Attachment 1.
(FACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B. Date 15/4/93

Principal Investigator Dr. Samuel Erny Trainee Investigator (if any) _____

Application No. 93-014/ Supporting Agency (if Non-ICDDR,B) _____

Title of Study respiratory disorders and wheezing-associated hypoxemia in hospitalized children under 5 years of age in rural Bangladesh

Project status:
(X) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects (Yes) No
   (c) Minors or persons under guardianship (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects (Yes) No
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) Yes (No)
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions Yes No NA
   (e) Benefits to be derived Yes No NA
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure Yes (No) NA
5. Will signed consent form be required:
   (a) From subjects Yes (No) NA
   (b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   X Protocol (Required)
   X Abstract Summary (Required)
   X Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ___ Informed consent form for subjects
   X Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   X Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee, for review.

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Samuel Erny
Principal Investigator

Trainee

A-03198

1 Principal Investigator: Dr. S. Erny

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3 Title of Project:

Wheezing-associated respiratory disorders and hypoxemia in hospitalized children under 5 years of age in rural Bangladesh.

4 Starting date: As soon as funding is provided

5 Date of completion: 1 year after initiation

6 Total budget requested: US$ 49,688

7 Funding source:

* Pulse oximeter: University of Basel, Switzerland
* Immunofluorescence: WHO Programme for the Control of Acute Respiratory Infections
* Remaining part: (US$ 49,688) yet to be determined

8 Head of Programme:

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submission to ERC: 15th April 1993

9 Abstract

To date only limited information is available on the epidemiology of the different clinical diagnoses included in the term acute lower respiratory infections (ALRI). ALRI includes pneumonia, bronchitis, tracheobronchitis, bronchiolitis and infection-induced wheezing. There is considerable overlap in the clinical presentation of these disorders. Often one finds a lack of clear case definitions in the literature.

Bronchiolitis, infection-induced wheezing, and asthma have similarities in pathophysiology, clinical presentation and partly in treatment. We therefore group these 3 diagnoses under the term "wheezing-associated respiratory disorders" (WARD).

In this prospective study we want to determine the contribution that WARD make to severe, life - threatening disease in children under five years of age hospitalized with respiratory problems in rural Bangladesh.

The overall aim of this study is to find out how WARD can fit in with WHO ALRI treatment programs. For this purpose baseline data will be collected on prevalence, clinical presentation, hypoxemia and viral etiology of WARD in our study population; that is, the cases admitted to Matlab hospital according to WHO diagnostic criteria for pneumonia.

In particular we want to describe the association of hypoxemia with simple clinical signs and with viral etiology.

Hypoxemia will be detected by pulse oximetry.

The study will answer questions regarding case detection and referral criteria for ALRI and WARD and at the same time it will raise new questions about prevention and treatment for these disorders. It is not the aim of this study to test any treatment, but such studies will be necessary subsequently.

10 Aims of project

10.1 Introduction

Our study population is a random sample of infants and young children referred to Matlab ICDDR,B hospital with presumed ALRI or asthma. For case definitions refer to chapter 13.3.

Our two **main outcome variables** are **oxygen saturation (continuous variable)** and **need for hospitalization** (yes / no = categorical variable).

Need for hospitalization will be assessed by:
* Pulse oximetry * Chest X-ray findings (by pediatric radiologist) * independent chart review by two pediatricians

Table 1: Need for hospitalization

Symptoms and clinical signs which can be assessed without a stethoscope by Paramedical Health Workers will be evaluated in this research.

The main signs are:	**The main symptoms are:**
* tachypnoea * dyspnoea * apnoea * chest indrawing * audible wheezing * "noisy breathing" * abnormal drowsiness * cyanosis	* fast breathing * difficult breathing * stops breathing * chest indrawing * audible wheezing * "noisy breathing" * abnormal drowsiness * cyanosis * inability to feed

Table 2: Respiratory signs and symptoms evaluated
(for definitions refer to chapter 13.3)

10.2 General aims

The aim of this research is to test the following hypotheses for this study population:

I.) The mean oxygen-saturation is lower in WARD than in radiographic or WHO defined pneumonia.

II.) A scoring system based on above clinical signs and symptoms (Table 2) can predict different levels of oxygen-saturation, and thus need for oxygen therapy and need for hospitalization (Table 1).

III.) The mean oxygen-saturation is lower in children with RSV infection than in children with all other respiratory viruses taken together or with no virus detected.

IV.) WARD, asthma, and RSV make up a significant proportion of the children requiring hospitalization in the study population.

10.3 Specific aims

In order to test these hypotheses we chose the following specific aims:

I.) To determine the mean oxygen-saturation in children with wheezing-associated respiratory disorders (WARD) and compare it with the mean oxygen-saturation among children with radiographic pneumonia in the study population.

II.) To develop and test a scoring system based on above clinical signs and symptoms (Table 2) which can best predict different levels of oxygen saturation and need for hospitalization (Table 1) in the study population.

III.) To determine the mean oxygen-saturation in children with RSV infection as compared to children with other or no viral infection in the study population.

IV.) To determine the proportion of WARD, asthma and RSV infection among the cases needing hospitalization.

10.4 Secondary aims

I.) For the seven respiratory viruses screened for in this study population, we will obtain the following descriptive information:

* Rates of positivity in different age groups
* Types of associated disease
* Seasonal variation

II.) To determine the prevalence of hypoxemia for the following diagnostic categories:

* WHO pneumonia
* WHO moderate ALRI
* WHO severe ALRI
* WHO very severe disease

} (6)

* ALRI needing oxygen therapy according to WHO criteria (6)
* Radiographic pneumonia
* Bronchiolitis
* Bronchiolitis with pneumonia
* Infection-induced wheezing
* Infection-induced wheezing with pneumonia
* Asthma

} chapter 13.3

* ALRI or WARD with RSV infection
* ALRI or WARD with other / no respiratory viral infection

III.) To determine sensitivity and specificity for the clinical signs and symptoms listed in Table 2 to predict above diagnostic categories and hypoxemia.

IV.) In a separate protocol response to oxygen therapy, predictors of response to oxygen treatment and short and long-term outcome will be analyzed for the above diagnostic categories. Main outcome variable will be mean time of resaturation in hypoxemic patients. (That protocol is now in preparation.)

10.5 Significance

10.5.1 WHO case management research priorities

The WHO Programme for the Control of Acute Respiratory Infections advocated in July 1992, the following case management research priorities for the assessment and classification of pneumonia in children age 2 months to 5 years:

> "- Identify the signs or symptoms that best identify children with severe pneumonia (and very severe disease) who are at higher risk of death and would benefit from hospital care (parenteral antibiotics, oxygen, greater clinical expertise, and more nursing care.)
> - Assess the prevalence of significant hypoxemia amongst children with pneumonia.
> - Evaluate the performance of the ARI protocol, including the management of children with wheezing, at first level facilities." (1)

Our study will address all of these priorities, but in addition pay special attention to wheezing-associated respiratory disorders.

To summarize, this study will have implications for case management and prevention of ALRI and WARD.

10.5.2 Implications for treatment

The study will show whether WARD contributes significantly to severe disease, and how urgent the need for specific treatment for these disorders is. It is NOT the aim of this study to determine what treatment this should be. Several options are available and need to be discussed. The improved understanding of the epidemiology of WARD will help in directing further studies to address feasibility, safety, efficacy and affordability of specific treatment to be employed at different levels of the health care system. The questions will be: What drug for what indication and age group, given by what route and what type of health worker ?

Treatment for wheezing disorders is already included in WHO guidelines for treatment of ALRI (6), but the recommended bronchodilator therapy by inhalation is not yet available in many parts of the developing world. In order to decide what priority the introduction of such specific antiobstructive therapy should be, we must know how much WARD contributes to severe, potentially fatal disease.

If we know the prevalence of hypoxemia in ALRI and WARD this will help deciding what priority the introduction of oxygen therapy or strengthening of oxygen supplies for peripheral hospitals in rural Bangladesh should get.

10.3.3. Implications for prevention

If WARD and RSV contribute in a major way to severe disease, their prevention must be given priority:

- RSV vaccine development and testing.
- Prevention of nosocomial infection with RSV - avoiding over-crowded wards especially during RSV epidemics. For example treating as many cases as possible outside the hospital.

11 Ethical implications

11.1 Nasopharyngeal aspirates

Nasopharyngeal aspirates are taken from the included children for research purpose only - the results will not influence treatment. The procedure is not more invasive than giving oxygen therapy by nasopharyngeal catheter. There is a limited danger of physical harm, nosebleeding occasionally occurs.

We include a consent form (App 3) and leave it to the Ethical Review Committee to decide whether written consent is needed. We suggest that oral consent should be sufficient.

11.2 Pulse oximetry

Pulse oximetry is a completely noninvasive technique. As usual with other diagnostic procedures, the mothers will be informed what this is for, but no written consent is needed. For the individual patient, pulse oximetry offers only advantages, because hypoxemia will easily be detected and oxygen inhalation will be given to hypoxemic patients. Continuous supply of oxygen is ensured through the ARI umbrella protocol (cylinders) and a new oxygen concentrator machine.

11.3 Other investigations

Other investigations are only ordered if justified for optimal clinical care.

12 Background

12.1 Epidemiology of ALRI

Important new information on the epidemiology of acute lower respiratory infections (ALRI) in preschool children in developing countries has been gained in the last ten years. For example the BOSTID studies have coordinated a unique series of both community and hospital based longitudinal studies on incidence and etiology of ALRI in children under 5 years from 4 continents (2). Important outcomes of the BOSTID studies were:

- viral agents were recovered more frequently than bacterial agents.
- Respiratory Syncytial Virus (RSV) was the virus most frequently identified.
- case-fatality ratios were highest among the youngest of children, especially among young infants (3).

