggested ribbing would improve operations when fingers get sweaty. Operational trials would aim at using a spectrum of vaccinators (perhaps 20 in each country) to more quickly find problems in use.

3. Maurice Hilleman was advised of the above and will get the appropriate people alerted, but will not start production until specifications are received based on the Guatemala experience. He has discussed the basic findings with Neal Halsey by phone.

4. In discussions with Ciro de Quadros, it was decided that most rapid progress could be made by building on the base Ciro has developed for the Guatemala studies. Therefore, on November 22, Bill Watson met with Roger Bernier, George Curlin, Neal Halsey, Stan Foster, Steve Jones, John Umhow and me to discuss Guatemala results and next steps:

   a. Neal Halsey will take responsibility for developing new specifications based on the experience in Guatemala and current WHO/UNICEF requirements.

   b. Those in attendance will provide us with the items they believe should be included in the operational protocol. We will do a rough protocol and send it to participants for comments.

   c. In addition to those at the meeting, we will ask The Task Force members and selected others to also provide their ideas for protocol development.

   d. By means of this memo, could we ask Rafe Henderson and Steve Joseph to recommend the programs they would select to do the studies?

   e. It is hoped that the protocol can be completed and shared with programs before the Ezejects become available to avoid any delay in testing. We would then hope to get ongoing reports (i.e., weekly) by telex from the participating countries, which we would collate and provide weekly to The Task Force.

5. We will also discuss with Maurice Hilleman the possibility of getting some Ezejects with DTP and tetanus toxoid to simultaneously, but in different settings, test sero-conversion rates and other requirements for licensing. Separate operational testing for these antigens would seem unnecessary if the measles operational tests are satisfactory. Neal Halsey has offered to do some of this work in pediatric clinics in this country.

6. We must also discuss with Dr. Hilleman ways that we could speed up the process of manufacturing if the operational tests so indicate, as well as ways to get the lowest possible price both now and in the future.

Sincerely,

Bill

William H. Foege
Executive Director

cc: Ken Bart
Roger Bernier
Newton Bowles
George Curlin
Stan Foster
Joe Giordano
Billy Griggs
Neal Halsey
D.A. Henderson
Rafe Henderson
Maurice Hilleman
Alan Hinman
Don Hopkins
Steve Jones
Steve Joseph
Tony Measham
John North
Ciro de Quadros
Tim Rothermel
John Umhow
Ken Warren
Bill Watson

CANOLFAN EFRYDIAU DATBLYGU
COLEG Y BRIFYSGOL ABERTAWE
PARC SINGLETON
ERTAWE SA2 8PP
CYMRU, Y DEYRNAS UNEDIG
FFÔN: 0792-205678

CENTRE FOR DEVELOPMENT STUDIES
UNIVERSITY COLLEGE OF SWANSEA
SINGLETON PARK
SWANSEA SA2 8PP
WALES, U.K.
TEL: 0792-205678

Please send cc's to Dr. Henderson, Foege & Joseph and circulate to Dr. Norton, Mrs. Bridgette & Mr. Lumm.

Dr. Anthony R. Measham.
Health Adviser,
Population, Health and Nutrition Department,
The World Bank,
1818 H Street N.W.
Washington DC 20433,
U.S.A.

9 November 1985

Dear Tony,

Colombian National Vaccination Crusade.

I have read with interest the briefing document prepared by Dr. Francisco Yepes and distributed at the recent meeting of the Bellagio Group in Cartagena, Colombia. I was particularly interested in the cost estimates contained in this paper since, as you indicated on the telephone, they appear substantially different from the estimates in the paper which Mrs. Dominguez-Uga and I recently produced.

On examining the contents of Annexes 10-11 in the Yepes document it appears that the work of Dr Buendia remains the principal basis for these figures. The annexes differ in two ways from Dr Buendia's previous work on the vaccination campaign costs, made available to us in mimeo as 'Capitulo 7: El Costo de las Jornadas'. Firstly, an item has been imputed for capital costs (38.48 million pesos), and secondly, a major downward revision has been made to Dr Buendia's original estimate of the salary and allowances cost for health personnnel. In Buendia's original paper this item was 622.4 million pesos: in the Yepes document it is 151.8 million pesos. This change explains why our figures - which are close to Buendia's originals - result in a total incremental cost estimate for the campaign which is almost twice as much (1-1.2 billion pesos, compared with 588 million) as the estimate in the Yepes paper.

Buendia's original calculation assumed that each of the 82000 health sector workers spent the equivalent of one working week in connection with the vaccination campaign. At an average monthly salary of 23,000 pesos, and with various "prestaciones sociales" adding some 43% to this salary base, this gives a total of:

23000 pesos average salary + 43.4% contributions=32982 pesos/month/health worker. Taking one week as 23% of a working month (approximately 7/30,as Buendia seems to have done) gives a salary cost per health-worker week of 7585.86 pesos. This times

82000 health workers gives the total of just over 622 million pesos.

It is not clear on what basis the lower wage figure of 151.8 million pesos has been estimated, but pro rata this reduction would imply only one quarter of the time assumed by Buendia as attributable to the vaccination campaign - less than two working days per health worker. Given that the campaign was actually held on three days this would seem, prima facie, to be an understatement.

Our discussions with health workers at the 10 health posts visited, and at departmental and national levels, led us to impute three working days per health worker to the actual campaign days and, in addition, quite substantial amounts of preparatory time involving the introduction or the intensification of channelling before the actual days of the campagn. Our Table 6 shows very clearly that the actual campaign day cost was often smaller (i.e less time consuming) than the preparatory work. It would thus seem unrealistic to make such a large scale downward revision of Buendia's original estimate, and we should be most interested to hear further of the rationale for this major change.

Thank you very much for keeping us informed of reactions and comments to our piece of analysis. It is a matter of some regret to us that this work has not, so far, been a basis for further dialogue regarding the methods and applications of cost appraisal in the Colombian health sector, but we await possible further responses with interest. I am copying this letter to Dr Ciro de Quadros to ask him to invite feedback from PAHO/Ministry of Health colleagues in Colombia.

Yours sincerely.

Andrew Creese.

ccs:

Sra Maria Alicia Dominguez-Uga, Escola Nacional de Saude Publica, Rio de Janeiro.
Dr CCiro de Quadros, PAHO, Washington.

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

IDN OR1017
ARH
Trici
Bellagio

Téléphone Central/Exchange: 91 21 11
Direct: 91 2489

In reply please refer to :
Prière de rappeler la référence : EPI I8/86/2
EPI I8/445/1

Dr Bill Foege
The Task Force for Child Survival
1989 North Williamburg Drive
Suite I
Decatur, Georgia 300033
Etats-Unis d'Amérique

11 September 1985

Dear Bill,

Applied research

Thank you for your letter of 3 September 1985. On the occasion of the SAGE meeting in Geneva during the week of 2 September, I had the chance to chat briefly with Drs Assaad, Merson and Warren about the possibility of adding a "vaccinology" steering committee to the SAGE which would be primarily concerned with issues relevant to the most effective field application of vaccines. On 11 September, Drs Assaad, Merson, Pierce, Keja and I met to discuss this further.

We came to the conclusion that it would be premature for the SAGE to take on additional responsibilities in the area of applied research for the time being. Ken Warren's primary focus seems to be on the biotechnology side, an example being pursuit of work on better adjuvants, with less interest in some of the field application issues (development of the Eze-ject system, evaluation of alternative vaccine administration techniques and of alternative immunization schedules, etc.). While SAGE may be able to take on some additional work concerned with the Biotechnology, work more oriented to the application of vaccines in the field seems beyond their present scope. We will continue to review this issue within WHO, maintaining especially close liaison between the Diarrhoeal Disease Control Programme, the WHO Vaccine Development Programme and the EPI, and both CDD and EPI will be attending meetings of the SAGE.

I support the proposals you have outlined in your letter for the role the Task Force might play in the area of applied research. I think this would be very useful, and would be entirely consistent with the way we have envisaged the Task Force functioning.

cc: Dr Assaad
Dr Merson
Dr Joseph
Dr North
Dr Rothermol
Dr Warren

It would be my hope that within the next six months or so, we might be able to take a more active role with respect to some of the applied research issues than we have done previously. Much will depend on the capacities of a new staff member who will be joining us in November. We will remain highly focussed on issues which promise high programme return in the short run and which can be addressed with a minimum of resources, however, and I foresee a continuing need to involve other groups in this field who could tackle less tractable problems over a longer term. Thus I think the Task Force has a relevant role to play in this area during the next few years.

With best personal regards,

Yours sincerely,

Dr R.H. Henderson
Director
Expanded Programme of Immunization

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033 (404) 325-2452 • Telex 8107518512
Administratively Affiliated with Emory University

TO: TASK FORCE MEMBERS

SUBJECT: APPLIED RESEARCH

DATE: SEPTEMBER 3, 1985

In rethinking our discussion on this subject, let me try a slightly different approach to see if we could speed up work in the area.

NEED ..... 1) To identify priority applied research needs.

2) To get individuals and groups to pursue the needs identified.

3) To rapidly test solutions in the field and replicate those deemed useful.

APPROACH .....The following approach would keep The Task Force in a central role, would avoid an unwieldy structure and would still be a catalyst to applied research. Instead of a global research superstructure, it would be more ad hoc, lean and informal, with low overhead and fast turnaround. We would not pretend to have a comprehensive view of the researchers in a particular field, nor would we go out with formal requests for proposal.

PROCESS ..... 1) To identify projects, we would spread the word that we are interested in protocols for a variety of projects. Upon receipt of protocols they would be mailed to recognized experts for their evaluation, using a standardized evaluation form.

PROCESS (cont.)... 2) The best proposals would be presented at the quarterly Task Force meetings for agreement on which proposals merit support and for a decision on the approximate level of funding, if resources could be secured.

Evaluation of the project would be done by giving Task Force members the first opportunity to take responsibility. That is, WHO might agree to evaluate the results of the Guatemala Ezeject project, etc. If none of the 5 Agencies wish to evaluate a project, someone else would be requested to do so, such as CDC, Pasteur, APMP, private contractor, etc.

The Atlanta staff would serve partially as a switchboard, but would also attempt to keep track of major activities in the field, identify workers interested in the area, identify resources and, periodically, share information with the 100-plus groups already on our "interested" list.

I believe the above would allow The Task Force to do something constructive for applied research without bogging us down in an inflexible structure. Would you be comfortable with this?

Best regards,

Bill

William H. Foege, M.D.
Executive Director

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033
(404) 325-2452 • Telex 8107518512
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August 6, 1985

A NOTE TO TASK FORCE FOR CHILD SURVIVAL MEMBERS

There are several items to follow up on after our meeting in New York. Many thanks to Ken for another magnificent job of tending the flock. The food and accommodations were conducive to clarity of thought, or at least to good thoughts.

We have no intent, nor would it make sense to do other than what The Task Force wants us to do. I think I misjudged the desire of the group on applied research at our last meeting. No corrections were suggested on the applied research portion of the minutes of that meeting (enclosed), and I thought our conversations with Rockefeller were consistent with your intent. We were looking for a flexible, lightweight system of putting money into specific research projects by soliciting proposals, having them appraised by mail and taking the top proposals to Task Force meetings for final selection. This would keep you in control and avoid a large infrastructure. It would not be management of applied research, but rather a way of doing only those things we, as a group, want to do.

Another possibility, developed since our meeting, would be to have SAGE develop a Subcommittee on Applied Research and have funding in a special account limited to applied research. The Task Force could seek funding to provide a staff person to develop priorities, process applications, follow-up on work done, etc. Would this be more acceptable? It institutionalizes responsibility in WHO, using an already developed research structure. A difficulty would be to get adequate attention in a basic research committee.

There may be a tendency to consider the Italian initiative only a UNICEF program. I hope the spirit of cooperation that has marked the past months will allow us all to contribute and capitalize on this opportunity.

Steve and I attended a PAHO-sponsored meeting on July 29 to seek commitments for polio eradication from the hemisphere. They estimated a need for an additional $44 million in the next 5 years over and above the country inputs. Rotary immediately committed to $10.7 million for vaccine,and it was obvious, through informal conversations, that the additional $33 million will be available from other donors, especially UNICEF, USAID and the IDB.

The terms of reference for Dr. P. Diesh in India are the following. He will work part time as a special consultant to The Task Force. His address is:

Dr. P. Diesh
Consultant
Public Health Advisor
Office of Health & Nutrition
Agency for International Development
American Embassy
West Building - Chanakyapuri
New Delhi-110021
INDIA

To advise D.I., the Regional Office N. Delhi

We are asking him to collect information from the Government on their immunization plans, needs, etc. In addition, he is providing an inventory of the various groups interested or involved in immunization and their current and intended activities. Our hope would be that he can set the stage for a meeting of all interested parties with the Ministry of Health to arrive at an agreement on how the various groups will contribute to the Indian plan. Any help your people can give him, would be appreciated. As we agreed, I would appreciate your notifying your representative in India of Dr. Diesh's responsibilities as soon as possible.

Best regards,

Bill/dh

William H. Foege, M.D.
Executive Director

Enclosure

Handwritten by Dr. Foege while on vacation. At his request, typed and signed in his absence.

July 10, 1985

Tony

FYI. Rose has informed David Knox, (verbally) VP, LAC of Mr. Clausen's acceptance to the Bellagio Conference.

Also, it has been noted on the file.

Alison.

8 de julio 1985

Excelencia:

Por medio de la presente deseo agradecer en nombre de mis colegas, el Señor John North y el Dr. Anthony Measham, y en el mío propio la invitación que usted nos ha tan cordialmente extendido para participar en la conferencia denominada Bellagio II que tendrá lugar en Cartagena de Indias a partir del 14 de octubre próximo.

Nosotros, en el Banco Mundial, deseamos participar activamente en esa conferencia porque estamos convencidos de que ella constituirá un hito importante en el proceso de reducir la mortalidad y la desnutrición infantil en el mundo.

Estamos seguros de que la conferencia obtendrá sus objetivos, ya que Su Excelencia ha claramente demostrado su interés en mejorar la salud infantil en el mundo. Pruebas fehacientes de ese interés son la realización del programa masivo de vacunación infantil llevado a cabo recientemente en su país bajo sus auspicios y el empeño demostrado por Su Excelencia en que Bellagio II se celebre en Colombia.

Lo anterior hace que nos sintamos honrados de ser invitados y de poder participar en la conferencia de Cartagena. Por lo tanto, me es muy grato informar a su Excelencia que el señor John North, el Dr. Anthony Measham y yo tendremos el placer de asistir a tan importante evento.

Con los sentimientos de mi más alta consideración,

A.W. Clausen

Excelentísimo Señor
Don Belisario Betancur
Presidente de la República
República de Colombia

cc: Mr. Southworth, Mr. North, Dr. Measham

RCuca/JDNorth/rmf

República de Colombia

Presidencia

Bogotá, 11 de Junio de 1985
ACV-85

Dr. Anthony R. Measham
Health Avisor
Health, Population and Nutrition
The World Bank
1818 H. Street, N.W.
Washington, D.C.20433

Estimado Amigo:

Por medio de la presente quiero transmitirle en nombre de mi gobierno y del pueblo colombiano, mi invitación más cordial a participar en la conferencia que tendrá lugar en Cartagena de Indias a partir del 14 de octubre próximo.

Se le ha dado a este certamen la denominación de "Bellagio II" pues su tema central será, como el del efectuado en marzo en esa ciudad italiana, "La protección de los niños del mundo: vacunas e inmunización". Colombia efectuó recientemente un programa masivo de vacunación infantil, cuya evaluación comenzó a hacerse en Bellagio, y que fue una demostración colectiva de la preocupación que la sociedad y el gobierno de mi país experimentan ante los problemas de la supervivencia y de la salud de nuestros niños, y de los esfuerzos que, dentro de limitaciones e incluso dentro de coyunturas de carácter crítico de todos conocidas, hemos efectuado ya y estamos denodadamente empeñados en intensificar en un futuro inmediato.

El empeño urgente de reducir la mortalidad y la desnutrición infantiles no son sino casos extremos dentro del repertorio de cuestiones de toda índole que a la humanidad en general, y en particular y dolorosamente a las naciones en menor grado de desarrollo, le plantea la atención a la infancia. Su diagnóstico y su cuidado son obviamente decisivos en el porvenir que le aguarda no tanto a las naciones individuales sino al conjunto y al común de la especie. Es esa la más dramática de las circunstancias que inspiran esa reunión de Cartagena, y esa es también la razón principal por la cual espero que usted nos haga el honor de prestarnos su distinguido concurso en "Bellagio II".

Con los sentimientos de mi más alta consideración,

Belisario Betancur

Bellagio

UNITED NATIONS CHILDREN'S FUND FONDS DES NATIONS UNIES POUR L'ENFANCE

UNITED NATIONS, NEW YORK, N.Y. 10017
CABLE ADDRESS: UNICEF - TELEPHONE: (212) 754-1234

7290G

(ATTACHMENTS IN ENGLISH)

CF/EXD-IC: 85-21

28 June 1985

TO: Regional Directors
Representatives
Resident Programme Officers

FROM: James P. Grant
Executive Director

RE:

Country level preparations towards the goal of universal immunization by 1990

As you are aware, UNICEF's Executive Board, in addressing the question of appropriate observance of the 40th Anniversary of the United Nations, urged all countries to continue to attach high priority to the needs and development of children as integral elements of national plans and policies, and resolved to reassert the goal (originally declared by all Governments in the World Health Assembly and the United Nations General Assembly) of achieving universal child access to immunization by 1990, and urging accelerated country action towards this goal. The proposition that renewed commitment to achieving the Universal Immunization/1990 goal, and of advancement of the Child Survival and Development Revolution in general, is a fitting manifestation "of the promise of the United Nations" in commemoration of its 40th Anniversary, should be foremost in your efforts, at the country level, in regard to 40th Anniversary observances.

In support of this proposition, Secretary-General Perez de Cuellar, on his initiative is writing to all Heads of State, including of your country, to draw attention to the Executive Board's resolution. [A copy of his letter is attached.] The Secretary-General expressly asks each Head of State to make reference to achievement of this goal in his or her presentation at the General Assembly this fall and as an appropriate focus of the 40th anniversary of the United Nations.

This letter is unprecedented as a request by the Secretary-General to Member States to positively address a specific action in their interventions at the General Assembly. It is a rare opportunity for promoting our interests in advancing the well-being of children from which we must not fail to seek maximum benefit. It will only be of real value if every UNICEF office seizes this opportunity at the country level.

Each Representative is therefore requested:

1. To ensure that the relevant ministries (planning, finance, foreign affairs, foreign economic cooperation, health, etc.), as well as your WHO counterpart, are alerted to the forthcoming arrival of the Secretary-General's letter, and to the need and opportunity for taking specific action. At the very least, I hope the group in each country concerned with immunization and preparation of such speeches will be galvanized to prepare several lively and committed paragraphs for the Head of State's statement and other interventions at the General Assembly.

2. To use the opportunity of the Secretary-General's letter to strengthen or initiate a serious review of immunization plans and performance and prospects in your country. Naturally our goal should be to move as quickly as possible to encouraging the establishment of some supportive group committed to achieving universal coverage by 1990 and with the authority and contacts to make it happen. There are many ways this can be done; to be effective, what is done must be closely adapted to the specific situation of each country.

3. To carefully review, within your office, and in consultation with your WHO counterpart, your capacity to support such country action, and to identify what support may be required from your Regional Office or Headquarters. I am asking Regional Directors at their next meeting with country Representatives to review these plans, country by country, to ensure we are prepared and that we are doing all that we can to support country action. These country plans will be further reviewed at the Regional Directors' Meeting in New York in October, for which I request that the Regional Directors forward country and regional plans and requirements to Headquarters through the DPFS Section Chiefs with copy to Dr. Stephen Joseph [see final paragraph, page 3] by mid-September.

I realise this is a great challenge - just as I hope each country realises this is a great opportunity. Not since the mobilization in late 1960s to eradicate smallpox, then taking an annual toll of 2 million lives, has such an opportunity presented itself. And as we all know, universal immunization by 1990 will in several respects be more difficult than the eradication of smallpox, since the challenge is to build a structure of immunization that both can be sustained and will serve as the cutting edge for a wide range of primary health care actions including particularly the other low-cost, mass applicability GOBI elements. But at the same time, we have several advantages, especially a new awareness of the power of communications and some dramatic examples of what has recently been done when political support is aligned with professional expertise and mass mobilization by government and a variety of non-governmental organizations. These efforts represent a dramatic collaborative acceleration of the WHO/UNICEF supported Expanded Programme of Immunization.

Headquarters support for country actions

As one part of Headquarters support, Mr. Luis Rivera will be organizing a workshop on social mobilization to be held in Colombia in mid-October for senior UNICEF staff. This will follow immediately after the second meeting of the Bellagio group, which includes the heads of UNICEF, WHO, UNDP, the World Bank and a number of major donor agencies. Each regional office will be invited to select three or four persons from the region to participate, as a step towards mobilizing ourselves within UNICEF and gaining first-hand knowledge of the recent UNICEF experience in countries in Latin America, Africa, the Middle East and Asia. We plan on involving at least 200 UNICEF staff including some key staff from every country and regional office, in similar workshops over the next 12 months.

[Also attached for your action is a memorandum which I have addressed to Mr. Rivera establishing the initial terms of reference which I perceive for his new assignment as Chief of Programme Communications in the Division of Programme Development and Planning (DPDP).]

Additional impetus in support of universal immunization by 1990 has been provided by Italy, which as a first response to the Secretary-General's appeal has pledged up to $100 million over the next 2-3 years to support child survival actions, with particular emphasis on universal immunization in 29 least developed countries. We are hopeful that other bilaterals will soon follow suit. In a related development, the UNICEF National Committees are considering a special $100 million fund-raising effort focusing on immunization against measles - which now takes an annual toll of 2 million children's lives.

Finally, I have charged Dr. Stephen Joseph, with Mr. Joseph Sclafani as his associate, with staff responsibility for strategy development for universal immunization by 1990, for continuous review of country progress and the effectiveness of UNICEF system-wide support of country programmes, arranging support for programme development with Regional Offices, WHO and the Government of Italy Special Fund, and maintaining other external links on Universal Immunization/1990, such as with the Bellagio Group. They will also be concerned with ensuring coordination of operational support from DPFS, DPDP, and all other divisions and organizations on Universal Immunization/1990 matters and activities through the Child Survival and Development Working Group chaired by Dr. Nyi Nyi. This unit will be situated in DPDP with links and access to my office. They will, of course, welcome being copied any early indications from you through regular channels of your support requirements from them and other Headquarters elements.

cc: Dr. Halfdan Mahler, Director-General, WHO, Geneva
Executive Staff
Directors: Geneva
Copenhagen
Sydney
Tokyo

UNITED NATIONS CHILDREN'S FUND FONDS DES NATIONS UNIES POUR L'ENFANCE

UNITED NATIONS, NEW YORK, N.Y. 10017
CABLE ADDRESS: UNICEF - TELEPHONE: (212) 754-1234

7298G

26 June 1985

TO: Mr. Luis Rivera
Chief-designate, Programme Communications (DPDP)

FROM: James P. Grant JPG
Executive Director

RE: Social mobilization/social marketing/programme communication

I am pleased that you will be assuming the Programme Communication responsibilities for UNICEF Headquarters and that your major responsibility for the next 12 months will be to synthesize and convey to our colleagues UNICEF's recent, rapidly growing experience in social mobilization of all forms of communication to empower parents in a short time with important knowledge relevant to the care of their children: in short, how to create the "demand" for the low-cost, mass-applicable GOBI measures now available.

Our particular challenge now is to communicate this experience over the next year to the approximately 200 UNICEF field staff most in need to know, and in this communication and training process to capitalize on the substantial experience these 200 participants will bring to the seminars, so as to further enhance our synthesis of experience in "going universal".

Several special considerations come to mind as you undertake this responsibility:

1. While programme communication plays an essential role in all of the GOBI-FFF programmes, the opportunity we now have to pursue Universal Immunization by 1990 in virtually every developing country implies a particular urgency for the immunization sector of our strategies.

2. In "going to scale" on any one of the GOBI sectors, it is important to remember that our broader goal is to advance all of the GOBI sectors during the 1980s and to do so in a way that will enhance primary health care generally and to achievement of Health for All by the Year 2000. In many countries universal immunisation by 1990 might be seen "as the leading edge of the cutting edge [GOBI]" for the advancement of PHC. It is also relevant, of course, in going to scale, to do so in a manner that offers a good prospect of becoming self-sustaining after the intensification or campaign period is over.

It is important in promoting social mobilization that there is constant reference to the above two factors both to ensure that they are adequately addressed and also to reassure the many whose co-operation we need who are skeptical of vertical-appearing programmes for fear of their non-sustainability and their advancement at the expense of the general progress in PHC which is ultimately required. (I sometimes think that we should modify "universal immunisation by 1990" by making it "universal immunisation by 1990^3", with the reference to the "third power" being to show our recognition of the necessity of achieving this goal on a largely self-sustaining basis and in a way that enhances the prospects for progress on the other GOBI fronts and PHC generally!)

3. In developing your syllabus for social mobilization, I encourage you to pursue your desire to develop a series of contrasting case histories for teaching purposes. This approach is not only an extremely useful way to teach but it also underlines the fact that each country will need to make its own adaptations and that there are alternative roads for "going universal".

Country case histories might include the following:

a) Cuba illustrates what is possible when there is a strong health services infrastructure reaching every local community. According to Dr. Sabin, the Cuban polio experience is worth noting. He claims that the two National Polio Days involving the immunisation of virtually all children in their homes led to a truly dramatic reduction of polio in the country because of the near elimination of the reservoir of the human-hosted polio virus as a result of immunising so many on the same day. Its replication in many countries, however, raises issues of time and cost, given its heavy use of professionals and medical facilities which are still lacking in most countries.

b) In 1980, Brazil initiated the custom of two national immunisation days for polio, with 90,000 immunization posts and 300,000 volunteers which, as in Cuba, resulted in a dramatic reduction of polio. This system was institutionalised and expanded to encompass measles and DPT in 1984. The Brazilians may be planning to continue the national immunisation day pattern indefinately.

c) You are intimately familiar with the Colombia experience, with its use of three national immunisation days as a temporary 2-year measure, complemented by a strong effort to strengthen the canalisation strategy so that the existing health infrastructure can maintain a high level of immunisation thereafter.

d) El Salvador is similiar to the Colombia model, with the major additional dimension of advancing universal immunisation in the midst of armed conflict. How this was achieved will be relevant for other countries, particularly in Africa.

e) Launching in November 1984, with national notice, Nigeria undertook "going universal" initially in one Local Government Area in each of the 19 states, with the strategy of adding an additional LGA in each state every

several months, with the objective of achieving universal immunisation by 1989. This approach permits a national mobilisation that involves every state, allowing state-wide replication based on experience within the state.

f) Carried out in a least-developed-country context, Burkina Faso initially emphasized immunisations - measles, yellow fever, meningitis - requiring only one shot. The sustainability of its approach and the extent to which it is broadened to include the more complex immunisations such as polio and DPT will be of great interest.

g) Historically the preference of governmental administrators has been to follow the Senegal practice of trying to demonstrate feasibility, in this case going universal with immunisation, in one region and then replicate it in others until the entire country is covered. This partial approach may make it easier for creating the necessary delivery systems, but makes much more difficult national social mobilization as seen in the preceeding examples.

h)Urban/Local Area experience: Addis Ababa, Delhi, Bidar provide useful experience. (The Bidar write-up already exists.)

I would expect a good discussion of these contrasting models at your seminar in Bogota in mid-October. I was interested in Dr. Sabin's recent intervention to the effect that he preferred the Brazil model for three sets of reasons: virtual universal immunisation on the same day or days dramatically reduces the reservoir of human-borne infections of polio and measles; national immunisation days permit by-passing the weakest link in most EPI delivery systems, i.e. refrigeration at the clinic level, since the new, more heat-stable vaccines could be taken straight from the central and regional cold storage facilities to localities of use; and repeated use of volunteers on the same institutional lines permitted their training to take greater responsibility, as with training immunisers and ORT teachers in every hamlet.

Your syllabus should also cover some examples of social moblisation for non-EPI activities - ORT (Egypt, for which we now have some good case material from the Boston seminar on CSDR in late-May, Haiti, Morocco), growth monitoring (Indonesia) and breastfeeding (Brazil). It also would be most useful if, in discussing immunisation, attention could be given to sustainability and expansion to encompass other sectors. Thus, Colombia and El Salvador are both broadening their efforts to include ORT and other activities, and Colombia provides experience in seeking to achieve sustainability through restructuring not only the health sector but also the education, religious and NGO community (Red Cross).

* * *

I look forward to hearing a progress report on my return from the Nairobi Conference on July 18.

By copy of this memorandum, all Regional Directors and country Representatives are invited to send to you relevant case material, to arrive by mid-September. Your material will also be useful in preparing for the Cartegena/Bellagio meeting and the Regional Directors' Meeting in New York in October at which we will be reviewing the EPI/1990[3] situation world-wide and by country.

cc: Regional Directors
Representatives
Mr. Knutsson
Mr. Jolly
Mr. Vittachi
Dr. Nyi Nyi
Mr. Himes
Dr. Joseph
Mr. De Boice

THE SECRETARY-GENERAL

10 June 1985

Excellency,

As we observe the 40th Anniversary of the founding of the United Nations, I should like to commend to your personal attention the contents of the enclosed resolution that was adopted unanimously by the UNICEF Executive Board at its recently concluded session.