Major problems still remain however, in spite of all the descriptive epidemiological information on ALRI:

- The long list of possible differential diagnoses included under ALRI makes the diagnosis imprecise.
- The important clinical overlap between many of these differential diagnoses is not well delineated.
- The lack of generally accepted gold standards for even the diagnosis of pneumonia makes is difficult to compare patients and different studies.

12.2 Wheezing-associated respiratory disorders (WARD)

Bronchiolitis, infection-induced wheezing and asthma are all considered under the term wheezing-associated respiratory disorders. Although asthma differs in that infection does not need to be present, viral infection triggering asthma is well known and asthmatic patients seem to suffer more frequent and severe ALRI's. There is evidence that children with bronchiolitis are at increased risk of recurrent wheezing attacks, persistent bronchial hyperreactivity and asthma in later childhood, although a causal association has not been established.

The public health importance of these diseases is very clear in industrialized countries: bronchiolitis is a major reason for hospital admissions in infants, and asthma is the most prevalent chronic disease of childhood. Several studies have shown increasing prevalence and mortality of asthma in western countries, but little information is available on the epidemiology of WARD in developing countries. Some authors assume that children in the third world do not die of asthma, but this may be due to underreporting, which may also account for some of the geographic variations.

Cherian et al (4) have recently reported from South India a high proportion (35 %) of bronchiolitis among a mixed outpatient and inpatient population of young children with ALRI. In the same study almost 100 % (113/114) of the infants with bronchiolitis had tachypnoea and/or chest indrawing, thus fulfilling the WHO diagnostic criteria for pneumonia. On the other hand one third of these bronchiolitis cases also had radiological evidence of pneumonia, thus confusing the diagnosis of bronchiolitis with radiographic pneumonia.

It has been suggested before that case definitions for epidemiological studies should be mutually exclusive, but the above example clearly illustrates how difficult this is to achieve.

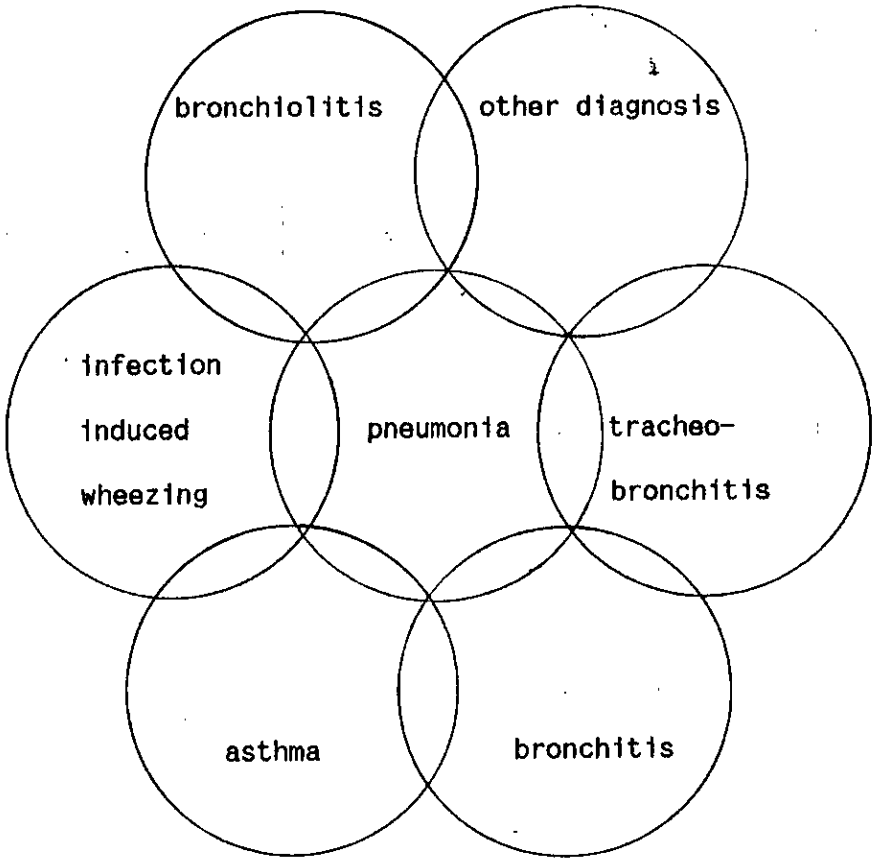

Fig. ALRI and WARD - How much overlap is there in clinical presentation ?

12.3 Standardized ALRI case management

The aim of WHO promoted ALRI intervention programs is to reduce ALRI related mortality worldwide. The main target disease is bacterial pneumonia and the principal strategy of treatment programs is standardized case management (5). This approach is based upon algorithms for diagnosis, referral and treatment of ALRI cases at all levels of the health system and in the community itself (6) and (App 1).

12.3.1 Standardized case detection

For the detection of severe ALRI the use of simple clinical signs is very promising since they can easily be taught to Paramedical Health Workers and mothers. It is also essential that parents recognize these signs, since ALRI can often lead to death within a few days.

Studies have shown good sensitivity and specificity for tachypnoea and chest indrawing as clinical signs of pneumonia, especially if the cutoff point for tachypnoea is adjusted for different age groups (7).

The problem remains however that interobserver agreement for respiratory signs is not very good, with kappa values usually not exceeding 0.5. Wang et al (8) found kappa of 0.38 for respiratory rate, 0.31 for wheeze and 0.25 for chest retraction in infants hospitalized with ALRI. In contrast kappa for oximetry was 0.88.

> "The statistic most often used to measure agreement between two observers on a dichotomous variable is kappa (K), defined as the agreement beyond chance divided by the amount of agreement possible beyond chance:
>
> $$K = O - C / 1 - C$$
>
> where O is the observed agreement and C is the chance agreement." (9)

For the interpretation of kappa values no absolute definitions are possible, but the following guidelines taken from Altman (10) can help:

Value of K:	Strength of agreement:
< 0.20	poor
0.21 - 0.40	fair
0.41 - 0.60	moderate
0.61 - 0.80	good
0.81 - 1.00	very good

Recently Mullholland et al (11) and Shaw et al (12) have shown that hypoxemia detected by pulse oximetry was the single best predictive sign for the need of hospitalization in infants with bronchiolitis.

12.3.2 Standardized treatment

In WHO promoted programs antibiotics are given to all children with moderate to severe ALRI, knowingly including those with viral infections (5). A second mainstay of treatment is oxygen given to severe, hospitalized cases.

13 Methods

13.1 Study type

This is a prospective study. It must be carried out for at least one year because seasonal variation of the studied disorders is expected and must be documented.

13.2 Eligibility criteria

All children under five years of age admitted with presumed ALRI or asthma (as defined under 13.3) to the ARI ward of Matlab ICDDR,B Hospital are eligible for inclusion in the study.

Most cases admitted to the ARI ward are referred by Community Health Workers previously trained according to WHO guidelines to detect moderate to severe ALRI.

13.3 Case definitions used as eligibility criteria

The following case definitions for ALRI and asthma are used as eligibility criteria:

A case of asthma is defined as:
= Acute episode of cough and/or wheezing and/or dyspnoea in a child older than one year with history of similar attacks. Further supporting the diagnosis are response to bronchodilator therapy and a family history of "hapani" (= Bangla term for asthma), but this is not required for inclusion.

A case of ALRI is defined as:
= at least one of the following signs present:

- tachypnoea > 60/min in infants up to 2 months of age
  > 50/min in infants from 2 to 12 months
  > 40/min in children from 1 to 5 years
- chest indrawing (subcostal)
- crackles (on auscultation)
- wheezing (audible with or without a stethoscope)
- cyanosis

This case definition follows the one designated by BOSTID (2) with the only differences being in the age-adjusted cutoff for tachypnoea and "crackles" replacing the term "rales".

Lung sound classification

(following the American Thoracic Society Nomenclature (14))

* crackles = discontinuous, interrupted explosive sounds
  (the terms crepitations or rales are often used as synonyms, but should not be used for the study)
* wheeze = continuous sounds, high pitched, a hissing sound
* rhonchus = continuous sounds low pitched, a snoring sound
* apnoea = stops breathing for more than 10 seconds

13.4 Entry of subjects into study

As summarized in the flow chart in Appendix 2 the following procedure is used to select subjects for entry into the study:

1.) One of the two study doctors is called to see each patient newly admitted to ARI ward of Matlab ICDDR,B Hospital during 5 working days per week.
2.) For each child admitted, the study doctor decides whether the eligibility criteria are met.
3.) From all the eligible children, a random sample is taken, using opaque sealed serially numbered envelopes.
4.) For the children chosen by random sampling, informed consent is obtained (consent form: App 3).
5.) For all included children, full examination and data collection is carried out by one of the study doctors .

Repeated admissions

Children who have been included before and are admitted for a second or third time during the study period are still eligible for inclusion, but if included, nasopharyngeal aspirates will not be taken.