The resolution articulates the possibility of achieving the goal of universal immunization of young children by 1990, through accelerated action in line with a goal already established by the World Health Assembly. The endeavour could result in saving the lives of several million children each year and in preventing a comparable number from suffering permanent disabilities.

Experience in several countries, some of which have doubled or even trebled their immunization rates in the recent past, has already shown that mobilizing a society's organizational and communications resources in support of an effective national immunization programme can have the most far-reaching cumulative effect. In particular, it can lend momentum to other primary health care approaches as supported by WHO and UNICEF. While much work remains to be done before the goals of the resolution are finally achieved, I am convinced that their reaffirmation in 1985 could have a significantly positive effect and I attach a brief background paper that elaborates this point.

With these considerations in mind I should like to express my hope, Excellency, that under your personal guidance your Government will reaffirm its commitment to these objectives in its statements during the 40th session of the General Assembly which will be held later this year. I am convinced that your leadership, in concert with that of other heads of government, would advance these most important efforts for the well-being of our children and the future of the world.

Please accept, Excellency, the assurances of my highest consideration.

Javier Pérez de Cuéllar

1945-1985
40 Years of
United Nations
Service to the World

UNICEF: The Children's Fund of the United Nations

25 April 1985

UNITED NATIONS CHILDREN'S FUND
Executive Board
1985 session

RESOLUTION BY THE EXECUTIVE BOARD OF UNICEF ON OBSERVANCE OF THE 40th ANNIVERSARY OF THE UNITED NATIONS

Bangladesh: draft resolution

The Executive Board of the United Nations Children's Fund,

Reaffirming its commitment to the principles and objectives of the Charter of the United Nations;

Taking note of resolution 39/161(A) of the General Assembly on the observance of the 40th Anniversary of the United Nations;

1. Urges that special attention should be paid to the well-being and interests of the children, future citizens of the world, in connection with the observance of the 40th Anniversary and that all countries should continue to attach high priority to the needs and development of children as integral elements of national plans and policies;

2. Draws the attention of world leaders to the importance of reaffirming on this occasion their increased commitment to accelerating the implementation of the child survival and development revolution and achieving universal immunization by 1990 with the objective of reducing dramatically the number of deaths among children from preventable causes;

3. Requests that the Declaration to be adopted by consensus on 24 October 1985 at the end of the commemorative session may also include reference to these important goals and objectives for the welfare of children;

4. Also requests the Executive Director to bring the contents of this resolution to the attention of all concerned.

Universal Immunization by 1990

At the World Health Assembly in 1974 member states committed themselves through their Health Ministers to achieving universal immunisation of all children by 1990. With the successful eradication of smallpox through the effort organized by WHO, universal immunisation seemed an increasingly attainable objective, which was included in the goal of "Health for All by the Year 2000 through Primary Health Care" adopted at the WHO-UNICEF conference at Alma Ata in 1978, and subsequently unanimously endorsed by the United Nations General Assembly in 1979.

Many factors have impeded progress, however, with the result that by 1983 less than one quarter of the children of the developing countries were fully immunised. The present reality is that across the developing world more than 4 million children die, and a comparable number are permanently disabled, by diptheria, whooping cough, tetanus, measles, poliomyelitis and tuberculosis. On the "supply" side, i.e. making effective immunisation available to children, the impeding factors included inadequate cold-chain systems (refrigeration for vaccines), lack of trained vaccinators, lack of transport, and insufficient primary health care infrastructures at the community level. An even more important lack is on the "demand" side, i.e. creating among parents the understanding of the importance of, and desire for, immunising their children for the three times required for full coverage against the six major diseases.

Fortunately, there is increasingly widespread recognition by national leaders that a virtual revolution in child survival and development could be achieved before the end of the century at low financial and political cost - if only people want it - by regular monitoring of children's growth, by the use of oral rehydration therapy to prevent many deaths from diarrhoeal dehydration, by protecting the practice of breast-feeding, and by immunizing every child against killing and maiming diseases for which vaccines exist.

The "supply" side is gearing itself up to respond to the present immunization opportunity. Better vaccines are increasingly available and inexpensive. While more funds for further improvements in supply are needed, totalling several hundred million dollars annually from both developing and industrialized countries, the amounts are modest in relation to the tremendous benefits from achieving high levels of immunisation.

An even more important need is on the "demand" side of a dynamic health equation - the education and motivation of all parents to recognize that their children can be saved from possible death and disablement from many killer diseases if they would only have them immunised. Until parents understand the value of this preventive measure and follow through despite the difficulties it may involve - including the onset of fever that often follows vaccination - they will not readily actively seek full immunisation for their children.

In 1984 and 1985, the full commitment of a number of political leaders to the need for immunising all children against a broad range of diseases has led to remarkable increases in the immunisation rates in such diverse countries as Brazil, Burkina-Faso, China, Colombia, El Salvador, Indonesia, Nigeria and Pakistan. In India, the rate of vaccination has been dramatically accelerated in several populous areas, and Universal Immunisation by 1990 has now been adopted as a Living Memorial to Indira Gandhi. These reports indicate tnat the Expanded Programme of Immunisation goal can be reached by 1990 in virtually all countries where national leadership is actively dedicated to supporting achievement of the goal and relatively modest amounts of external financial support are available.

These recent successes demonstrate that through the investment of effective political will at the highest levels a wide range of national resources can be mobilised and galvanised at extremely low financial cost to create the climate of hope and trust needed to generate active demand for immunisation from parents, particularly of the poorest and most vulnerable families. The news media, interpersonal communications channels, religious bodies of every denomination, health workers and school teachers, trade unions, and the business community will rally to save a nation's children from preventable disease and disability if a clarion and sustained call is made by respected national leaders.

Information and knowledge about simple but essential health actions can now reach people by the penetration of communication media into the most remote rural communities. And the development of social marketing techniques can now effectively convey simple messages designed to bring about changes in attitude and practice which are easily understood by mothers, even those with low education levels.

The United Nations system, and particularly WHO and UNICEF with the active support of Secretary-General Perez de Cuellar, has been working hard over recent years not only to raise the necessary funds but also to mobilise political will and enthusiasm needed to pursue this objective as one of the realistic possibilities of intensifying these efforts which are humanitarian in character and also essential prerequisites for long-term social development.

It is now indeed possible, through the child survival and development actions proposed, to raise health conditions to levels that would permit the great majority of all children of today, who will be the citizens of the world in the year 2000, to lead a socially and economically productive life. There could be no more eloquent argument for the value of the United Nations system.

Bill.

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June 11, 1985

Dr. Alan Berg
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear Alan:

It was good to hear from you and to have a chance to recall ancient history. I have often thought of your writings on the "Bihar famine" as I had a chance to work in Bihar on smallpox eradication during the mid-1970's.

I hate to admit such a defect in recent memory, but I'm not sure of the nutrition quote that Tony Measham mentioned. I suspect it came from a recent Bellagio meeting where I referred to nutrition as the most important health intervention, being "obligatory". Enclosed is a rough summary statement from that meeting.

I hope we have a chance to get together again soon. Thanks for making the contact.

Best regards,

Bill

William H. Foege, M.D.
Executive Director

Enclosure

SUMMING UP STATEMENT
BY
WILLIAM H. FOEGE, M.D.

First, some qualifying statements:

1) I believe in a cause and effect world (even when I don't understand the causes).

2) I believe the reasons for success in these four countries are totally explainable (but not necessarily by us).

3) We have an obligation to make some judgments, even in the absence of all the facts, as this is the essence of wisdom and extrapolating from the facts we do have.

4) I believe the trip to good health has many roads. There are some barriers which may be universal, some almost universal, but many are infrequent and a few even rare. My judgment on overcoming these barriers results both from this conference and the material that Ken Warren has provided on primary health care.

Starting with our objective (Figure 1), I see as the endpoint the desire for a reduction of premature mortality, a reduction of unnecessary morbidity and an improvement in the quality of life. While we can develop different models, I see two final pathways to achieve this objective of improved health.

The first pathway is the promotion of a healthy person which involves improved nutrition, education, child spacing, etc.

The second pathway involves countering insults to the person. While there are many insults, most can be classified in three categories:

1) Micro-organisms

2) Chemical insults (including cholesterol, tar & nicotine, etc.)

3) Injuries

Interventions

There are many possible interventions for promoting health and countering incidents, and we, therefore, have to choose the most important and attempt to prioritize them. Most interventions have alternatives, with few being absolutely mandatory. I will list my understanding of the most important interventions:

The first, being obligatory, is not sufficient, namely nutrition (Figure 2). It is obligatory in the sense that below a certain point, health cannot be maintained regardless of how many interventions one rallies. For instance in Nigeria during the civil war, measles mortality was as high as 50% in malnourished children.

We have seen at this conference, the absolutely remarkable change in mortality rates in Sri Lanka between 1946 and 1953. During that time, infant mortality decreased from 141 to 71. Some of the age-specific mortality rates (Figure 3) are even more impressive. As for instance, the 10 to 14-year-old females with a mortality decrease from 5.2 to 1.4 in 7 years. Even the next two decades could not match that percentage decline. While many things were happening during this 7-year period, 1946 to 1953, one of the most important was an increase in food availability by 50%.

In the next category (Figure 2), a very important, but not obligatory intervention, would be education, in particular, the education of women. This cannot be put in the obligatory category because we have examples of cultures achieving remarkable gains by a dictator or single leader imposing changes even without education. But education is an important concept that not only provides improved health, but provides improved quality of life. It allows people to be open to the commerce of other minds and to truly becoming global citizens. A remarkable correlation between literacy rates in women and declining infant and childhood mortality rates should be noted. Literacy rates really indicate access to information. In the electronic age, it may be possible to take short-cuts by providing women access to information even before literacy rates are improved.

Under the category of important interventions, I would first list vaccines. We should work hard to deliver what we now have. It is a tragedy of our times that children still must go through life crippled because of polio. We must deliver what is available, and at the same time, exploit the new possibilities for better vaccines, better delivery mechanisms, etc.

This conference has convinced me, and I am impressed with the statements of Bucky Greenough, that the introduction of soap and its adequate use could have a marked primary prevention effect on diarrheas, and perhaps even respiratory diseases.

Oral rehydration therapy must be a priority. It provides for a fast return on investment because it deals with an immediate problem and becomes a bridge between the medical system and the community. It is also a bridge between the sick care system and the well care prevention system. As it provides immediate concern plus education for the future, it also is a bridge to the pediatric age group and offers great returns for the investment required.

Family planning was not discussed in detail this week, and yet we all know the importance. It complements our other approaches, provides access to adults, provides longer range perspectives, helps develop community support systems, etc.

Finally on the important intervention list, I would include health facilities at the periphery. Steve Joseph is correct in his argument that the world has changed dramatically in the past decades. We can now offer not just oral rehydration, but antibiotics and chloroquine for malaria. One recent study in West Africa showed the majority of children received chloroquine within the first 24 hours of fever. It is important to have systems that can deliver this type of therapy, as well as to have an adequate response to the frequent injuries that are a part of life in all societies. I would limit the health facilities to a small number of specific activities with the workers highly drilled to perform those activities. A major importance of health facilities may be the expression of concern which they convey. They provide for quality of life and a back-up system for the community.

I have not mentioned surveillance and epidemiology despite their importance. The reason is that they are already operating to some degree or there would be no response. They are not a solution, in themselves, rather a tool to better define problems and evaluate interventions.

Are there some unifying themes or conditions which should be sought as a background for these interventions? What I have understood from these days is that we respond both as individuals and as members of a group.

If we look first at individual response (Figure 4), the healthiest state is to have some control. Education provides that, and is one reason to promote education, especially for women. It is important to teach children that this is a cause and effect world, not a fatalistic world. Voting and social participation are expressions of control (fatalists don't vote) and with this control comes hope. This cause and effect belief with its resulting hope is both cross cultural and cross time. Cross culturally, we see the lowest socio-economic groups in the United States not only have the lowest rates of voting, but the highest risk factor rates such as cigarette smoking and alcohol abuse. Yet we find they have a mortality rate higher than predicted, even if one controls all known risk factors. This mortality goes beyond the explicable, and may well be an expression of the complexity of fatalism and lack of control. It may be an expression of people not having the emotional and mental resources to handle the problems before them. But, it is also cross-time and may turn out to be the most important future tool we have in prevention. What people do for themselves may be much more powerful than what 20th century science can do for them.

It may be that individuals reach a point of self-image, self-control, self-determination, or self-reliance that is difficult to reverse even under strained conditions. Levi's book, Survival at Auschwitz, demonstrates coping in the extreme by individuals even in uncontrollable environments. The four programs that we studied are all remarkable examples of people exerting control over their own health and destiny.

The other unifying condition deals with society rather than individuals per se. The ideas may be comparable, that is society did not see these problems as fatalistic or they would not have developed the plans that they did. The healthiest societies may be those that collectively convey a cause and effect philosophy expressed through a feeling of responsibility for others. The key concept in such a society may be "a willingness to act beyond my interests." Political structure may be secondary.

Certain social acts accelerate the process beyond the sum of individual decisions. In Sri Lanka, immunization is a requirement for school entry. This provides a social norm that accelerates the process of immunization beyond what would happen if individual parents were making the decisions. Handwashing with soap could become the community norm, and people not using soap would be acting against the social norm.

As with individuals, societies may well reach a point of self-determination and concern or responsibility towards each other, which is hard to reverse. It may be hard to eliminate this concept even under adversity. One example would be famine in the Netherlands during World War II. The society remained cohesive and was particularly protective of children.

While acting beyond my interests is the key, we should promote maximal distance in this act. For example, the concept is easily understood by an extended family in Africa, and even by tribes. It is harder to get this kind of identity on a national level in many countries, and the ultimate, namely operating beyond my interest globally, is especially difficult to promote.

When this point is reached, society develops a sense of maintenance that transcends the individual and maintenance already implies self-determinism.

In Sri Lanka, malaria control, while important in itself, is really a symptom of concern rather than a full explanation of health changes. (Mortality rates decreased for many diseases in this same time period.)

Society has to pay for this and where they are willing, they have passed the critical point. That is, either enough people have passed the point individually or the right people have. The proliferation of primary health care is already an expression of social concern.

The crucial point is when societies determine that it is possible to plan a rational health future. All four examples that we studied this week demonstrated that happening.

The unifying social concept is that the measure of civilization is how we treat each other. The concept of reciprocity may be the important social goal to pursue in order to lay the groundwork for both the power of individuals and the specific interventions which can improve health.