13.5 Data collection

Full examination of all included patients must follow the steps summarized in the flow chart, Appendix 4, in this order:

1.)	Full medical history and physical examination	13.5.1
2.)	Pulse oximetry	13.5.2
3.)	Nasopharyngeal aspirate	13.5.3
4.)	Chest X-ray	13.5.4

13.5.1 Medical history and physical examination

Full medical history and physical examination will be recorded on preprinted admission forms (App 5) by one of the study doctors, S.E. and R.S. Only after this is completed, will pulse oximetry be performed. History taking and examination of the child should follow the order given on the admission form. For example it is important to ask first the symptoms volunteered by the mother, before asking her for specific symptoms. The respiratory rate must be counted and chest indrawing observed first, when the child is not crying, before disturbing the child with more "invasive" examinations like palpation of the abdomen, or looking into throat or ears.

13.5.2 Pulse oximetry

Measuring the oxygen saturation of hemoglobin transcutaneously is a noninvasive diagnostic technique and has been suggested for scientific use in the third world (14). It is a safe, painless, well established and easy-to-handle diagnostic tool, which is now routinely used in the West.

"An oximeter is a spectrophotometric device which measures the differential absorbtion of light by oxy- and deoxyhemoglobin and reports the oxyhemoglobin saturation" (15).

We use the machine PULSOX 5 produced by MINOLTA, Japan. This is a portable, battery driven two-wavelength pulse oximeter, which is used in infants and neonates with the sensor UD-5 (App 6).

In order to minimize movement artifacts, the measurement is made when the child is in a quiet state, preferably sleeping. The sensor is applied to the hand or foot in infants and to a finger in older children.

Over 5 minutes pulse rate and oxygen saturation (SaO2) are recorded on preprinted forms (App 7) simultaneously every 15 seconds with the help of a stopwatch. On this form state of activity of the child is also recorded. At the beginning and end of this measurement, the pulse rate is counted over 1 minute by auscultation and recorded. Low readings of SaO2 with simultaneous low readings in pulse rate (>20 heartbeats lower than mean obtained from auscultation) are considered to be caused by movement artifacts and therefore excluded from analysis. For the remaining values the mean is calculated and used for further analysis.

13.5.3 Nasopharyngeal aspirates and virology

Nasopharyngeal aspirates will be taken from all included children, following the instructions in the flow chart (App 4).

Samples will be stored in Matlab at 4 degrees C and transported once a week in a cool box to Dhaka ICDDR,B Laboratory Science Division (LSD), where Enzyme linked Immunosorbent Assay (ELISA) will be performed by G.P. and L.U. Detailed procedures will follow instructions used in the Laboratory for Virology in Children's Hospital, University of Basel, Switzerland (App 8).

In addition, fixed slides will be prepared for Immuno-fluorescence (IFAT) to be done by WHO Reference Laboratory in Stockholm. These slides will be prepared according to specifications given by the WHO Programme for Control of Respiratory Infections (App 9). The slides will be stored in special containers provided by WHO and send to Stockholm every 3 months by DHL.

Screening will be done for the following viruses both by IFAT and ELISA:

- Respiratory Syncytial Virus
- Adenovirus
- Influenzavirus A
- Influenzavirus B
- Parainfluenza 1
- Parainfluenza 2
- Parainfluenza 3

13.5.4 Chest X-rays

Chest X-rays (frontal posteroanterior and lateral) will be taken by a X-ray technician within 24 hours after admission, but ideally on the day of admission. In his/her absence (vacation or illness), replacement must be organized.

The interpretation of coded chest X-rays will be done by a group of pediatric radiologists who do not get the clinical data. This will be organized through WHO Programme for the Control of Acute Respiratory Infections.

13.5.5. Other investigations

Other investigations such as complete blood count, throat swabs for bacteriology, urine tests and blood cultures will only be carried out at the discretion of the treating doctor, but not on a routine basis. From severely ill children a blood culture will be taken. From children who are clinically anemic, capillary blood will be taken for determination of hematocrit.

For children with the clinical picture of tropical pulmonary eosinophilia, as described in (16), with eosinophilia > 2000/mm^3 blood and suggestive chest X-ray, blood will be examined for filaria. For this purpose, blood samples must be taken between 9 pm and 2 am at night.

13.6 Followup

During daily followup until discharge respiratory signs will be observed and pulse oximetry performed and results recorded on preprinted forms (App.7 and 10). Followup for respiratory morbidity and mortality will be through Record Keeping System (RKS) until 3 months after discharge.

13.7 Controls

13.7.1 Reference intervals for oxygen saturation and respiratory rate

Hypoxemia will be defined as oxygen saturation (SaO_2) more than 2 standard deviations below the mean of SaO_2 determined in a group of age stratified children randomly chosen from the community. The random sample will be obtained from Block A using Record Keeping System.

The six age groups used are:

0 - 2 months	12 - 24 months
2 - 6 months	24 - 36 months
6 - 12 months	36 - 60 months

Only children who had no cough, nasal discharge or difficult breathing in the last 3 days are included. Respiratory rate will be counted at the same time, when the child is not crying.

The sample size is calculated for comparison of means between groups, using the nomogram given by Altman (10, p. 456), with standardized difference = 1, power = 0.9 and significance level = 0.05 we get N = 40 for each age group, so totally 240 healthy children will be examined.

13.7.2 Virus carrier rates in matched controls without ARI

Virus carrier rates will be determined in 303 controls matched for age, sex and time of admission who are admitted to Diarrhoea Treatment Centre of Matlab Hospital with diarrhoea, and did not have cough, a running nose or difficult breathing in the last 3 days.

A control should be found within 2 weeks (maximum 4 weeks) of admission for each case. Nasopharyngeal aspirates will be taken on the day of admission of the control.

13.8 Data entry and analysis

Data entry into dBaseIV format will be done in Matlab. In order to minimize data entry errors, double entry will be performed.

Analysis will be done using SPSS.

13.8.1 Univariate analysis

For specific aims I.) and III.) (page 3) analysis will be based on the comparison of mean arterial oxygen saturation in two groups, namely:

Specific aim I.): wheezing group and non-wheezing group
Specific aim III.): RSV positive and RSV negative group.

The difference in mean oxygen saturation between these groups will be calculated and also the confidence interval for this difference.

13.8.2 Multivariate analysis

Main outcome variable = oxygen saturation

(continuous outcome variable)

A multivariate linear regression model will be developed that can best predict different levels of oxygen saturation from simple clinical signs and symptoms.(Table 2, p. 2)

From this model, a clinical scoring system will be developed.

Main outcome variable = hypoxemia / need for hospitalization

(categorical outcome variable)

A multivariate logistic regression model will be developed that can best predict hypoxemia and/or need of hospitalization (Table 1) from clinical signs and symptoms.

Also from this model a clinical scoring system will be developed.

13.8.3. Kappa statistics

To describe interobserver agreement, kappa statistics will be calculated for physical findings in a subsample of children, who are examined by the two study doctors immediately after each other, when they do not know each other's results.

13.9 Case definitions used for analysis

13.9.1 A case of radiographic pneumonia is defined as:

= signs of ALRI plus radiological signs of pneumonia, when the coded X-ray is read by a group of 3 independent pediatric radiologists who will not get any clinical information. Required agreement is between 2 out of 3 radiologists.

13.9.2 A case of WHO defined pneumonia is:

= at least one of the following signs present:

- tachypnoea > 60/min in infants up to 2 months of age
  > 50/min in infants from 2 to 12 months
  > 40/min in children from 1 to 5 years
- chest indrawing (subcostal)
- crackles (on auscultation)
- wheezing (audible with or without a stethoscope)
- cyanosis

13.9.3 A case of upper respiratory infection (URI) is defined as

= at least one of the following signs present:

- sore throat, cough, purulent nasal discharge, or earache / discharge without signs of ALRI.

(follows BOSTID definition (2) exactly .)

13.9.4 A case of bronchiolitis is defined as:

= Tachypnoea (as defined under 13.9.2), chest indrawing and generalized expiratory wheezing with or without crackles in an infant (less than 12 months) who suffered from URI within the last 10 days. No history of similar episode. Further supporting the diagnosis, but not a necessary feature are signs of hyperinflation on the chest X-ray (13) .

Radiological signs of hyperinflation are: depressed diaphragm, increased radiolucency, increased AP diameter on lateral films.

13.9.5 A case of RSV bronchiolitis is defined as:
= above clinical diagnosis plus detection of RSV antigen in nasopharyngeal aspirate.

13.9.6 A case of bronchiolitis with radiographic pneumonia is defined as:
= a case fulfilling the conditions under 13.9.1 and 13.9.4 with or without detection of RSV.

13.9.7 A case of infection-induced wheezing is defined as:
= case of ALRI with generalized expiratory wheezing if child is older than one year with the first episode of wheezing or an infant with repeated episodes. This is a grey-zone category for the wheezing child who does not meet the criteria for asthma or bronchiolitis.

13.10 Sample size calculation:

Based on above outline for analysis the sample size calculation is performed separately for specific aims I.) to III.), always using the formula:

$$\frac{\epsilon}{\sigma\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}} = Z_\alpha + Z_\beta$$

where the following variables remain constant:
ϵ = difference to be detected = 0.02
σ = standard deviation = 0.02
Z_α = 2.575 for significance level 0.01
Z_β = 1.645 for 95 % power of the test

and only n1 and n2 change for the three specific aims:
n1 and n2 = size of populations compared

Specific aim:	Assumptions about n1 and n2:	Results:
I.)	n1 / n2 = n wheezing / n non-wheezing = 1 /4	n1 = 23 n2 = 89 N = 112
II.)	n1 / n2 = n high clinical score / n low clinical score = 1 / 9	n1 = 20 n2 = 178 N = 198
III.)	n1 / n2 = RSV pos. / RSV neg. = 3 / 7	n1 = 26 n2 = 60 N = 86

If we expect 10% loss due to absconding and discharge on request and 25% loss due to non-pneumonia and non-WARD ALRI(= bronchitis, tracheobronchitis) then we need an initial sample of 305 cases to get the required 198 cases for final analysis (194x100/65).

The number of admissions of cases with ALRI and WARD to the ARI ward of Matlab ICDDR,B hospital were: 760 in 1991 and 540 in 1992. If we take the median of the two years, we would project 650 admissions for 93/94, out of which around 5/7 would be expected on working days = 464.

If we take a random sample of 8/10 of all eligible children admitted on 5 working days per week, we would still get the required 303 cases, even if we would have a year with admission numbers as low as in 1992 (540 x 5/7 x 8/10 = 308). On the other hand, if we expect another year with peak admissions, even higher than 1991, say 800 admissions, we would expect to include 514 children. If we want a true, predefined random sample, we can not predict the precise number of children included, but we must plan the budget for the maximal number.

The total number of nasopharyngeal aspirate samples processed will be:

- at least: 303 cases plus 303 controls = 606
- maximal: 540 cases plus 303 controls = 843

13.11 Treatment of subjects

The treatment follows WHO guidelines (6).

14 ABSTRACT SUMMARY FOR ETHICAL CONSIDERATION

1.) Subject population : children under 5 years of age referred to Matlab hospital with acute lower respiratory tract infections (ALRI) or wheezing-associated respiratory disorders (WARD). The rationale for using this specific group of subjects lies in the high morbidity and mortality associated with these disorders in this age group.

2.) Potential risk for the subjects included in study:
when taking nasopharyngeal aspirates (NPA) nosebleeding occasionally occurs.
The alternative to NPA would be to take throat swabs, but several studies have shown a lower sensitivity for the detection of respiratory viruses in throat swabs as compared to NPA's.

3.) Procedure for minimizing the risk of nosebleeding: the catheter must be inserted gently.
For the case of persistent nosebleeding, medical gauze is kept ready for tamponade.

4.) Safeguarding confidentiality: questionnaires and PC will be kept under lock and key.

5.) (a) We include a consent form, but we suggest that only verbal informed consent is obtained, since taking NPA's is not more invasive than giving oxygen by nasopharyngeal catheter, and is only done once.
(b) Withholding of information: not applicable.
(c) No treatment will be given for minor, selflimited nosebleeding. Treatment will be available for persistent nosebleeding.

6.) The interview consists of taking the full medical history, taken by a medical doctor, which would be taken anyway, also without this protocol.

7.) The benefit for the individual subject is obviously that hypoxemia will be accurately and non-invasively detected and supplemental oxygen inhalation therapy will be given to hypoxemic patients by nasopharyngeal catheter.
Benefits for society: The gained understanding of the epidemiology of severe hypoxemic ALRI and WARD will help directing further planning of health interventions, for prevention, timely detection, and treatment of these disorders.

8.) The study requires sampling of nasopharyngeal aspirates. Blood is drawn only if needed for optimal medical care, not routinely.

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16 Flow chart

January 1993:	Internal review and adjustments after review
February:	external review and adjustments after review
March:	Research Review Committee
April:	Ethical Review Committee
May:	Find funding
	Ordering Laboratory Equipment
	Setting up of ELISA in Laboratory Science Division
June:	Start of study
June 1994:	Completion of data collection
July/Aug:	Data analysis
September:	Writing up of results

17 Budget

Personnel:	level:	months:	rate/mth	total
International staff:				
1 MO	MO	12	-	-
National staff:				
1 Med. officer:	NOB	6	690	4,140
S.H.A.	GS4	6	450	2,700
X-Ray Technician	GS3	12	260	3,120
H.A.	GS3	6	340	2,040
Lab Assistant	GS3	3	260	780
				12.780

Operating costs:	each	required	total
ELISA Kits (7 viruses)*	17	850	14,450
X-Ray films	2	1200	2,400
Capital equipment:			
2 filing cabinets	200	2	200
Computer equipment			3,200
Oxygen concentrator*			1,600
Suction machine*			900
Inhalation equipment*			600
Travel:			
Matlab transport			1,000
Interdept services:			
Mailing costs (IFAT slides to Sweden)			500
Computer diskettes, printing costs, stationary			300
AL DIRECT COSTS			37,930
OVERHEADS (31%)			11,758
GRAND TOTAL			**49,688**

* = including spareparts and shipment costs

18 POSTSCRIPT

I would like to thank the following people who are not included in the protocol but reviewed it at earlier stages and gave valuable comments:

- Prof. RB. Sack, Associate Director, CHD & LSD, ICDDR,B
- Dr. M.Desmet, CHD, ICDDR,B
- Dr. AM. Vanneste, CHD, ICDDR,B
- PD Dr. med. M. Rutishauser, pediatrician / pulmonologist
  Children's Hospital, University of Basel, Switzerland.
- Dr. A. and R. Ronan, CSD, ICDDR,B
- D. Leonard (editing)

As well as Dr. Bairagi, Director Population Studies for his statistical advise.

19 Appendix / INDEX

✓ = included in this edition

ANNEX 2: First-level facility ARI case management charts

MANAGEMENT OF THE CHILD WITH COUGH OR DIFFICULT BREATHING

ASSESS

ASK:

- How old is the child?
- Is the child coughing? For how long?
- Age 2 months up to 5 years: Is the child able to drink?
  Age less than 2 months: Has the young infant stopped feeding well?
- Has the child had fever? For how long?
- Has the child had convulsions?

LOOK, LISTEN:

(Child must be calm)

- Count the breaths in one minute.
- Look for chest indrawing.
- Look and listen for stridor.
- Look and listen for wheeze. Is it recurrent?
- See if the child is abnormally sleepy, or difficult to wake.
- Feel for fever, or low body temperature (or measure temperature).
- Look for severe undernutrition.

CLASSIFY THE ILLNESS

Does child have danger signs?

THE CHILD AGE 2 MONTHS UP TO 5 YEARS

SIGNS:
- Not able to drink,
- Convulsions,
- Abnormally sleepy or difficult to wake,
- Stridor in calm child, or
- Severe undernutrition.

CLASSIFY AS: VERY SEVERE DISEASE

TREATMENT:
- Refer URGENTLY to hospital.
- Give first dose of an antibiotic.
- Treat fever, if present.
- Treat wheezing, if present.
- If cerebral malaria is possible, give an anticonvulsant.

THE YOUNG INFANT (AGE LESS THAN 2 MONTHS)

SIGNS:
- Stopped feeding well,
- Convulsions,
- Abnormally sleepy or difficult to wake,
- Stridor in calm child,
- Wheezing, or
- Fever or low body temperature.

CLASSIFY AS: VERY SEVERE DISEASE

TREATMENT:
- Refer URGENTLY to hospital.
- Keep young infant warm.
- Give first dose of an antibiotic.

Does child have pneumonia?

SIGNS:	• Chest indrawing. [If also recurrent wheezing, go directly to ▸ *Treat Wheezing*]	• No chest indrawing, and • Fast breathing (50 per minute or more if child 2 months up to 12 months; 40 per minute or more if child 12 months up to 5 years).	• No chest indrawing, and • No fast breathing (Less than 50 per minute if child 2 months up to 12 months; Less than 40 per minute if child 12 months up to 5 years).
CLASSIFY AS:	SEVERE PNEUMONIA	PNEUMONIA	NO PNEUMONIA: COUGH OR COLD
TREATMENT:	▸ Refer URGENTLY to hospital. ▸ Give first dose of an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. (If referral is not feasible, treat with an antibiotic and follow closely.)	▸ Advise mother to give home care. ▸ Give an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. ▸ Advise mother to return with child in 2 days for reassessment, or earlier if the child is getting worse.	▸ If coughing more than 30 days, refer for assessment. ▸ Assess and treat ear problem or sore throat, if present (see chart). ▸ Assess and treat other problems. ▸ Advise mother to give home care. ▸ Treat fever, if present. ▸ Treat wheezing, if present.

SIGNS:	• Severe chest indrawing, or • Fast breathing (60 per minute or MORE).	• No severe chest indrawing, and • No fast breathing (LESS than 60 per minute).	
CLASSIFY AS:	SEVERE PNEUMONIA	NO PNEUMONIA: COUGH OR COLD	
TREATMENT:	▸ Refer URGENTLY to hospital. ▸ Keep young infant warm. ▸ Give first dose of an antibiotic. (If referral is not feasible, treat with an antibiotic and follow closely.)	▸ Advise mother to give the following home care: ▸ Keep young infant warm. ▸ Breast-feed frequently. ▸ Clear nose if it interferes with feeding. ▸ Return quickly if: ▸ Breathing becomes difficult. ▸ Breathing becomes fast. ▸ Feeding becomes a problem. ▸ The young infant becomes sicker.	

	Reassess in 2 days a child who is taking an antibiotic for pneumonia:		
SIGNS:	WORSE • Not able to drink. • Has chest indrawing. • Has other danger signs.	THE SAME	IMPROVING • Breathing slower. • Less fever. • Eating better.
TREATMENT:	▸ Refer URGENTLY to hospital.	▸ Change antibiotic or Refer.	▸ Finish 5 days of antibiotic.

TREATMENT INSTRUCTIONS

▶ Give an Antibiotic

- Give first dose of antibiotic in clinic.
- Instruct mother on how to give the antibiotic for five days at home (or to return to clinic for daily procaine penicillin injection).