FIGURE 1

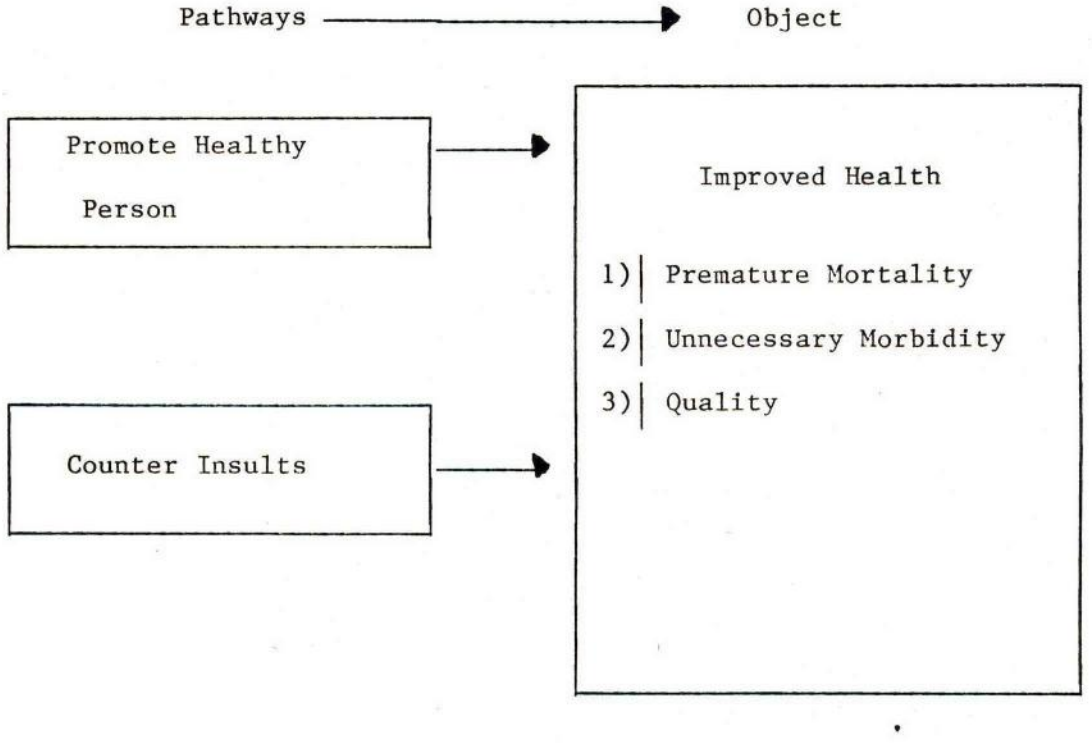

Pathways
Object
Promote Healthy Person
Counter Insults
Improved Health
1) Premature Mortality
2) Unnecessary Morbidity
3) Quality

FIGURE 2

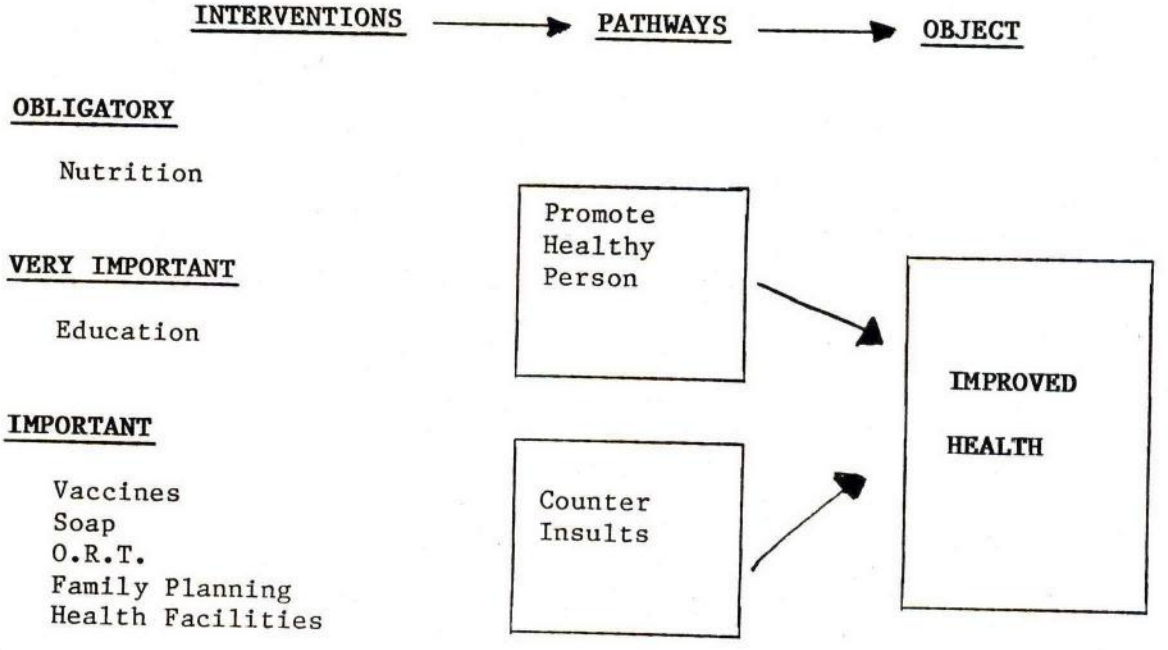
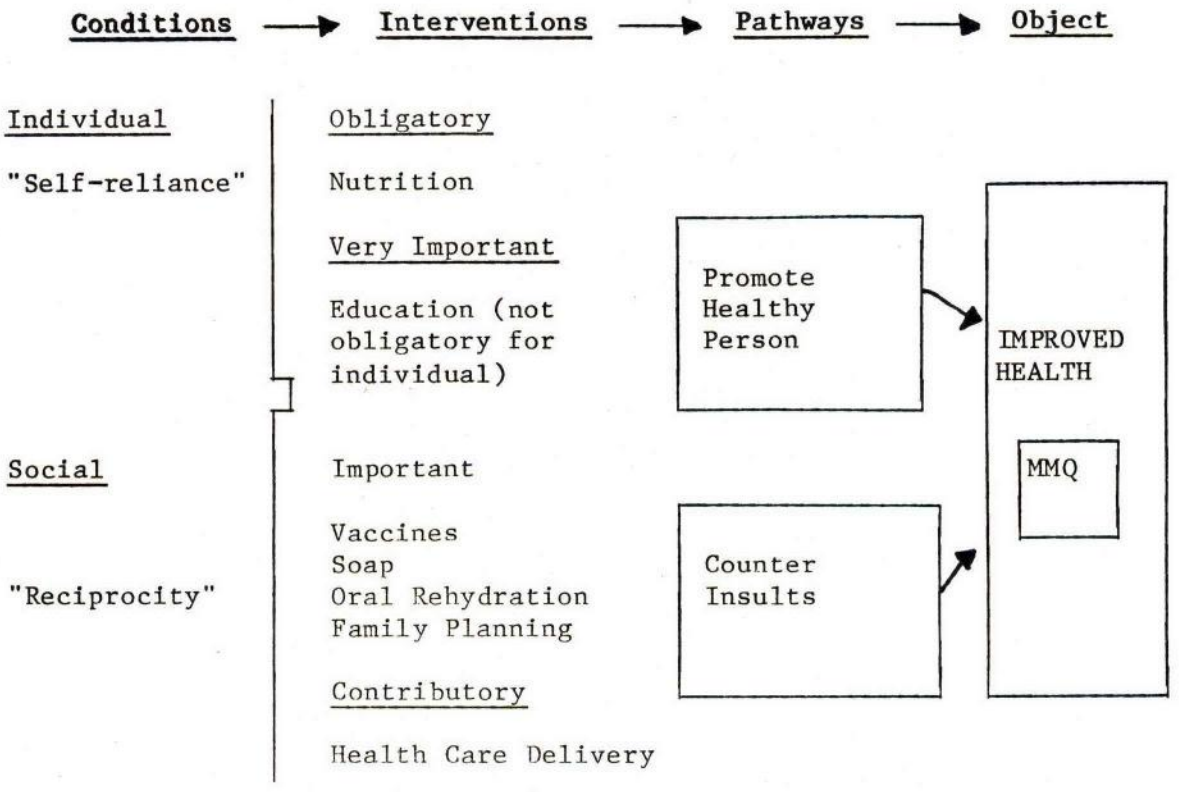

INTERVENTIONS
PATHWAYS
OBJECT
OBLIGATORY
Nutrition
VERY IMPORTANT
Education
IMPORTANT
Vaccines
Soap
O.R.T.
Family Planning
Health Facilities
Promote Healthy Person
Counter Insults
IMPROVED HEALTH

FIGURE 3

Age Specific Mortality Rates for Certain Groups - Sri Lanka

Age & Sex Category	1946		1953		1971
10-14 F	5.2	→	1.4	→	1.0
15-19 F	6.6	→	2.2	→	1.4
15-19 M	4.9	→	1.6	→	1.5

FIGURE 4


Conditions
Interventions
Pathways
Object
Individual
"Self-reliance"
Social
"Reciprocity"
Obligatory
Nutrition
Very Important
Education (not obligatory for individual)
Important
Vaccines
Soap
Oral Rehydration
Family Planning
Contributory
Health Care Delivery
Promote Healthy Person
Counter Insults
IMPROVED HEALTH
MMQ

~~JDA~~
ARM
FILE

April 26, 1985

Tony - ft. discuss

Dear Dr. Foege:

Many thanks for your letter concerning your trip to India. Your findings on the immunization program there are certainly encouraging, and I appreciate having this background before I visit in July.

I am passing a copy of your letter on to John North for his information as well. If anything of note arises out of my trip, I will get in touch and, otherwise, look forward to seeing you in Cartagena.

Sincerely,

A. W. Clausen

Dr. William H. Foege
Executive Director
The Task Force for Child
Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033

bcc: Mr. North (w/ copy of incoming)

MH

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5216

April 19, 1985

Mr. A. W. Clausen
President
The World Bank
1818 H. Street, N.W.
Washington, D.C. 20433

Dear Mr. Clausen:

My India trip was most interesting, and several developments are worth passing on before your July trip.

1. The Indo-U.S. Science and Technology Subcommission meeting contained a Health Work Group. That group selected immunization as the #1 priority for Indo-U.S. collaboration within the coming years.

2. The Indian Government has completed a National Immunization Plan. They are to send us copies within the next few weeks, and I will share a copy with you directly or through John North and Tony Measham.

3. It is possible that the Prime Minister will bring a specific immunization item to his meeting with President Reagan in June.

4. While there has been a great deal of turnover in the Ministry of Health during the past 6 months, the interest in immunization is building rather than dissapating.

5. Although commodities (vaccines and cold chain equipment) are generallly available through UNICEF, WHO, Rotary International, SIDA, and others, the Indians may well raise other aspects of the immunization program with you when you visit.

I will be out of the country for several weeks, but will be happy to follow-up with any specifics you desire on my return.

Sincerely,

Bill

William H. Foege, M.D.
Executive Director

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TO: RECIPIENTS OF STATUS REPORTS

FROM: WILLIAM H. FOEGE, M.D.

DATE: JUNE 17, 1985

SUBJECT: STATUS REPORT

As we look forward to Bellagio II, in Cartagena, Colombia October 14-17, I am gratified at growing support for the effort begun at Bellagio I. This includes both national and international interest in expanding immunization activities.

The Task Force members feel that the five sponsoring agencies can and should continue to support the activities of The Task Force itself. All possible donors to immunization programs should be encouraged to continue to support the country program activities, hopefully through UNICEF, WHO and other established ongoing organizations.

PAHO POLIO ELIMINATION CAMPAIGN

On Tuesday, May 14th, Dr. Carlyle Guerra de Macedo of The Pan American Health Organization announced a campaign to eradicate polio from the Western Hemisphere by 1990. This is a courageous landmark decision. It provides a definite and understandable objective which can serve as a catalyst to improve all immunization activities. The plan of PAHO is to improve immunity levels for all of the childhood immunizations, improve surveillance for all vaccine-preventable diseases and investigate all cases of polio. Other regions will follow the progress with great interest to learn from the experience which will be gained in this effort.

ROTARY INTERNATIONAL AND POLIO 2005

Rotary International has announced a campaign they have entitled "Polio 2005," in which they are committing themselves to assist in eliminating polio from the world by their 100th anniversary in the year 2005. Mr. Herbert Pigman, General Secretary and Mr. John Stucky, Program Manager from Rotary visited the staff of The Task Force and The Centers for Disease Control in Atlanta on May 13th to discuss how work might be

coordinated in implementing their program. Not only is this one more indication of the interest being generated for immunization, but new lessons are being learned on how to combine this effort of a private organization into a global program to strengthen the whole and, at the same time, allow appropriate identification with a part.

APPLIED RESEARCH PRIORITIES

Using a paper developed by Dr. Rafe Henderson, Director of the Expanded Immunization Program, World Health Organization, we asked Drs. Don Francis and Roger Bernier to help develop a listing of the most important priorities. They polled workers with field experience in immunization programs, asking them to provide suggestions and ideas on the barriers they would most like to see eliminated. Using their report, we assembled the top 10 research needs and have circulated these to some 150 people. You should have received our letter on this subject by now. The response has been very good, giving us a better idea of who is interested in specific areas and raising possibilities for inclusion on the "second 10" list. We are now attempting the more difficult task of devising ways to link resources to specific research areas.

BELLAGIO II/CARTAGENA, OCTOBER 14th-17th

Plans for the Cartagena meeting are progressing quite satisfactorily. The letters of invitation have been sent, and the responses, to date, have been most encouraging. Mr. Watson, of The Task Force staff visited Colombia the week of May 20th to make final plans and decisions with respect to logistics, accommodations, etc.

WARM SPRINGS

The Roosevelt Warm Springs Institute held a special celebration on May 16, 1985, to launch a new phase in their long history of rehabilitative efforts. They are eager to make their facilities and experience available to other countries. Mr. Carlton Spitzer, American City Bureau, 505 South Omni International, Atlanta, Georgia 30303, can be contacted for additional information.

SALK INSTITUTE MEETING

The National Council for International Health sponsored a meeting at the Salk Institute in March on "Immunization and the Developing World: The Role of the Private Sector." Recommendations were made in these areas:

1. Research, Development and Manufacturing
2. Management of Distribution (Vaccine and Other Supplies)
3. Delivery and Use of Immunizations

A call for action was drafted to enlist additional involvement of the private sector:

I. Each year, 8 million children in the developing world die or are crippled as a result of six major vaccine-preventable diseases: tetanus, measles, polio, diphtheria, whooping cough, and tuberculosis. The means to prevent early disability, suffering and death from these diseases now exist.

II. A decade ago, the number of children immunized in developing countries was negligible. Today, because of the efforts of national and international agencies, nearly one-third of all children are immunized. These efforts, coupled with future biotechnical breakthroughs, will mean that the goal of immunizing all children in the developing world by 1990 is possible.

III. The advancement of this goal demands a renewed commitment and partnership by all sectors of society. Special efforts are appropriate to secure the full involvement of the private sector, whose potential in this area remains largely untapped. Leaders in both the public and private sectors are called upon to seek ways of improving their partnership in support of immunization services.

IV. This partnership will benefit all sectors of society, resulting in technological breakthroughs, expanded markets, improved management, and, most importantly, it will accelerate the immunization of the world's children.

V. Efforts, such as the La Jolla conference, should continue at the national and international levels to identify issues and resolve problems. As a result, leaders in the public and private sectors can be mobilized for more effective joint actions in the field of immunizations.

For more detailed information, contact Dr. Russell Morgan, National Council for International Health, 2100 Pennsylvania Avenue, N.W., Suite 740, Washington, D.C. 20037.

COUNTRY REPORTS

Senegal

The Ministry of Health has developed an immunization program proposal which has now been sent by the Ministry to UNICEF. UNICEF has agreed to support the program for the first year. There are hopes for support, in future years, by USAID, France, the World Bank, and others. Dr. Philippe Stoeckel has been instrumental in pursuing the commitment and plan for a national immunization program. The assignment of Mark LaPointe to Senegal, under the sponsorship of UNICEF, is part of the proposal.

COUNTRY REPORTS (continued)

Nigeria

We have recently received a personal communication from Paul Litchfield, a UNICEF representative in Lagos, who is assigned full time to the immunization program. Paul reports that the Nigerian program is proceeding very satisfactorily, and that he is optimistic about its future. Early data indicates that immunization levels of 80% are being achieved in target areas. There is also a well developed plan to integrate these campaigns into the ongoing primary health care program. Nigeria has the largest population of any country in sub-Sahara Africa, and the development of a model program there could be important to the entire continent. Dr. Stan Foster has recently reviewed the program for UNICEF and reports that vaccine supply is now adequate, the cold chain is exceptionally good, immunization levels are rapidly improving, the target age group has become more specific (aiming at children under 24 months) and that the program workers are optimistic and energetic.

Burkina Faso

As reported earlier, the indications are that the program in Burkina Faso met the goals which were set. A team has been in Burkina Faso assisting with a sample survey which will help in evaluating the coverage achieved and assist in determining what needs to be done in the way of a continuing program.

Turkey

The Turkish government is planning a campaign-type program starting in late 1985. The campaign will not be conducted in single days, as was done in Colombia, but there will include 10-day type campaigns. Richard Reid, the UNICEF representative, who was so instrumental in assisting with the Nigerian program, is being transferred to Turkey. He and a delegation of eight people from Turkey visited the UNICEF headquarters in New York, the Centers for Disease Control in Atlanta and Colombia during April.

El Salvador

The immunization program in El Salvador received a great deal of positive publicity, focusing on the fact that both sides were willing to stop hostilities during this campaign. The program successfully reached 300,000 children. Dr. Ciro de Quadros of PAHO reports that a good evaluation of the program is being done and will be available by the time of the Cartagena meeting.

India

India has taken many steps, in recent months, to accelerate immunization activities. National Program Managers met in New Delhi from April 30th to May 3rd to review the expanded program. Special emphasis has been given to 30 districts (about 70 million population) to conduct intensified surveillance, to eliminate polio and to reduce neonatal tetanus mortality to 1 per 1,000 live births (currently 3.2/1,000 in urban areas and 13.3/1,000 in rural areas). Measles vaccine has been officially added to the national immunization plan. India now has an operational handbook for immunization, recognition cards for disease surveillance, and is developing guidelines for each part of the program. Field testing of ice lined and solar refrigerators are being conducted, and a commitment has been made to operational research to find the most suitable techniques for delivery immunizations in India.

Sincerely,

Bill Foege

William H. Foege, M.D.
Executive Director

Bellagio

March 27, 1985

To: Tony Measham
From: Karen Hall KH

Re: Preliminary Comments of the Colombia vaccination campaign evaluation team.

Thanks for sharing this preliminary report. I fully endorse evaluation team's expressed concerns. A couple of points that might be worth noting at your April meeting on subject paper, having not seen "Informe Preliminar" --

(1) With regard to costs of campaign days --
cost per child attended is not very useful since denominator will be large obviously and tend to understate key measure which is actually needed - cost per child fully immunized, immunized meaning not just received full doses, e.g. 3 DPT etc., but per child reached at the right age with effective vaccine. This reflects my continuing concern about whether campaigns at fixed points in time can reach target groups at varying ages with proper timing and spacing of immunizations.
Further, at least on limited scale, consideration should be given to exploring the cost of immunization per death averted, as has been done in referenced studies.

(2) Campaign vs fixed approaches
most striking facts to me are: (a) low coverage in highest risk groups, especially <1s, (though 1-3s too only 70% coverage), particularly in highly urbanized Colombia where exposure to communicable diseases tends to be great at younger ages than rural areas; (b) the apparent dampening of efforts post-jornadas (Table 5) in >1s which fuels my concerns about the fast fix but faster fizzle danger of campaigns, particularly if they become a substitute for, rather than complement to, ongoing immunization programs. If campaigns were perceived as valuable tool for creating constituency, building momentum, it is not clear that they succeeded.

Both these facts argue for caution in endorsing campaign approaches too enthusiastically without better understanding of factors critical to their success, and adequate measures of them, e.g. beyond merely number of children vaccinated.

It would appear useful in full evaluation report for Colombians to delineate actual administrative links and program protocols between the jornadas and regular immunizations activities within MCH programs.

(3) "non-immunized"
in analyzing data from the sample survey on coverage, is it possible to identify key distinguishing characteristics of non-immunized children which might provide clues to guide program designs to reach them? e.g. are they from single mother households, etc.?

Note possible bias introduced by sample survey's design (recorded in Table 2) suggesting overrepresentation of urban population (74% vs. 66% actual) and underrepresentation of <1s (25% vs. 28% actual), therefore, probably exaggerating actual coverage levels. Urge data be made available, disaggregated by urban/rural residence, to complement existing data disaggregated by discrete age groups, permitting adjustment of coverage levels, as appropriate, thus reflecting true impact of jornadas in difficult to reach, especially remote rural, areas.

(4) efficacy

Though not substitute for laboratory control, tracking of incidence levels of respective diseases is clearly an affordable, acceptable measure of vaccine efficacy. This underscores the importance of instituting immediately planned epidemiologic surveillance system, as team suggested.

If quality control of biologics was and will continue to be an integral part of immunization programs, specific related expenditures should be included in calculations (not evident in existing cost table).

Overall, the evaluation is a very positive step in improving international health community knowledge of the cost-effectiveness of alternative delivery designs and I feel the Bank should fully endorse and support this and follow-on activities through the Bellagio Task-Force.

Bcc.

The World Bank
INTERNATIONAL BANK FOR RECONSTRUCTION AND DEVELOPMENT
INTERNATIONAL DEVELOPMENT ASSOCIATION

1818 H Street, N.W.
Washington, D.C. 20433
U.S.A.

(202) 477-1234
Cable Address: INTBAFRAD
Cable Address: INDEVAS

March 8, 1985

Mr. John North

RE: Colombia Immunization Campaign Evaluation

John:

Attached is the preliminary report from Colombia. It is disappointing. Much of the work is incomplete, and there were political problems with one report. It falls far short of the plans and our needs for Bellagio II.

I have communicated the above to Bill Watson and suggested that:

(1) Dr. Steve Jones be asked to prepare a brief report on the results in hand for our April 4-5 meeting.

(2) The Task Force pin down when the full report will be finished, and offer additional assistance if necessary.

Larry.

Bello

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March 1, 1985

Dr. Anthony R. Measham,
The World Bank
Health Advisor
Health, Population and Nutrition
1818 H Street, N.W.
Washington, D.C. 20433

Dear Tony:

Enclosed are the two documents we received from Dr. Steve Jones concerning the evaluation program in Colombia.

I have received permission from Steve and Dr. Ciro de Quadros to make these available to our sponsoring agencies, and plan to include them as part of the package, when we circulate the agenda for our April 4th-5th meeting.

Sincerely,

Bill

William C. Watson
Project Manager

Enclosures

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AM
W. desire your attendance, in addition
4/2/85

February 15, 1985

Mr. John North
Director
Health, Population and Nutrition
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear Mr. North:

We are writing to invite you to attend a follow-up conference to the one held last March in Bellagio, Italy on the subject of "Protecting the World's Children: Vaccine and Immunization". Our second meeting will be held in Cartagena, Colombia, October 14-17, 1985. Colombia has mounted an exciting immunization effort since last March, and we think that it is particularly appropriate that this next meeting be held there. President Betancur and other Colombian officials are enthusiastic about serving as our hosts, and are making the Presidential villa in Cartagena available for our use. You also will receive a personal invitation from President Betancur.

Since our conference in Bellagio, considerable progress has been made in implementing the plans which evolved from that meeting. India, Senegal and Colombia are making progress in accelerating their immunization programs. Encouraging developments with respect to research plans are also taking place. The Task Force for Child Survival, consisting of a senior representative from each of our agencies, has been formed and is vigorously pursuing the goals developed in Bellagio. The former Director of the Centers for Disease Control, Dr. William H. Foege, is serving as the Executive Director and has engaged a small staff to assist him. The Task Force meets quarterly with Dr. Foege and his staff to do everything possible to ensure that the effort continues to flourish.

The Task Force is developing an agenda for the conference, and working with Colombian officials regarding logistics and meeting arrangements. The conference will focus on plans for meeting the WHO 1990 Objectives for Immunization, a report on the progress made since last March, a discussion of how immunization programs can be used to build better primary health care systems, and an update on vaccine development.

In addition to the original participants in last year's conference, we plan to invite a small number of people who were unable to participate in the "Bellagio I" meeting.

Please hold the dates of October 14-17, 1985 on your calendar and plan to be with us at "Bellagio II." Your participation is essential to the continuation of the important effort which we have undertaken.

Yours sincerely,

Halfdan Mahler
Director General
World Health Organization

James P. Grant
Executive Director
UNICEF

A.W. Clausen
President
The World Bank

Bradford Morse
Administrator
United Nations Development Programme

Richard W. Lyman
President
The Rockefeller Foundation

Please send replies to:

William H. Foege
Executive Director
The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

FORM NO. 89
(2-83)

THE WORLD BANK Bellagio

ROUTING SLIP	Date Feb. 13, 1985

OFFICE OF THE PRESIDENT

Name	Room No.
cc: Mr. North	N-437
AM.	

	To Handle		Note and File
	Appropriate Disposition		Prepare Reply
	Approval		Per Our Conversation
XX	Information		Recommendation

F ks

Roy Southworth

From

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033 (404) 325-2452 • Telex 8107518512
Administratively Affiliated with Emory University

February 8, 1985

184

Mr. A.W. Clausen
President
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear Mr. Clausen:

This is the third in our series of reports to keep you updated on activities since we met in Bellagio, Italy last March.

As you know from our previous reports, Colombia completed the third of its three planned Jornadoes, or National Immunization Days in which the Colombians estimate that a total of five million doses of vaccine were given. The program in Colombia continues to receive strong political support from President Betancur and others, and the level of enthusiasm for the program continues. Evaluation of the program is now going on, and is expected to be completed in February 1985. Technical consultants from the Pan American Health Organization and CDC visited Colombia in November 1984 to assist and advise in the development of the evaluation activities. The Colombians continue to take enormous pride in what they have accomplished, and are now taking the next step, namely, developing their Primary Health Care program on a long-term basis.

Colombia has invited us to hold "Bellagio II" in Cartagena, and the Task Force has accepted their gracious offer. The meeting will be held October 14-17, and you will be receiving an invitation to attend in the very near future.

Dr. D.B. Bisht, Director-General of Health Services in India, visited with us in Atlanta October 15-17, 1984. From this visit, subsequent correspondence, and from my visit to India, it appears that collaboration with India will fall into three general areas: (1) collaboration in developing their vaccine production, particularly for polio and measles vaccine; (2) working with them to procure additional vaccines until production is geared up; and (3) improvement of their cold chain system. Mr. Rajiv Ghandi, the newly elected Prime Minister of India, has committed his government to an expanded national immunization program which is included in their new 5-year plan.

Mark LaPointe has completed a 90-day detail to Senegal under the aegis of UNICEF to assist in the development of a plan for their immunization program. We expect that this plan will be completed within the next few weeks and forwarded to UNICEF for action. Part of this plan calls for Mark to return to Senegal for a 2-year assignment as a consultant under the sponsorship of UNICEF. The plan, as conceived, calls for initiation of accelerated programs in 10 selected sites in Senegal, and a training program for personnel engaged in the program.

Burkina Faso completed a 10-day immunization campaign in December 1984. The enclosed information indicates that they, too, met the goals they set for themselves. Dr. Stoeckel's APMP was instrumental in this undertaking, and Russ Charter was there on short-term assignment under the sponsorship of UNICEF. They are now in the process of developing a follow-on long-term program, and plans are being developed for Russ to return on a long-term, 2-year assignment, again under the sponsorship of UNICEF.

Richard Reid, the UNICEF representative in Nigeria, visited Atlanta in December 1984. Nigeria has launched a very well planned campaign. Initially, the campaign will include one department in each of Nigeria's 19 States. Senior and mid-level personnel have already been trained in immunization program management. Appropriate equipment (vehicles, refrigerators, needles, and vaccine) has been procured. Early data indicates that immunization levels of over 80 percent are being achieved. There is also a well developed plan to integrate these campaigns into the ongoing primary health care programs. Nigeria has the largest population of any country in sub-Sahara Africa, and the development of a model program there could be important to the entire continent. The UNICEF representative in Lagos has been instrumental in assisting in the development of the program. As in Senegal and Burkina Faso, part of the future UNICEF contribution will be the assignment of an additional full-time consultant for a 2-year period. He will arrive in Nigeria on February 10, 1985.

Enclosed is mortality data which we have just received from a survey in Liberia. These data confirm once again the enormously high death rate among young children, so much of it from the vaccine preventable diseases.

Drs. Donald Francis and Roger Bernier of CDC, utilizing a paper developed by Dr. Rafe Henderson of WHO, are taking the lead in developing a priority list of the top 10 or 12 research and development projects which would contribute most to the improvement of immunization programs and which, hopefully, can be completed in a short time frame. A meeting on how to improve and expedite the process from vaccine discovery to actual vaccine use will be held at the Salk Institute on March 18-20, 1985.

Sincerely yours,

William C. Watson, Jr.
for William H. Foege, M.D.
Executive Director

Enclosures

EXCERPTS FROM CABLES
(DATED DECEMBER 12th AND DECEMBER 14th, 1984)
FROM UNICEF, OUAGADOUGOU, BURKINA FASO

Final data for 23 out of 30 completed provinces is:

VACCINE	NUMBER VACCINATED	PERCENT TARGET POPULATION
Measles	942,283	72
Yellow Fever	1,571,651	60
Meningitis	2,086,097	80

Total data for seven partial provinces and 23 completed provinces is as follows:

VACCINE	NUMBER VACCINATED	PERCENT TARGET POPULATION
Measles	1,035,515	79
Yellow Fever	1,804,519	69
Meningitis	2,307,163	89

A random sample evaluation (will be) conducted in early 1985 to determine the vaccination coverage. (The UNICEF consultant) recommends that a stratified random sample be used in order to obtain valid coverage data for each province as well as the nation. Without good statistical base line data on each province, it will be very difficult to measure any improvements made my EPI. UNICEF and WHO should make every effort to assist the government in conducting an evaluation which will provide valid data by province.