AGE or WEIGHT	COTRIMOXAZOLE (trimethoprim + sulphamethoxazole) ▸ Two times daily for 5 days			AMOXYCILLIN ▸ Three times daily for 5 days.		AMPICILLIN ▸ Four times daily for 5 days.		PROCAINE PENICILLIN ▸ Once daily for 5 days.
	Adult Tablet single strength (80 mg trimethoprim + 400 mg sulphamethoxazole)	Pediatric Tablet (20 mg trimethoprim + 100 mg sulphamethoxazole)	Syrup (40 mg trimethoprim + 200 mg sulphamethoxazole per 5ml)	Tablet 250 mg	Syrup 125 mg in 5 ml	Tablet 250 mg	Syrup 250 mg in 5 ml	Intramuscular injection
Less than 2 months (< 5 kg)*	1/4*	1*	2.5 ml*	1/4*	2.5 ml	1/2	2.5 ml	200,000 units
2 months up to 12 months (5-9 kg)	1/2	2	5 ml	1/2	5 ml	1	5 ml	400,000 units
12 months up to 5 years (10-19 kg)	1	3	7.5 ml	1	10 ml	1	5 ml	800,000 units

+ Give oral antibiotic for 5 days at home only if referral is not feasible.

* If the child is less than 1 month old, give 1/2 pediatric tablet or 1.25 ml syrup twice daily. Avoid cotrimoxazole in infants less than one month of age who are premature or jaundiced.

▶ Advise Mother to Give Home Care *(For the child age 2 months up to 5 years)**

▶ Feed the child.
- Feed the child during illness.
- Increase feeding after illness.
- Clear the nose if it interferes with feeding.

▶ Increase fluids.
- Offer the child extra to drink.
- Increase breast-feeding.

▶ Soothe the throat and relieve the cough with a safe remedy.

▶ Most important: In the child classified as having No Pneumonia: Cough or Cold, watch for the following signs and return quickly if they occur:
- Breathing becomes difficult.
- Breathing becomes fast.
- Child is not able to drink.
- Child becomes sicker.

→ This child may have pneumonia.

* See section on young infant for home care instructions for that age group

▶ Treat Fever

- Fever is high (≥ 39 °C).
  - ▸ Give paracetamol.
- Fever is not high (38-39 °C).
  - ▸ Advise mother to give more fluids.

In a falciparum malarious area:
- Any fever, or
- History of fever.
  - ▸ Give an antimalarial (or treat according to your malaria programme recommendations).

- Fever for more than five days.
  - ▸ Refer for assessment.

PARACETAMOL dosage: → Every six hours

Age or Weight	100 mg tablet	500 mg tablet
2 months up to 12 months 6-9 kg	1	1/4
12 months up to 3 years 10-14 kg	1	1/4
3 years up to 5 years (15-19 kg	1 1/2	1/2

FEVER ALONE IS NOT A REASON TO GIVE AN ANTIBIOTIC EXCEPT IN A YOUNG INFANT (AGE LESS THAN 2 MONTHS).

GIVE FIRST DOSE OF AN ANTIBIOTIC AND REFER URGENTLY TO HOSPITAL.

▶ Treat Wheezing

Children with First Episode of Wheezing

If in respiratory distress → Give a rapid-acting bronchodilator and refer.

If not in respiratory distress → Give oral salbutamol.

Children with Recurrent Wheezing (Asthma)

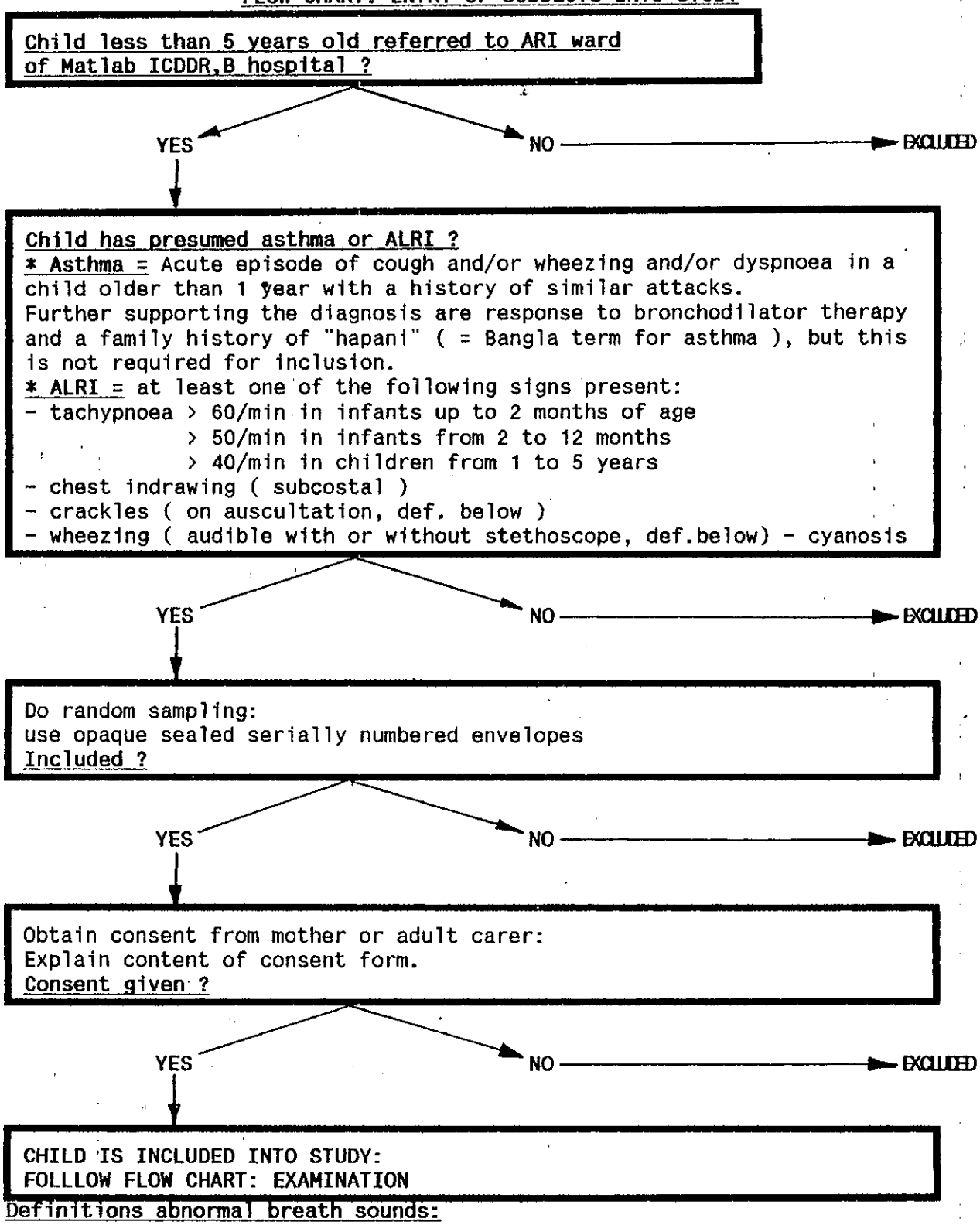
- Give a rapid acting bronchodilator
- Assess the child's condition 30 minutes later:

IF:	THEN:
RESPIRATORY DISTRESS OR ANY DANGER SIGN	→ Treat for SEVERE PNEUMONIA or VERY SEVERE DISEASE (Fever).
NO RESPIRATORY DISTRESS AND:	
FAST BREATHING	→ Treat for PNEUMONIA. Give oral salbutamol.
NO FAST BREATHING	→ Treat for NO PNEUMONIA: COUGH OR COLD. Give oral salbutamol.

RAPID ACTING BRONCHODILATOR		ORAL SALBUTAMOL ▸ Three times daily for five days	
Nebulized Salbutamol (5 mg/ml)	0.5 ml Salbutamol plus 2.0 ml sterile water	AGE or WEIGHT	2 mg tablet	4mg tablet
Subcutaneous Epinephrine (adrenaline) (1 : 1000 = 0.1%)	0.01 ml per kg body weight	2 months up to 12 months (< 10 kg)	1/2	1/4
		12 months up to 5 years (10-19 kg)	1	1/2

APP 2

FLOW CHART: ENTRY OF SUBJECTS INTO STUDY



Definitions abnormal breath sounds:

* crackles = discontinuous, interrupted explosive sounds.
* wheeze = continuous sounds, high pitched, a hissing sound
* rhonchus = continuous sounds low pitched, a snoring sound
(the terms crepitations or rales are often used as synonyms for crackles, but should not be used for the study)

APP 3

CONSENT FORM

We at the ICDDR,B are concerned about the many children with pneumonia or asthma who have infections with viruses. Virus infections can not be treated with antibiotics, but other drugs are sometimes helpful. Also oxygen will help if the child is severely ill.

We want to take some secretion from the nose of your child. We will put a thin plastic tube in his nose and suck out some of the secretion. This will not do any harm to your child. It is almost the same as when we clean the child's nose with a thin plastic tube, which will help him to breath more easily. Very rarely, nosebleeding can occur, but this is not serious.

From this secretion we will check if your child has got a virus infection or not. We need to do this only once, and it will be done just after admission. So there is no need for you to stay any longer in hospital than normal. Your child will be discharged as normal, as soon as he or she has recovered enough.

If you take part in this study you can help us to find out more about virus infections and asthma, which are both a big problem among children in Bangladesh.

You do not have to participate in this study. If you do not want to take part your child will get exactly the same treatment and there will be no disadvantage for him or her.

All the information that we get from this study will be kept under lock and no information about your child will be handed over to other people.

If you agree to take part in this study, please give your signature or thumb print below.

DATE: .....

SIGNATURE OR THUMB PRINT: .....

APP 3b

Bangla translation of consent form

সম্মতি পত্র

আমরা (আই,সি,ডি,ডি,আর,বি) শিশুদের নিমোনিয়া ও হাঁপানি রোগ সম্পর্কে খুবই উদ্বিগ্ন যাহা এক প্রকার ক্ষুদ্র জীবাণু (ভাইরাস) দ্বারা সংক্রমিত হয় । ভাইরাসের সংক্রামন এন্টিবায়টিক দ্বারা চিকিৎসা করা যায় না কিন্তু শিশু গুরুতর অসুস্থ হ'লে অক্সিজেন শিশুর জন্য সহায়ক হয় ।

এই রোগ সম্বন্ধে আরো বিস্তারিত জানার জন্য আমরা আপনার শিশুর নাকের কিছু শ্লেষার নমুনা নিতে চাই । ইহার জন্য শিশুর নাকের ভিতর একটি প্লাষ্টিক টিউব বসিয়ে উহার সাহায্যে নাকের ভিতর হইতে শ্লেষা নেওয়া হবে । ইহাতে আপনার শিশুর কোন ক্ষতি হবে না । ইহা অনেকটা শিশুর নাককে যেভাবে প্লাষ্টিক টিউব দ্বারা পরিস্কার করা হয় সেই ভাবে করা হবে এবং তাহাতে শিশুর শ্বাস-প্রশ্বাসে সুবিধা হবে । কোন কোন সময় ইহাতে নাক হইতে রক্ত আসতে পারে তবে সেটা মারাত্মক বা ক্ষতিকারক নয় ।

সংগৃহিত নাকের শ্লেষা পরীক্ষা করে আমরা দেখব আপনার শিশু ভাইরাস দ্বারা সংক্রমিত হয়েছে কিনা । হাসপাতালে ভর্তি হওয়ার পর এই কাজটা একবারই করা হবে এবং এই পরীক্ষার জন্য আপনার শিশুকে চিকিৎসার জন্য প্রয়োজন এর চেয়ে বেশী সময় হাসপাতালে থাকতে হবে না । শিশু আরোগ্য লাভের সংগে সংগেই তাকে হাসপাতাল থেকে ছেড়ে দেয়া হবে ।

যদি আপনি এই গবেষণায় অংশ গ্রহনে সম্মত হন তবে আপনি আমাদিগকে শিশুদের নিমোনিয়া ও হাঁপানি সম্পর্কে বহু তথ্য দিয়ে সাহায্য করতে পারবেন যাহা বাংলাদেশের শিশুদের জন্য একটা বিরাট সমস্যা সমাধানে সহায়ক হবে । যদি আপনি ইহাতে অংশ গ্রহন নাও করেন তবুও আপনার শিশু নিয়মিত চিকিৎসার কোন অসুবিধা হবে না ।

আপনার শিশুর কাছ থেকে পাওয়া তথ্য গোপনীয়ভাবে রাখা হবে এবং তাহা কাহারও নিকট হস্তান্তর করা হবে না ।

যদি আপনি এই কাজে সম্মত হন তাহলে নিচে আপনার নাম দস্তখত বা টিপ সহি দিন ।

তারিখ _____

দস্তখত বা টিপ সহি _____

APP 4

FLOW CHART: EXAMINATION OF SUBJECTS

1.) TAKE HISTORY AND DO PHYSICAL EXAMINATION FOLLOWING THE ORDER GIVEN ON ADMISSION FORM

2.) PERFORM PULSE OXIMETRY FOLLOWING THE ORDER ON FORM FOR RECORDING PULSE OXIMETRY RESULTS

3.) TAKE NASOPHARYNGEAL ASPIRATE:

* Connect the mucus extractor "Pädiatrie" Vigon 534.10 with vacuum pump.
* The patient sits with head bent backwards.
* If there is not much secretion, irrigate the nose with a little sterile saline solution from a syringe (0.5 to 1 ml per nostril).
* Insert the tube with the bigger diameter (at least 5 to 6 centimeters, not too vertical) and put suction on to get material out.
* Rinse the tube with a little saline solution from the syringe, but dilute as little as possible.
* Disconnect the tubes, close the lid, write identification on specimen container.
* Keep the material in the fridge.
* WEEKLY FORWARDING OF SAMPLES TO DHAKA.

4.) Order X-ray to be done within 24 hours after admission, but ideally on the day of admission.

ICDDR,B-DISC RESEARCH PROJECT DATA INPUT SHEET

Database name: **DPROJ**

Rec. no.: 85 Input date-ISO (005): Rev date-ISO (006):

Title of project (100): Wheezing-associated respiratory disorders and hypoxemia in hospitalized children under 5 years rural Bangladesh

PIs and coinvestigators' name (110): Ezzny S Y. de Francisco A Y. Yunus M Y. Chakraborty J Y. Shaheen R Y. Unicomb L Y. Podder G Y. Gyr K

Organizations involved/ Associated bodies (112): ICDDR,B ~~Centre for Health and Population Research~~ in Bgl

Project number (140): 93-014

Project duration (year only) (143): Starting year ^a Ending year ^b	Project status (144): ☐ Ongoing ☑ Completed	Accession no. (1 65): A- 031982

General note (155):

Descriptors/subjects (300): <Respiratory sounds> x <Anoxemia> Y. <Respiratory tract infections> (Prospective studies) Hypoxemia ?? check (Seasonal variation)

Geographic descriptors (302): (also study place, if applicable) <Bangladesh>	Location (410): REF Call no. (411): ^a^b^c a WS 280 6E65W 1c 1993
Documentalist (430): AM	Budget (516): ~~US$ 49,688~~

Funding information note (530): ~~Entered by~~

Checked by: Approved by: 10/11/93

00085
ID: 20010517
TI: Wheezing-associated respiratory disorders and hypoxemia in hospitalized children under 5 years in rural Bangladesh
PI: Erny S, de Francisco A, Yunus M, Chakraborty J, Shaheen R, Unicomb L, Podder G, Gay K
OA: International Centre for Diarrhoeal Disease Research, Bangladesh
PN: 93-014
AN: A-031982
MD: Respiratory sounds / Anoxemia / Respiratory tract infections / Prospective studies / Seasonal variation
GD: Bangladesh
LN: REF
CN: WS 280/E65w/1993
DT: AM/Anis

00086
ID: 20010517
TI: Antenatal care services in Dhaka, Bangladesh
PI: Nahar Q, Arifeen SE
OA: International Centre for Diarrhoeal Disease Research, Bangladesh
PN: 95-032
AN: A-31945
MD: Health services / Pregnancy / Obstetric care
GD: Bangladesh / Dhaka
LN: REF
CN: WQ 100.JB2/N153a/1996
DT: Anis

00087
ID: 20010517
TI: Obstetric care in a district hospital in Bangladesh: an organizational ethnography
PI: Leppard M, Ross J
OA: International Centre for Diarrhoeal Disease Research, Bangladesh
PN: 95-010
AN: A-31943
MD: Health services / Obstetrics / Obstetrics care / Hospitals, District / Anthropology, Cultural
GD: Bangladesh / Chandpur
LN: REF
CN: WQ 100.JB2/L598o/1995
DT: MN/Anis

00088
ID: 21010517
TI: History of nightblindness: a tool for xerophthalmia screening in Bangladeshi children
PI: Stoll BJ, Molla A, Kabir I
OA: International Centre for Diarrhoeal Disease Research, Bangladesh
PN: 82-009
AN: A-031941
MD: Xerophthalmia / Night blindness
GD: Vitamin A deficiency
LN: REF
CN: WD 110.JB2/S875h/1982
DT: Anis

APP 5

ADMISSSION FORM - PNEUMONIA WARD

PATIENT:	ADMISSION:
ADM.No:	DATE:
NAME:	TIME: ☐ 1 AM ☐ 2 PM
DATE OF BIRTH:	STUDY DOCTOR: ☐ 1 R. Sheheen
AGE: Y M D	☐ 2 S. Erny
SEX: ☐ 1 male ☐ 2 female	

STUDY INCLUSION	Yes	No		Yes	No
Eligible for inclusion ?	☐ 1	☐ 2	*Consent given ?*	☐ 1	☐ 2
Randomization: Included ?	☐ 1	☐ 2	*Included in study ?*	☐ 1	☐ 2

REFERRED FROM FIELD: ☐ 1 CHW ☐ 3 Physician
☐ 2 Other Paramed. Worker ☐ 4 Not referred

HISTORY OF PRESENT ILLNESS:

→ ASK FIRST: *Major Complaints volunteered by carer ?*	*Admitted on questioning?*		*Duration:*
COUGH:	☐ 1	☐ 2	days
FEVER:	☐ 1	☐ 2	days
DIFFICULT BREATHING:	☐ 1	☐ 2	days
CHEST INDRAWING:	☐ 1	☐ 2	days
NOISY BREATHING:	☐ 1	☐ 2	days
FAST BREATHING:	☐ 1	☐ 2	days
INABILITY TO FEED:	☐ 1	☐ 2	days

OTHER (specify) .....

HISTORY OF TREATMENT RECEIVED:

☐ 1 Antibiotics
☐ 2 Histamines
☐ 3 Anti asthma therapy
☐ 4 Other allopathic drugs
☐ 5 Homeopathic treatment

Other (specify) : .....