"Vaccination commando" (with all its problems and shortcomings) can be termed a success for many reasons:

1. The population was mobilized beyond all expectation.

2. The population was informed about vaccinations and what they do for each person.

3. Large quantities of vaccine were administered across the country in a relatively short period of time - 15 days.

4. The government has focused the population's attention on preventative health measures, and thus has provided a foothold from which to launch EPI.

5. The government and the people have proved to themselves that when they determine to accomplish something, given the resources, they can achieve their goal.

The real proof of success will be provided during the months of January through May when measles, yellow fever, and meningitis diseases normally occur in epidemic proportions in Burkina Faso. If only small outbreaks or scattered cases of these diseases are seen among the target populations then the campaign can be termed a real success. After all the real goal of "vaccination commando" was to reduce the incidence of these diseases among the target population and thereby reduce infant mortality caused by the diseases.

LIBERIA
CAUSE OF DEATH IN CHILDREN UNDER 5 YEARS

CAUSE	NUMBER	PERCENT
All	1,380	100
Tetanus	96	7
Measles	311	23
Diarrhea	274	20
Malaria	167	12
Unknown	155	11
Uncoded	213	15
Other	164	12

Bellagio

The Task Force for Child Survival
1989 North Williamsburg Drive • Suite I • Decatur, Georgia 30033
(404) 325-2452 • Telex 8107518512
Administratively Affiliated with Emory University

January 18, 1985

Anthony R. Measham, M.D.
Health Adviser
Health, Population and Nutrition
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear Tony:

As discussed at our January 11 meeting, enclosed are the two letters of invitation to "Bellagio II" which require Mr. Clausen's signature.

After Mr. Clausen signs the letters, please return them to us, unfolded, in the enclosed envelope. When we receive the letters signed by all five agency heads, we will combine the signatures for the final letters. We would like to mail these letters by February 1, so we would appreciate your expediting this process.

Thank you for your assistance. We enjoyed having you with us on January 11.

Sincerely yours,

Bill

William H. Foege, M.D.
Executive Director

Enclosures

FORM NO. 75
(6–83)

THE WORLD BANK/IFC

ROUTING SLIP	DATE: 2/21/85

NAME	ROOM NO.
Dr Measham	N 440
① Mr. Norem 2/22/85	
For information.	
Please return	
② Measham	

	APPROPRIATE DISPOSITION		NOTE AND RETURN
	APPROVAL		NOTE AND SEND ON
	CLEARANCE		PER OUR CONVERSATION
	COMMENT		PER YOUR REQUEST
	FOR ACTION		PREPARE REPLY
	INFORMATION		RECOMMENDATION
	INITIAL		SIGNATURE
	NOTE AND FILE		URGENT

EMARKS:

J. Salk gave me this copy which is not relevant to my assignments but may be of interest to you -

FROM:	ROOM NO.:	EXTENSION:
Andrei Rosa	322	61597

The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

5-32
MacA

January 3, 1985

Jonas Salk, M.D.
Founding Director
The Salk Institute
10010 North Torrey Pines Road
La Jolla, California 92037

Dear Jonas:

I hope 1985 is a good year for you and for global immunization efforts. Your name has been mentioned frequently in discussions with President Carter over the last several months, and I hope you will have an opportunity to meet with him again as we begin discussing international health projects. Our consultation in November at the Carter Center on domestic priorities was a very useful meeting.

In reviewing immunization research needs over the last months, we have reached the conclusion that, while the immunization research process may still have many problems, in general, a system now exists through EPI, the Diarrheal Disease Program, the Tropical Disease Research Program, and SAGE, to look at priorities and basic vaccine research. Therefore, there is a feeling that The Task Force should focus on three areas:

1) Application or operational research needs
2) Fund raising for vaccine research
3) Means to improve or expedite the process from vaccine discovery to actual vaccine use.

The meeting that you will host in March, addressing the role of industry, will approach many of the problems inherent in the third area of concentration. Would you be willing to go even beyond your March agenda and, on behalf of The Task Force, either alone or with a number of colleagues, develop your thoughts on the research agenda required to get vaccines from the discovery phase to actual use in health programs? This would provide an enormous help to The Task Force in being able to raise required funds.

A second request involves India. We have reached the conclusion that it would be useful to approach India with a summary of the various offers that have been made by WHO, UNICEF, The Rotary Club, CIDA, etc., so that they know what they can anticipate in international assistance over the next 5 years. That should help precipitate a plan and speed up the entire process. If Bill Watson and/or I can arrange to carry such a plan to India in

the next 4 to 6 weeks, would you potentially be available to also be in India for several days? It might give you an opportunity to meet with the new Prime Minister and promote immunization, in Jim Grant's words, as a "living memorial to Indira Gandhi." Let me know if this is even a possibility.

Finally, since our last conversation in New York, I have raised the proposed title of "The Task Force for Healthy Children" with our sponsoring agencies. Steve Joseph agreed to take that proposal to UNICEF, but expressed the belief that they would have great reluctance in changing the name because the term "child survival" has become such an important part of UNICEF program activities. He was correct in this assumption, and Ken Warren has also had conversations with people at UNICEF who feel it is essential that The Task Force retain the name "The Task Force for Child Survival." Because this is apparently such an important issue for UNICEF, the concensus is that, whatever its limitations, we are best served by continuing with that title. While I know this is not the ideal solution from your point of view, I hope it is acceptable in the overall strategy of improving global immunization.

We have, in recent weeks, succeeded in obtaining and providing vaccine for Ethiopia; we now have a plan that is very reasonable for immunization in Senegal; a request for a full-time person to work as an operations officer in Senegal; and a request to find a person to work in Burkina Faso. In addition, Colombia has offered to host the "Bellagio II" meeting, so things are beginning to move.

Very best regards.

Sincerely,

Bill

William H. Foege, M.D.
Executive Director

The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

December 6, 1984

Mr. John North
Director
Health, Population and Nutrition
The World Bank
1818 H Street, N.W.
Washington, D.C. 20433

Dear John:

Since Bill Foege's letter of October 20, 1984, Dr. Duque has confirmed that facilities for "Bellagio II" have been reserved for October 14-17, 1985 in Cartagena, Colombia. We have also confirmed that these dates are satisfactory with the five agencies of The Task Force.

We are now ready to start the process of getting out official invitations, which everyone agrees should go from the agency heads.

Enclosed are two draft letters. One, a revised invitation to participants in "Bellagio I." The second, an invitation to the small number of people who will be invited to the meeting, but who did not attend "Bellagio I." We are sending these drafts to The Task Force representatives of all five sponsoring agencies for review and comment.

I would appreciate your giving me your suggestions by phone as soon as possible so that we all can hopefully come to agreement on the content and phrasing of the letters. At that point we propose that you get Mr. Clausen's approval of the letters. After all agency heads have approved the letters, we will send each representative finished copies for his agency head's signature. If those signed copies can then be returned to us, we will do a composite printing of the letters with all five signatures, and mail them from here.

Sincerely yours,

Bill Watson

William C. Watson
Project Manager
The Task Force for Child Survival

Enclosures

cc: Dr. Tony Measham

The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

December 6, 1984

Ⅲ

Dear Ⅲ:

In 1983, some five million children in developing countries died, and another five million were crippled, blinded or otherwise disabled from six diseases preventable through immunization. We estimate that, at most, 30% of the world's children are now protected against these diseases, in spite of the fact that effective vaccines exist. A meeting was convened . . . ?

Out of a shared concern about this deplorable situation, our agencies, The Honorable Robert McNamara and Dr. Jonas Salk, convened a meeting at The Rockefeller Center in Bellagio, Italy in March 1984 to consider a global effort to protect the world's children. A copy of the report of that conference is enclosed.

Since the Bellagio conference, considerable progress has been made in implementing the plans which were developed there. Colombia, India and Senegal, the countries selected at the meeting for special emphasis programs, have all made progress in developing country-based plans for accelerating their immunization programs. Encouraging developments with respect to research plans are also taking place. The Task Force for Child Survival has been formed and is now operational, with Dr. William H. Foege, former Director of the Centers for Disease Control, as its Executive Director. Representatives from each of our organizations have been meeting quarterly with Dr. Foege and his staff to do everything possible to insure that the effort we have now begun continues to flourish. This important global effort to improve the health of the children of the world deserves continued support from everyone.

Therefore, we are writing at this time to invite you to attend a second meeting which we will hold in Cartagena, Colombia October 14-17, 1985. Colombia has mounted an exciting immunization effort during the last several months, and we think that it is particularly appropriate that this next meeting be held there. President Betancur and other Colombian officials are enthusiastic about serving as our hosts. We are asking The Task Force for Child Survival to draw up an agenda for the conference and to work with Colombian officials regarding logistics and meeting arrangements. Dr. Foege and his staff will be providing this kind of information to you at a later date.

We hope you will hold these dates on your calendar and plan to be with us at this most important meeting. We will need your counsel and advice in deciding on plans for the future. Please join us in this continuation of our great venture.

Yours sincerely,

Richard W. Lyman
President
The Rockefeller Foundation

A.W. Clausen
President
The World Bank

Bradford Morse
Administrator
United Nations Development Programme

Halfdan Mahler, M.D.
Director General
World Health Organization

James P. Grant, M.D.
Executive Director
UNICEF

Please send replies to:

William H. Foege, M.D.
Executive Director
The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

The Task Force for Child Survival
1989 North Williamsburg Drive
Suite I
Decatur, Georgia 30033
(404) 325-2452

December 6, 1984

[redacted]

RE: Meeting in Cartagena, Colombia on October 14 - 17, 1985

Dear [redacted]:

Since our conference in Bellagio in March, 1984, considerable progress has been made in implementing the plans which evolved from that meeting. The selected emphasis countries (India, Senegal and Colombia) have all made progress in developing country based plans for accelerating their immunization programs. Encouraging developments with respect to research plans are also taking place. The Task Force for Child Survival has been formed and is now operational, with Dr. William H. Foege as its Executive Director. Representatives from each of our organizations have been meeting quarterly with Dr. Foege and his staff to do everything possible to insure that the effort we have now begun continues to flourish. It is incumbent upon us all to continue to support this important global effort to improve the health of the children of the world.

Therefore, we are writing at this time to invite you to attend a second meeting which will be held in Cartagena, Colombia, October 14 - 17, 1985. Colombia has mounted an exciting immunization effort since our first meeting in March, and we think that it is particularly appropriate that this next meeting be held in one of the participating countries. President Betancur and other Colombian officials are enthusiastic about serving as our hosts. We are asking The Task Force for Child Survival to draw up an agenda for the conference, to work with Colombia officials regarding logistics and meeting arrangements, and to keep you appropriately informed. We plan to invite a very small number of world leaders who did not participate in the Bellagio meeting.

We hope you will hold these dates on your calendar and plan to be with us at this most important second meeting. We will need your counsel and advice in deciding on plans for the future. Please join us in this continuation of our great venture.

Yours sincerely,

Richard W. Lyman
President
The Rockefeller Foundation

A.W. Clausen
President
The World Bank

Bradford Morse
Administrator
United Nations Development Programme

Halfdan Mahler, M.D.
Director General
World Health Organization

James P. Grant, M.D.
Executive Director
UNICEF

Please send replies to:

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Bellagio

TESTIMONY BEFORE THE SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATION OF THE COMMITTEE ON ENERGY AND COMMERCE

MARCH 13, 1985

WILLIAM H. FOEGE, M.D.
EXECUTIVE DIRECTOR
THE TASK FORCE FOR CHILD SURVIVAL

Sponsoring Agencies: WHO UNICEF World Bank UNDP RF

I. INTRODUCTION

The past two decades have witnessed a remarkable improvement in vaccine development, manufacturing capability, and delivery of immunizations, both domestically and internationally. Interest has increased in many countries in improving primary health care programs, often with immunizations as the cutting edge of health delivery.

Twenty years ago, conditions were favorable for an international coalition to eliminate smallpox from the globe. Conditions are now right for an international coalition to change childhood immunization from a promise to a reality for all children of the world. Success in this venture would have a major impact on childhood mortality, as well as on the quality of life for children and parents.

A three-point program has been proposed:

(1) Accelerate the expansion of immunization coverage to those developing countries where children contribute disproportionately to vaccine-preventable disease mortality;

(2) Simultaneously provide increased support for immunization services to all other developing countries, to assure that they are not constrained by the lack of vaccine, supplies, equipment, or technical assistance;

(3) Intensify research and development to improve current immunization and delivery system technology

These actions should be designed and made available in such a way as to contribute to the the development of national health infrastructures.

II. DOMESTIC EXPERIENCE

A. Immunization Program

National immunization programs are relatively new in public health as practiced in the United States. The diphtheria, tetanus and pertussis vaccine was first licensed as a trivalent vaccine in 1949. Inactivated polio vaccine was licensed 6 years later in 1955. Oral polio vaccine was first licensed in 1961, and a trivalent preparation containing all three types of oral polio vaccine was licensed in 1963. Measles vaccine was first licensed in 1963, but not until 1971 was a triple vaccine containing measles-mumps-rubella available for use. While major gains were achieved in reducing disease incidence for all of the above diseases before 1977, the Nation lacked a unified system with maximum efficiency and effectiveness for disease control. For example Federal funding would rise and fall and the introduction of new vaccines sometimes led to the elimination of Federal funds for vaccines previously supported. A decreased disease incidence often led to complacency regarding maintenance with a reduction in funding, less attention to program activities and apathy on the part of parents in seeking immunizations.

During fiscal years 1969, 1970 and 1971, no Federal grant money was provided for measles control. Subsequent increases in measles cases led to the reestablishment of Federal assistance in measles control.

In 1977, a National Childhood Immunization Initiative was developed to provide a national approach, long-range planning and adequate resources. Two major objectives were adopted in 1977: (1) To increase immunization levels from the existing 60-75% to 90% by October of 1979; and (2) To develop a maintenance system to assure that those levels would continue in the future. In 1978, an additional objective was adopted, namely, to eliminate indigenous measles transmission in the United States. It was recognized that as long as measles exists in the remainder of the world, we will continue to have importations; therefore, total elimination of the disease is not possible in this country.

B. Results

These innovations of selecting targets, focusing on particular problems such as measles, and providing national support, including money and people, had dramatic results. Coverage rates not only reached the objective of 90% but have continued to improve to the point, that, at the present time, 97-98% of all children entering school have been immunized against diphtheria, tetanus, pertussis, polio, measles, mumps and rubella. Because there will always be children who have medical reasons for not receiving vaccine, and because some parents have religious convictions against accepting immunization, we are very close to the maximum coverage possible. Indeed, the United States is close to perfection in providing immunization to its children (Attachment I).