GIVEN BY: ☐ 1 Qualified Physician ☐ 3 Village Pharmacy
☐ 2 Kobiraj ☐ 4 Caretaker

PHYSICAL EXAMINATION I :

(CHEST)

Appearance: ☐ 1 healthy looking
☐ 2 ill looking ☐ 3 very ill looking

→ RESP. RATE (counted over 1 minute)

→ PULSE RATE (counted over 1 minute)

RR & Pulse counted when child:
☐ 1 sleeping ☐ 4 restless
☐ 2 awake quiet ☐ 5 crying
☐ 3 active ☐ 6 feeding

CHEST SIGNS:

	absent:	slight/mod.	severe
Chest indrawing:			
Subcostal:	☐ 1	☐ 2	☐ 3
Intercostal:	☐ 1	☐ 2	☐ 3
suprasternal:	☐ 1	☐ 2	☐ 3
nasal flaring:	☐ 1	☐ 2	☐ 3

Chest indrawing observed when child:
☐ 1 sleeping ☐ 4 restless
☐ 2 awake quiet ☐ 5 crying
☐ 3 active ☐ 6 feeding

Abnormal breath sounds audible without stethoscope ?

	absent:	slight/mod.	severe:
Wheezing (expiratory)	☐ 1	☐ 2	☐ 3
Stridor (inspiratory)	☐ 1	☐ 2	☐ 3
Noisy breathing	☐ 1	☐ 2	☐ 3

Auscultation:	absent:	slight/mod.	severe	Where?
Crackles:	☐ 1	☐ 2	☐ 3	
Wheezing:	☐ 1	☐ 2	☐ 3	
Rhonchi:	☐ 1	☐ 2	☐ 3	
Reduced breath sounds:	☐ 1	☐ 2	☐ 3	
Bronchial breath sounds:	☐ 1	☐ 2	☐ 3	
Transmitted sounds:	☐ 1	☐ 2	☐ 3	

PHYSICAL EXAMINATION II

(GENERAL)

	absent	slight	moderate	severe:	Remarks:
Restless:	☐ 1	☐ 2	☐ 3	☐ 4	
Dehydrat:	☐ 1	☐ 2	☐ 3	☐ 4	
Anaemia:	☐ 1	☐ 2	☐ 3	☐ 4	
Jaundice:	☐ 1	☐ 2	☐ 3	☐ 4	
Oedema:	☐ 1	☐ 2	☐ 3	☐ 4	
Cyanosis:	☐ 1	☐ 2	☐ 3	☐ 4	
Scabies:	☐ 1	☐ 2	☐ 3	☐ 4	

Neck: ☐ 1 supple ☐ 2 rigid

Fontanelle: ☐ 1 normal ☐ 3 bulging

☐ 2 sunken ☐ 4 closed

Kernig's sign: ☐ 1 absent ☐ 2 present

ABDOMEN	not palpable	not assessed:	palpable	cm below ribs?
Liver:	☐ 1	☐ 2	☐ 3	cm
Spleen:	☐ 1	☐ 2	☐ 3	cm

TEMPERATURE (rectal):

Weight: kg Weight for age: Percentile

Length or Height: cm Height for age: Percentile

		Yes	No		Yes	No
Ears:	Pus from ear	☐ 1	☐ 2	Injected eardrum	☐ 1	☐ 2
	Eardrum seen	☐ 1	☐ 2	Bulging eardrum	☐ 1	☐ 2

	normal:	inflamed:
Throat:	☐ 1	☐ 2
Tonsils:	☐ 1	☐ 2

Other findings:

DIAGNOSIS: 1.) 4.)

2.) 5.)

3.) 6.)

DIFFERENTIAL DIAGNOSIS: 1.) 2.)

Signature of examiner:

COMPLETE HISTORY

(Can be taken after physical examination, pulse oximetry, and taking of nasopharyngeal aspirates are completed)

	No	Yes
Family history of asthma ?	☐ 1	☐ 2
Hx of previous admission with resp. problems ?	☐ 1	☐ 2
Hx of sibling died with respiratory problems ?	☐ 1	☐ 2

		Yes	No
FEEDING HISTORY:	exclusively breastfed ?	☐ 1	☐ 2
	gets water with breastmilk ?	☐ 1	☐ 2
	started weaning at	months	
	fully weaned at	months	

IMMUNIZATION HISTORY: (For children from Observation Area only)

	Yes	No		Yes	No
DPT 1st dose	☐ 1	☐ 2	BCG	☐ 1	☐ 2
DPT 2nd dose	☐ 1	☐ 2	Measles	☐ 1	☐ 2
DPT 3rd dose	☐ 1	☐ 2			

LAST DOSE OF VITAMIN A RECEIVED: (date)

SOCIAL HISTORY:

Crowding	Number of adults or children > 5y	Number of children < 5y	Number of smokers
Sharing same bed most of time			
Sharing same bedroom			

(The complete history can not be taken by S.E., because of the language barrier)

APP 7

OXIMETRY - FORM

PATIENT	MONITORING
ADMISSION No:	DATE:
NAME:	TIME:
DATE OF BIRTH:	BY: ☐ 1 R.Shaheen ☐ 2 S.Erny

PRE-MONITORING EXAMINATION: (count 1 minute)

RESP. RATE:

PULSE RATE:

STATE OF ACTIVITY:

☐ 1 Sleeping ☐ 4 restless
☐ 2 quiet ☐ 5 crying
☐ 3 active ☐ 6 feeding

SENSOR USED: ☐ 1 UD5 ☐ 2 SP8 (adult)

SENSOR APPLIED TO:

☐ 1 palm ☐ 3 forefoot
☐ 2 finger ☐ 4 toe

finger/toe I II III IV V (circle)

THICKNESS OF MEASURING SITE INCLUSIVE SENSOR: mm

OXYGEN RECEIVED: FLOW: l/min

Duration: Stopped:

POST-MONITORING EXAMINATION: (count 1 minute)

RESP. RATE

PULSE RATE

STATE OF ACTIVITY:

☐ 1 Sleeping ☐ 4 restless
☐ 2 quiet ☐ 5 crying
☐ 3 active ☐ 6 feeding

OXIMETRY FORM page 2

ADMISSION No: DATE: TIME:

TIME	SAO2	PULSE	ACTIVITY	MOVE.SENS	REMARKS
0' 00"					
15"					
30"					
45"					
1' 00"					
15"					
30"					
45"					
2' 00"					
15"					
30"					
45"					
3' 00"					
15"					
30"					
45"					
4' 00"					
15"					
30"					
45"					
5' 00"					

ACTIVITY: USE THIS CODE:

S = sleeping R = restless

Q = quiet C = crying

A = active F = feeding

APP 8

VIROLOGICAL METHODS: ELISA

ANTIGEN DETECTION OF RESPIRATORY VIRUSES FROM NASOPHARYNGEAL ASPIRATES

Method according to P. Halonen, Turku, 1984

Taking the samples:

Connect the mucus extractor "Pädiatrie" Vigon 534.10 with vacuum pump. The patient sits with head bent backwards. If there is not much secretion, irrigate the nose with a little sterile saline solution from a syringe (0.5 to 1 ml per nostril). Insert the tube with the bigger diameter (at least 5 to 6 centimeters, not too vertical) and put suction on to get material out. Rinse the tube with a little saline solution from the syringe, but dilute as little as possible. Disconnect the tubes, close the lid, write identification on specimen container. The material can be kept in the fridge if no virus isolation is planned. Otherwise keep at - 70øC or send to lab immediately.

EIA

Microtiter plates 1 x 8 wells, Flow Titertek Nr 78-596-c5 (irradiated)

Coating:

Dilute guineapig - antiviral serum to optimal dilution (as given by producer) and add 100 ul per well, seal with film, incubate over night at room temperature, then keep at 4 øC.
Buffer for coating: Carbonate pH 9.6: 1.6 g Na_2CO_3, 2.9 g $NaHCO_3$, NaN_3 0.2 g, H_2O 1l.

Preparing the sample:

Dilute the sample 1 / 5 with PBS + 20 % fetal calf-serum + 2 % Tween 20 + 0.0001 M Merthiolate. Remember to split the material, if virus isolation is planned. If the material has been diluted already with saline, then add less PBS.
Sensitivity: strongly positive samples can be diluted up to 1/20 (corresponding to 1-30 ng viral protein per ml). Then treat with ultrasound until the sample is clear.

Test:

all volumes are 100 ul. Take strips of coated wells from fridge, put them into the frame and wash them 2-3 times with PBS + 0.1 % Tween. Dry well (beating them out on several layers of absorbing paper) and add samples, one well per patient per virus.

Controls: 3 wells for standard virus in 3 dilutions, 2 wells for buffer control.

Standard virus dilutions:
Adenovirus, Influenzavirus A and B: 100, 10, 1 ng
Parainfluenzavirus 1,2, and 3, RSV: 1000, 100, 10 ng

Seal the plates with film, and incubate in incubator at 37 øC over night,(simple incubator, no humid chamber required).

Next morning wash 4 times, dry well. Dilute rabbit - antiviral antibody according to specifications
Children's hospital, University of Basel:

Influenza A: 1 : 1000
Influenza B, Parainfluenza 2, RSV: 1 : 3000
Adenovirus, Parainfluenza 1 and 3: 1 : 4000

add to corresponding strips, seal the plates with film and incubate for 1 hour at 37 øC. Then wash 4 times and dry well.

Incubate with peroxidase linked anti-rabbit Immunoglobulin:
dilution determined for each conjugate.