Disease rates were falling even before the 1977 Initiative. For most of the vaccine-preventable diseases, declines of over 99% have been recorded in the last decades. For example by 1977, diphtheria, the scourge of children early in this century, had declined to 84 cases. However, in 1984 there was only a single case of diphtheria in the entire country. Rubella cases fell from over 20,000 in 1977 to 745 in 1984, and measles declined from over 57,000 cases in 1977 to 2,534 in 1984 (Attachment II).

Any parent who has nursed children through episodes of these diseases would willingly pay money in excess of treatment costs, if only they could have prevented the episode. Happily, the immunization program has not only prevented millions of cases of illness and thousands of deaths, but has also saved this country considerable sums of money. An independent study done by Schoenbaum in 1976, concerning the savings associated with the rubella vaccine program, indicated the benefit-cost ratio of rubella immunization given in combination with measles vaccine to be 23:1. A recent study soon to be published, concerning measles-mumps-rubella vaccine in 1983 indicated without an immunization program, an estimated 3.3 million cases of measles would have occurred as compared to the 2,872 that actually occurred in 1983. Instead of an expected 1.5 million rubella cases, only 3,816 cases were reported in 1983. Mumps cases were lowered from 2.1 million to 32,850 actual cases. Comparable reductions in the disease-associated complications, sequelae and deaths were realized because of the immunization program. Without an immunization program, costs for these three diseases would have been approximately $1.4 billion.

Based on the actual incidence of disease in 1983, costs were estimated to be approximately $14.5 million, resulting in savings of over $1.3 billion. Expenditures for immunization, including vaccine and administration costs, and the cost associated with vaccine reactions, totaled $96 million. The resulting benefit-cost ratio, for the measles-mumps-rubella immunization program was approximately 14:1. In other words, for every dollar invested in the measles-mumps-rubella program by Federal, State and local programs, the United States realized a savings of $14.

Similar savings have been documented for polio immunization in this country, with benefit-cost ratios in the range of 10:1. No vaccine is perfect, and the benefits enjoyed by the society are purchased with some risks to a small number of individuals. For many vaccines, including mumps, measles and rubella, the risks are very small. Even with pertussis vaccine, a highly favorable benefit-cost ratio is realized in this country. A study published on June 15, 1984, in the Journal of the American Medical Association, calculates that a program reaching 90% of children with pertussis vaccine, even when calculating the costs of hospitalization and maintenance of children who suffer vaccine complications, would still provide a benefit-cost ratio of 11:1 providing $11 of benefit for every dollar invested in the program (Attachment III).

C. Remaining Problems

For all the improvements in the program, the benefits achieved and the lessons learned, there are still major problems to be overcome. The decrease in companies willing to produce vaccines because of low profits, fear of litigation, etc. is of concern. When only a single manufacturer provides a vaccine, and stockpiles are insufficient, a single lot that does not pass quality or safety standards or a fire in a warehouse, can result in disruptions in our ability to protect America's children. We will continue to have a need for new vaccines, improved vaccines and, in some cases (such as hepatitis B) less expensive vaccines. There will also continue to be a need to produce vaccines with fewer adverse reactions. The current reactions to pertussis vaccine provide an urgent reason for finding an improved product.

D. Lessons

A number of lessons have been learned but will be mentioned only briefly:

(1) The need for broad-based professional support. Professional groups, such as the American Medical Association, the American pediatric community, nurses, educators, etc. have all provided indispensable support.

(2) The support of legislative bodies in requiring that a child be immunized prior to school attendance has been crucial in achieving this public health miracle.

(3) The selection of immunization coverage rate targets has provided a simple mechanism for focusing activities and for measuring and comparing the success of programs. The selection of indigenous measles elimination as a target served as a leading edge, which has accelerated the remainder of the immunization program in its wake. For example, in order to eliminate measles transmission, immunization coverage rates had to exceed 90%. Immunizing children against measles has brought other vaccine coverage rates to record-high levels as well. In order to measure measles activity, surveillance systems had to become increasingly sensitive, and this sensitivity had a favorable effect on other disease surveillance systems.

(4) The cooperation and coordination, which has developed between Federal, State and local juristictions has been one of the best in public health. Again, clear objectives and dependable Federal funding have made it possible for State and local health departments to do better planning. Likewise, the coordination between public and private groups, and between medical and non-medical groups has been exemplary, and has provided a model for program development in other public health activities.

(5) We have learned that the infrastructure provided by delivering one vaccine is easily expanded to make maximum use of new vaccines as they are developed. For example, it was easy to add rubella and mumps to the ongoing program by simply combining vaccines. Even when vaccines could not be combined, it has been much easier to add a new vaccine to the schedule than to develop entirely new programs. This would suggest that the United States would realize the earliest possible benefits from the development of future childhood vaccines.

(6) It has also been clear that immunization programs do not reach their maximum efficiency and effectiveness if simply added to other public health programs, with the hope that they will receive adequate attention. There must be people at Federal, State and local levels who are identified as having immunization as their absolute priority, and who are held accountable for the program results.

III. INTERNATIONAL EXPERIENCE

A. The Problem

The size of the global problem is hard to overstate. Some diseases, such as measles, are so ubiquitous that every child born in the world can expect to have measles if they do not die of some other reason first, or if they have not been immunized. But in addition, a disease such as measles is more severe and causes greater mortality in children suffering from other problems, including malnutrition. For example in West Africa, death rates from measles as high as 5-10% have been recorded on many occasions, and during times of famine, mortality rates exceeding 25% have been observed. It is estimated that 5 million children die annually due to the vaccine-preventable diseases. Attachment IV shows the estimated number of annual deaths from only three causes, neonatal tetanus, measles and pertussis, for 25 countries. In these 25 countries, 2 million children die each year from measles alone.

But death is not the only cost of these diseases. It is estimated that an additional 5 million children are crippled each year, many from polio. Others suffer mental retardation or blindness due to measles. The burden imposed on society by long-term crippling and by the diseases themselves provide an unnecessary barrier to life quality. Health, disease and population have complex interactions. However, it is clear that the traditional disease burden in Third World countries heavily involves infectious diseases, malnutrition and population pressures. While malnutrition makes many infectious diseases worse, it is also clear that repeated infectious diseases, including measles and diarrheal diseases, in turn, contribute to malnutrition, both by requiring excess calories for a diseased child, and also because of the loss of calories through diarrhea and the restricted intake of calories because of illness. By the same token, population pressures often facilitate disease transmission or impair sanitation, making infectious diseases worse.

The paradox is that increasing childhood mortality does not lead to reductions in population pressures, indeed, the converse appears to be true. The highest net increases in population are now seen in the countries with the highest infant and child mortality rates.

Death control appears to be an important ingredient in birth control and must be pursued vigorously. Ideally, maximum assistance should be given to countries to reduce unnecessary deaths, to reduce unnecessary illness, and to provide knowledge about and supplies for family planning. If children are saved from a measles death will they simply die of something else? That is an argument advocated by some who doubt the wisdom of immunization programs. The answers are far from complete, but it is clear that:

(1) Much crippling can be reduced.

(2) Not all spared from vaccine preventable diseases will succumb to other childhood diseases.

(3) Children dying of measles never have the luxury of testing their survivability from other conditions.

(4) The remarkable increase in life expectancy this century in the United States (over 25 additional years at birth) is the result of one advance after another cumulating to an additional quarter century of life. The infants spared did not necessarily die in childhood of other diseases.

B. The Response

The current response to the global problem of immunization is laudable in terms of the number of agencies involved, and the rapid increase in activities. The World Health Organization has pioneered programs throughout the world. The majority of countries in the world have some immunization activities. UNICEF has greatly strengthened its capacity to promote immunization, and has targeted immunizations as one of the key programs in its "child survival" strategy.

Bilateral immunization activities are sponsored by many countries; and foundations, voluntary agencies and service organizations are increasingly selecting immunization as a key activity. Despite the great increase in interest, the percentage of children in Third World countries receiving immunizations is only about one-third of all children needing immunizations. While we can take comfort in the rapid increase in coverage from 10% or less to approximately one-third, the inescapable fact is two-thirds of the children of the world receive no benefit from these technological marvels.

We know that much more is possible. In Colombia, an attempt to increase immunization coverage from about 40% to over 60% in 1984 was successful. President Betancur provided personal leadership, and on special immunization days, actually immunized a child on national television to demonstrate the importance to his country. As in the United States, the Colombians mobilized medical and non-medical resources, including radio and television stations, the police, the military, churches, etc.

Senegal is currently launching a program to make immunizations part of the ongoing primary health program as are Nigeria and India, and other countries are planning a rapid expansion of immunization activities.

In an effort to improve coordination, the World Health Organization, UNICEF, the World Bank, the UNDP and The Rockefeller Foundation have formed The Task Force for Child Survival to assist in program operations in selected countries, and to look more broadly at barriers to immunization, research needs and operational techniques that might improve global immunization.

C. Barriers

Current abilities and experience indicate there is much more that could be done to improve immunization levels. In addition, there are barriers that, if surmounted, could facilitate the process. These barriers can be classified under the general headings of engineering, biotechnical and operational.

Some problems appear to be straightforward engineering questions. If sufficient interest and resources were developed, answers could be expected in a relatively short-time period. For example, how do we improve and simplify the cold chain, that is, the system that keeps vaccines cold from the time of manufacture through shipment and distribution until actually injected into a child under village conditions? It includes improvements in insulation material, power sources, devices for recording temperature, etc. Another engineering problem is the need for a simplified method of injecting vaccine. Answers could range from an inexpensive single-dose disposable needle and syringe to simplified jet injectors useful under field conditions.

Biotechnical barriers include the need to develop vaccines with more stability, ideally requiring no refrigeration at all. If the cold chain could be totally eliminated, operations would be greatly simplified. Improved vaccines that are not only more stable, but more potent, requiring fewer doses, and smaller quantities--vaccines with fewer adverse reactions--vaccines that could be combined physically--and vaccines that could be given earlier in life should be developed.

Operational barriers include the need for simplified surveillance systems, discovering what is needed to insure better compliance, better health education techniques, improved evaluation, simplified managerial programs, etc.

IV. WHAT NEEDS TO BE DONE?

(A) The possibilities must be understood. The possibility of a global collaborative effort to significantly reduce the burden of vaccine-preventable diseases sounds difficult, if not impossible. However, we have a model to follow. Twenty-years ago, delegates from the United States and from the Soviet Union presented a convincing argument to the World Health Assembly that smallpox could be eliminated from the world. A resolution was passed by the member countries, and in late 1966, program activities began. For a decade member countries, under the auspices of the World Health Organization, identified problems, identified resources, and brought those resources to bear on the smallpox problem. Year by year, the number of infected countries declined, until by 1977 only one country, Somalia, continued to have smallpox (Attachments V and VI). In October 1977, the last naturally-occurring case of smallpox was reported, and the world became smallpox free. Ironically because of the improved surveillance system for detecting cases of smallpox that would have gone unreported in earlier years, the reported cases of smallpox increased in the years immediately prior to world eradication (Attachment VII). This program established that it is possible for the countries of the world to set global health objectives, work together collaboratively and reach global targets.

(B) Benefits must be understood. While the entire world benefited from the elimination of the threat of smallpox, U.S. economic benefits were very direct. The United States spent approximately $150 million a year to keep smallpox out of this country during the 1960's, despite the absence of cases in the United States since 1949. An investment of approximately $27 million over a 12-year period helped achieve global elimination. This means that the United States is recouping its investment every 3 months at the present time. Because of smallpox eradication, the United States now saves more money each year than we invest in the World Health Organization.

Benefits to Third World countries from immunization programs are substantial. Not only is the clinical burden of vaccine-preventable diseases eliminated, freeing up medical resources that can be used in other ways, but immunization programs provide an ideal entry program for primary health care.

Immunization programs are relatively inexpensive. They also become the vehicle for the development of logistics systems, managerial systems, surveillance capabilities, and a framework on which other programs can be added. In addition, as mentioned earlier, immunization programs provide an important ingredient in improving the climate for family planning and population control.

(C) Goals must be articulated. The World Health Organization has set an objective of making immunization programs available to all children of the world by 1990. This is a laudable objective, worthy of support. Increased efforts will be required to make that objective realizable. A commitment by the United States to see that goal achieved would be a powerful influence. In addition, specific goals should be selected for specific diseases. For example, many countries could sharpen their immunization focus if they would set an objective to reduce infant tetanus deaths and measles deaths, by a given amount, say 50-75%, by a particular date. The goal of eliminating smallpox provided a new focus for multiple countries to discuss a coordination of strategies. Dr. Ciro de Quadros, Regional Advisor for the PAHO/WHO Expanded Program on Immunization, has suggested that the Western Hemisphere commit itself now to eliminating polio. This is exactly the kind of goal needed to provide the force to catalyze the entire immunization program much as a goal of eliminating indigenous measles in the United States has improved this Nation's overall domestic program. The United States could play an important role in supporting such an objective for this hemisphere.

(D) Resource needs must be estimated. Various attempts have been made to predict the cost for global immunization. One estimate, made for a meeting held in Bellagio in 1984, indicated that a program for the 10 countries (excluding China) accounting for two-thirds of the total deaths in the world due to vaccine-preventable diseases, would need to reach approximately 40 million infants per year (at a maximum cost of $15 per infant), and 40 million pregnant women (at a maximum cost of $3.50 per woman) giving a total maximum cost of approximately $745 million a year in 1985 dollars. Even doubling the target to 80 million children a year would allow for the immunization of Third World children for less than $1.5 billion per year. This is less than is spent yearly on advertising tobacco in the United States. The majority of resource requirements must come from within Third World countries, in terms of staff salaries and program support. Therefore, only a portion of that amount would have to be raised from external sources.

Compared to military assistance and arms sales, the United States has the opportunity, at a relatively small cost, to help catalyze a global effort to protect the children of this world. A response, in the spirit of the Marshall Plan, could have a decisive impact on the future of the world, promote medicine as an instrument of peace, and help Americans identify as global citizens.

ATTACHMENT I

Immunization levels of school entrants United States, 1983–1984 school year

Vaccine	Immunization level weighted average
DTP	97%
Polio	97%
Measles	98%
Rubella	98%
Mumps	97%

ATTACHMENT II

REPORTED CASES OF SELECTED DISEASES IN THE UNITED STATES
(Excluding Territories)

YEAR	RUBELLA	MEASLES	DIPHTHERIA	TETANUS	PERTUSSIS	POLIO (total)	MUMPS
1960	na	441,703	918	368	14,809	3,190	na
1961	na	423,919	617	379	11,468	1,312	na
1962	na	481,530	444	322	17,749	910	na
1963	na	385,156	314	325	17,135	449	na
1964	na	458,083	293	289	13,005	122	na
1965	na	261,904	164	300	6,799	72	na
1966	46,975	204,136	209	235	7,717	113	na
1967	46,888	62,705	219	263	9,718	41	na
1968	49,371	22,231	260	178	4,810	53	152,209
1969	57,686	25,826	241	185	3,285	20	90,918
1970	56,552	47,351	435	148	4,249	33	104,953
1971	45,086	35,290	215	116	3,036	21	124,939
1972	25,507	32,275	152	128	3,287	31	74,215
1973	27,804	26,690	228	101	1,759	8	69,612
1974	11,917	22,094	272	101	2,402	7	59,128
1975	16,652	24,374	307	102	1,738	8	59,647
1976	12,491	41,126	128	75	1,010	14	38,492
1977	20,395	57,345	84	87	2,177	18	21,436
1978	18,269	26,871	76	86	2,063	15	16,817
1979	11,795	13,597	59	81	1,623	34	14,225
1980	3,904	13,506	3	95	1,730	9	8,576
1981	2,077	3,124	5	72	1,248	6	4,941
1982	2,325	1,714	2	88	1,895	8	5,270
1983	970	1,497	5	91	2,463	15	3,355
1984	745	2,534	1	64	2,187	4	2,921

ATTACHMENT III

BENEFIT-COST-RATIOS BY VACCINE TYPE

Vaccine	Benefit-Cost-Ratio
Measles-Mumps-Rubella (MMR) (1)	14.4:1
Measles-Rubella (MR) (2)	23.0:1
Polio (3)	10.3:1
Pertussis (4)	11.1:1

(1) Unpublished analysis utilizing 1983 data.

(2) Based on analysis of rubella vaccination policy in the United States 1976.

(3) Fudenberg, HH. Returns of Biomedical Research. Journal of Investigative Dermatology 1973: Vol.61 (321).

(4) Hinman, AR and Koplan, JP. Pertussis and Pertussis Vaccine - Reanalysis of Benefits, Risks, and Costs. JAMA 1984 June: Vol.251 (23) p. 3109-3113.

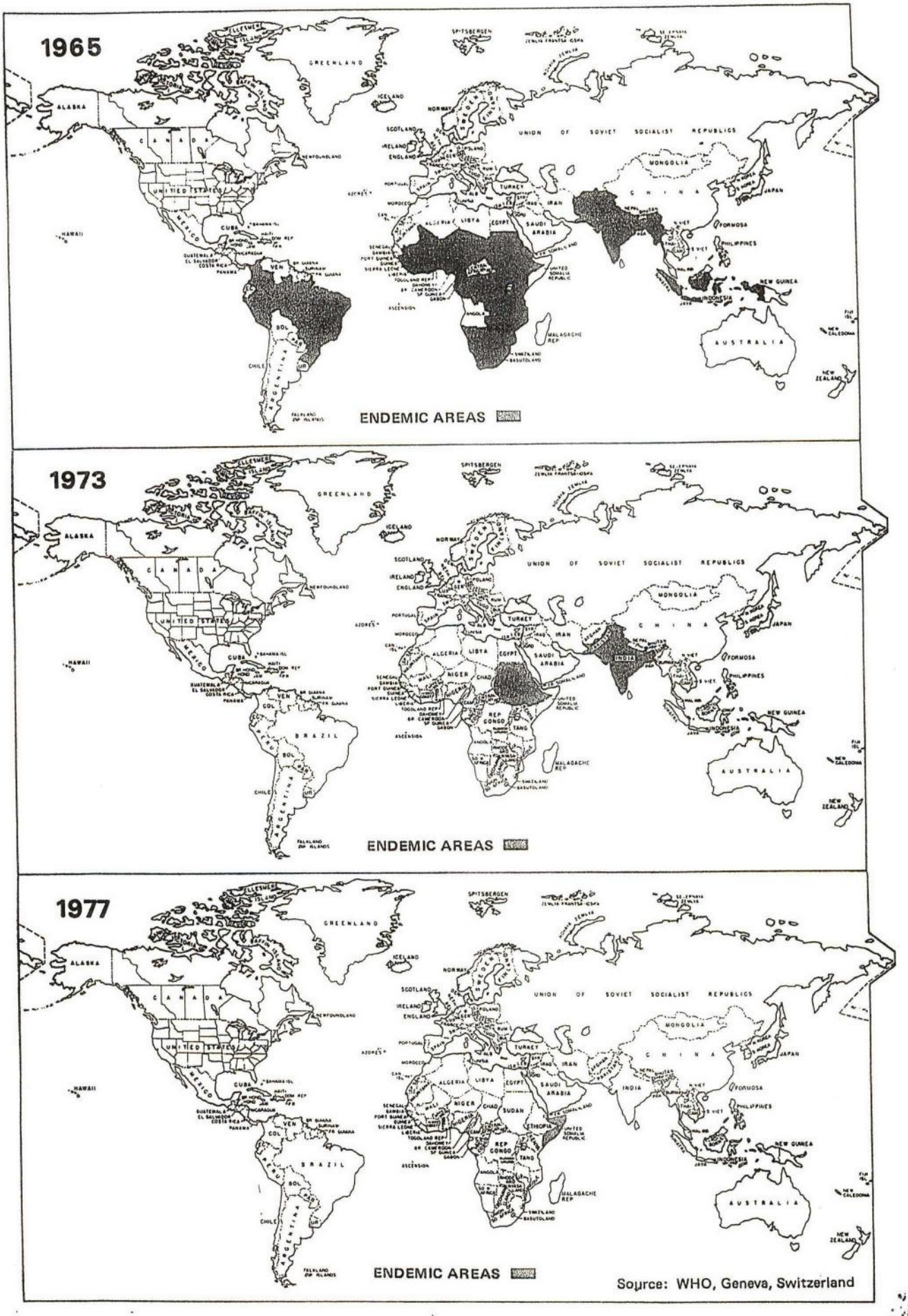
ATTACHMENT IV

DEVELOPING COUNTRIES RANKED BY NUMBER OF DEATHS FROM SELECTED VACCINE PREVENTABLE DISEASES (EXCLUDING CHINA), 1983

Country	Estimated number of annual deaths		
	Neonatal Tetanus (000's)	Measles (000's)	Pertussis (000's)
1. India	288	745	171
2. Pakistan	126	155	53
3. Bangladesh	113	165	55
4. Indonesia	68	208	61
5. Nigeria	61	163	54
6. Mexico	29	54	16
7. Ethopia	15	58	20
8. Zaire	20	43	15
9. Philippines	11	56	14
10. Brazil	26	35	17
11. Burma	19	41	13
12. Thailand	10	53	13
13. Vietnam	11	44	15
14. Kenya	9	35	12
15. Egypt	15	30	10
16. S. Africa	11	33	11
17. Sudan	8	34	12
18. Afghanistan	10	26	9
19. Iran	16	19	8
20. Algeria	10	24	7
21. Morocco	10	20	5
22. Turkey	8	16	5
23. Colombia	9	13	4
24. Tanzania	6	8	6
25. Rep. Korea	5	9	2
TOTAL	**914**	**2,088**	**608**

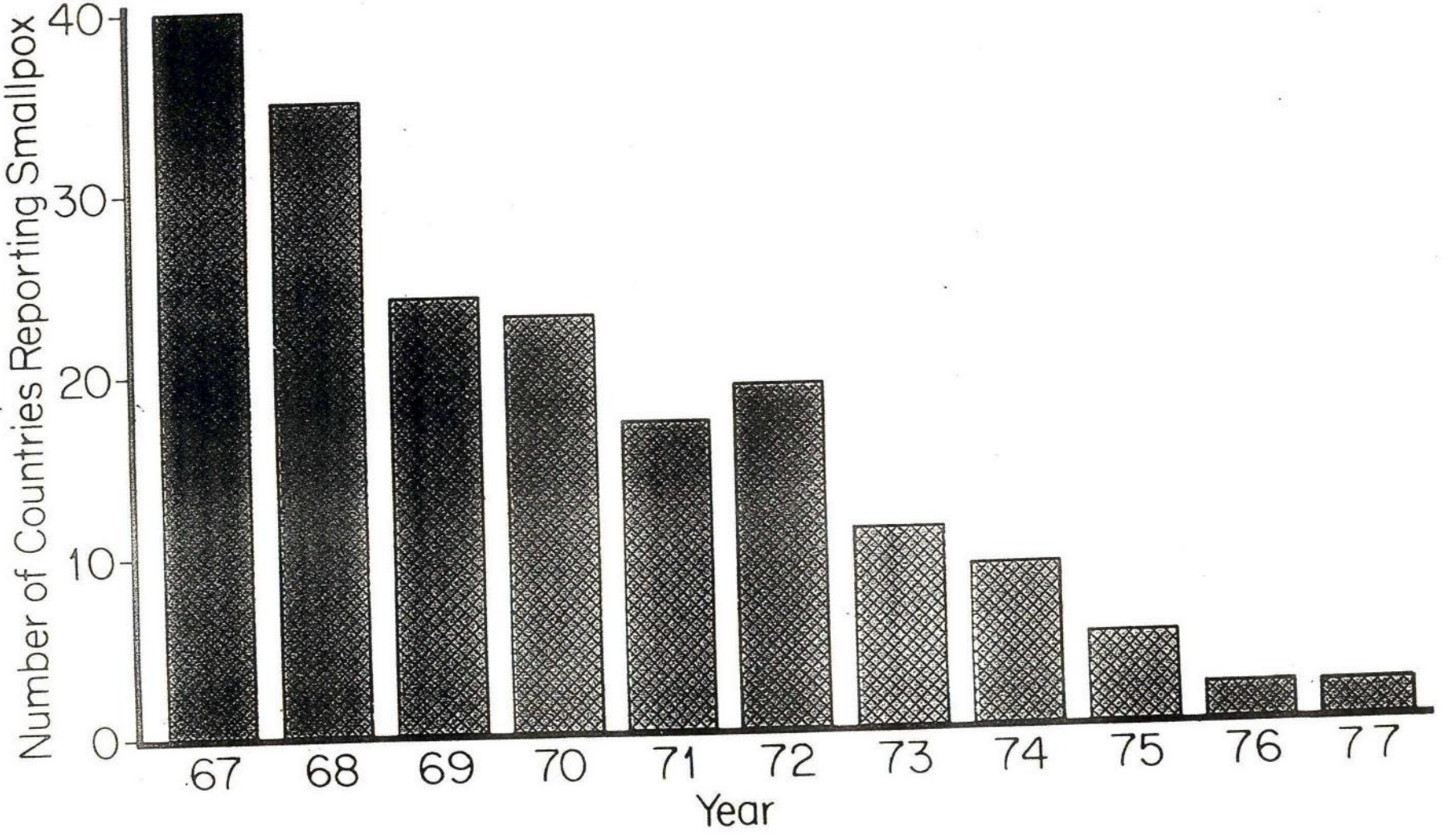
ATTACHMENT V

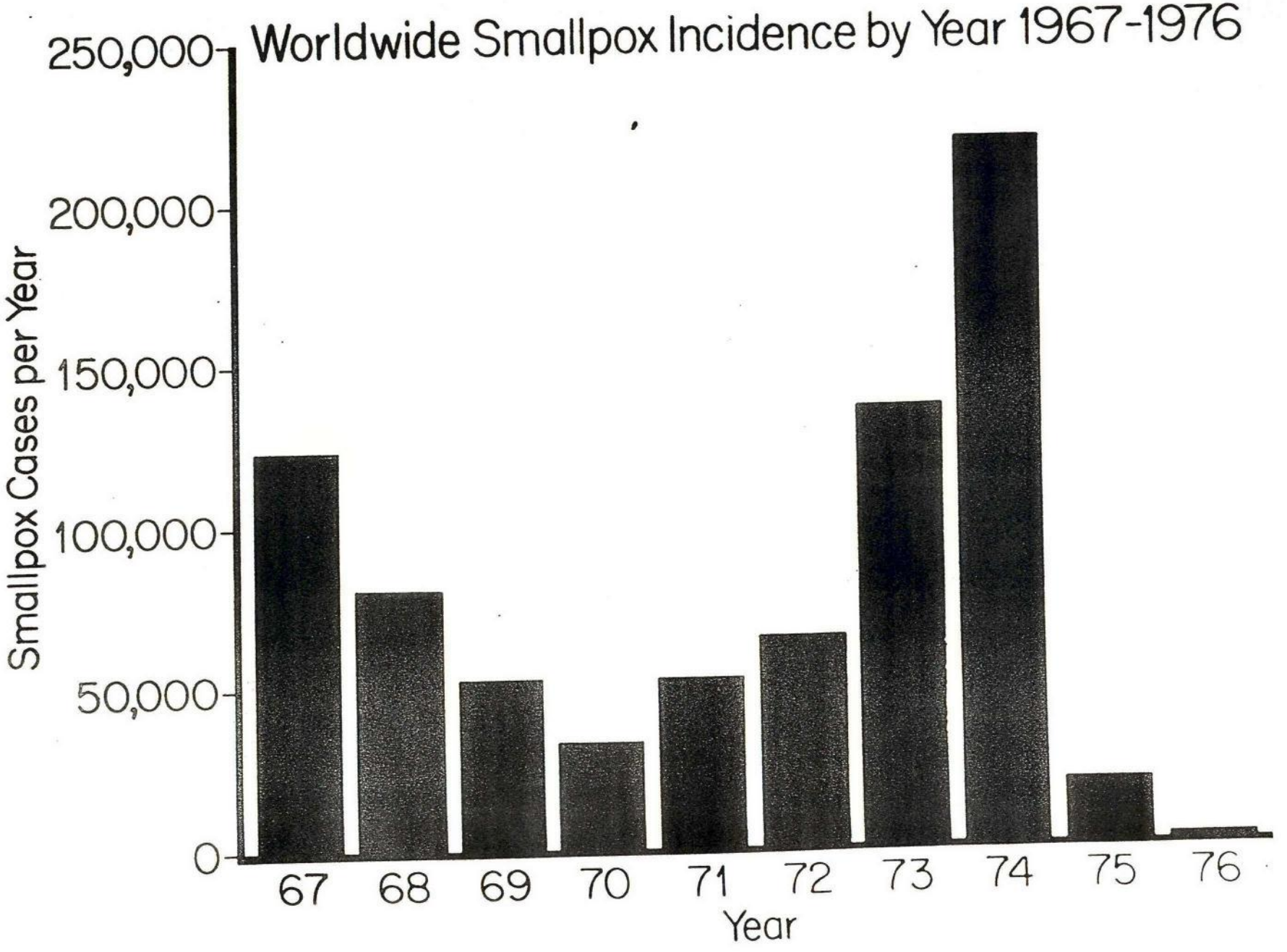
WORLD-WIDE SMALLPOX ENDEMIC AREAS, 1965, 1973, 1977



ATTACHMENT VI

Countries Reporting Smallpox 1967-1977




Worldwide Smallpox Incidence by Year 1967-1976
Smallpox Cases per Year
250,000
200,000
150,000
100,000
50,000
0
67
68
69
70
71
72
73
74
75
76
Year