Incubate for 1 hour at 37 øC, wash 3 times with PBS Tween, then 2 times with PBS, 1 time with Citrate-Phosphate-buffer. Dry well.
Add substrate: o-Phenyldiamin 3 mg/ml Phosphate-Citrate-buffer 10 ul H2O2 (20-60 %)/ 15 ml Phosphate-Citrate (C6H8O7.H2O 4,67g,Na2HPO4. 2 H2O.2 H2O 9.9 g, H2O = 1 l, pH 5,5) incubate for 30 minutes in the dark at room temperature, and stop with 0.1 ml 1 NHCl. Read at 492 nm

Evaluation:
Negative samples are those that give a positive / negative ratio of less than 3 (negative = wells with buffer only) smaller than 2-3 times empty value for buffer.

Questionable results are OD values from 0.18 to 0.3. If the results are questionable, then a confirmatory test is performed.

Confirmatory test for demonstration of viral specificity
Wash and dry the strips that are coated with viral antiserum.
Dilute standard antigen: 30 ng for Adeno-, Influenza A and B
300 ng for Parainfluenza 1,2 and 3, RSV

3 wells are used for standard and patient sample, 2 wells for buffer.

Incubate over night at 37 øC, wash 4 times, dry well by beating on table with cloth.
For each sample add to 1st well: antiviral guinea pig - hyperimmuneserum, diluted 1/250 or 1/500 according to specifications.
2nd well: normal guineapig-serum diluted as above
3rd well: Dilution buffer

Incubate for 1 hour at 37 øC, do not wash

Add antiviral rabbit-serum in double concentration, (i.e. volume = 0.2 ml) to all wells and incubate at 37 øC for 1 hour, then wash 4 times

Peroxidase conjugated anti rabbit serum, substrate is added as for normal test.

Evaluation:
1st well = virusspecific block: if the OD value is lower, then this proves virus specificity. If the value remains the same, then the reaction was non-specific.
2nd well: non-specific block: if the value is lower, then the reaction was non-specific. If the value remains the same, this means there was no non-specific reaction.

3rd well: control. This value should remain unchanged.

Substrate for horseradish-peroxidase:

buffer:

A: 22 Citricacidmonohydrate 0.1 M	10.51 g / 500 ml
B: 81 Na2HPO4 . 12 H2O 0.2 M	35.8 g / 500 ml

pH 5.5: mix 1 part A + 1.275 parts B

substrate:

1,2-phenylenediamine	1 mg / ml
H2O2 stock solution 3% diluted 1 : 1000	0.1 ml / 10 ml

stop the reaction with 1 N HCl

Literature: Meurman O., Ruuskanen O., Sarkkinen H.
J.Clin.Microbiol. 18, 1190-95, 1983

4.4 VIROLOGICAL METHODS - IFAT

The best specimen for diagnosis of respiratory infections is a nasopharyngeal aspirate (NPA); it *should be used to prepare cell smears for immunofluorescence (IF) testing as well as for virus isolation. Nasal swabs are used only when an NPA is not possible to collect. Nasal swabs contain considerably less cell material which is usually inadequate for preparation of more than a few cell smears.* Post-mortem samples of bronchial secretions or lung tissue can also be investigated.

The NPA is obtained by suction of secretion through a thin tube into a mucus extractor (or collector). Best results (more secretion) are obtained by the following procedures. The following equipment is required:

A sterile, size FG8 polythene or rubber feeding tube with a blunt end and two wide openings near the tip;

A sterile plastic mucus extractor with two outlets;

A suction apparatus (pump) giving a negative pressure of not less than 100 mm Hg (1 to 2 kg/cm^2 or 14 to 24 $lb/inch^2$).

4.4.1 Method for obtaining nasopharyngeal aspirate

a) If a child, sit the patient on the mother's, or nurse's, lap and immobilize the head, or immobilize in the bed.

b) The tube is attached to one of the outlets of the mucus extractor. The other outlet is connected with a suction pump.

c) With the pump on, gently work the pinched tube down one nostril until the tip is judged to be at the nasopharynx (approximately half the distance from the nostril to the base of the ear).

d) Release finger pressure on the tube, work the tube up and down, rotate it and, finally, withdraw it.

e) Repeat this process through the other nostril.

f) If necessary remove remaining mucus in the tube by rinsing with 0.5 ml saline.

4.4.2 Processing of specimen for immunofluorescence staining

a) If required, first remove portions of the aspirate for bacteriological studies (using a sterile, dry, dacron swab) and isolation of mycoplasma and ureaplasma (into transport media).

b) Collect the remainder of the specimen into 4 to 5ml of phosphate-buffered saline, pH 7.6 (PBS) in a conical centrifuge tube.

c) Using a Pasteur pipette, suck up and down vigorously to break up mucus and cell aggregates *or shake by hand 10 times.*

d) The collected material is centrifuged at about 350g (1500-2000 rev/min.) for 10 minutes to pellet the cells present in the secretion. (If virus isolation is attempted, centrifuge at +4°C.) The supernatant fluid is removed and may be inoculated into cell culture medium for virus isolation.

e) The pellet contains cells and mucus. It is resuspended in 1-2 ml PBS and broken up by pipetting with a Pasteur pipette until a smooth suspension is obtained. Another 4 ml PBS is added little by little while the pipetting continues. The extractor (or centrifuge tube) is now inspected and any remaining thick lumps of mucus are removed.

f) The cell deposit is resuspended in a few drops of newly added PBS so that the final cell suspension is opaque but not "sticky". (If the final cell suspension still contains much mucus, another cell wash is required and the above procedure should be repeated.)

g) Microscope slides are numbered and placed on the table.

h) Drops of the cell suspension are evenly spread on small, previously etched areas (5-6 mm x 5-6 mm) on the slides, preferably 3-6 on each slide. If possible three slides should be prepared for each specimen. One will be frozen and two will be stained.

i) The preparations are air dried and fixed in anhydrous acetone for 10 minutes at +4°C (or 5 minutes at +20°C) and again dried in air.

4.4.3 Storage of slides for IFAT

The slides can be stored at +4°C for a day or two, and at -70°C for periods ranging from 6 months to several years.

Repeated freezing and thawing of the microscope slides with cell deposits destroys viral antigens in the infected cells. Therefore the slides should be stored in boxes containing a small number of slides (5 in each) to avoid unnecessary exposure to condensed water produced by the opening of the box. WHO/ARI is providing these boxes for the study.

If a -70°C freezer is not available, process the slides immediately and mail duplicate slides immediately to the reference laboratory (each site will have 50 slide boxes and can receive more).

Please ascertain that the slides or slide boxes are marked with study number or other identification, date and name of laboratory. Include results of the immunofluorescence investigation.

4.4.4 Titration of reagents

The monoclonal antibodies to RSV, parainfluenza, influenza A, influenza B and adenovirus should be *checked before use at recommended working dilutions*. For these reagents[1] [supplied by CDC (Dr Alan P. Kendal)] start with a 1:100 dilution. The measles monoclonal antibodies [supplied by Dr E. Norrby, Karolinska Institute] are a 1:1 pool of anti-NP and anti-P mabs; start with a dilution of 1:100. Each kit contains Dakopatts anti-mouse FITC conjugate at a dilution of 1:20.

4.4.5 Immunofluorescent staining

a) Add 15 to 30 ul of each virus specific antibody (appropriately diluted) to a separate spot of cells making certain the reagents do not run together or otherwise mix. Especially with high avidity monoclonal antibodies, there may be a technical problem in washing the slides after incubation with the antibodies if more than one antibody is added to the same slide, i.e., cross-contamination of walls. Incubate for 30 minutes at 37°C in a moist chamber.

b) Flush slides quickly with PBS from a squeeze bottle, then wash slides twice in PBS for 10-minute time periods. Let slides drain thoroughly by propping them with their long sides on paper towels and let them dry for several minutes in this position. *You can also carefully dry the area around the cellspot with a clean lint-free cloth.*

c) Add 15 to 30 ul of appropriately diluted anti-mouse IgG-FITC conjugate to each spot and spread it evenly. Incubate for 30 minutes at 37°C in a moist chamber, then wash as in (b) above.

d) *Counterstaining: slides can be immersed in Evans' Blue (1:30 000) counterstain for 4 minutes at this stage. Alternatively 0.1% naphtalene black is added to the PBS used for dilution of the FITC anti-mouse conjugate.*

e) Rinse slides briefly in distilled water. Add a drop of mounting medium (90% glycerol-10% PBS *pH 7.6-8.2*)) to each spot of cells and cover with a cover slip.

f) *Observe under fluorescence microscope (40 x objective) for specific fluorescence and record results.*

Note: Read results as soon as possible to avoid fading of fluorescence due to exposure to light. For the same reason, avoid undue exposure to excitation light.

4.4.6 Quality control and verification of results

Sites will receive coded specimens on slides for checking their identifications. In addition, they can send positively identified specimens on slides to the reference laboratory to verify the identifications and a sample of negative slides. Duplicate slides can be stored for a period of one or two months at -70°C and sent as a batch, or can be sent weekly to the reference laboratory (Dr Monica Grandien) *together with results*.

INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE
RESEARCH, BANGLADESH

Memorandum

TO : Dr. Samuel Erny, CHD

DATE: March 24,1993

FROM : Demissie Habte, MD
Chairman,Research Review Committee

SUBJECT: Protocol No.93-014 entitled "Wheezing-associated respiratory disorders and hypoxemia in hospitalized children under 5 years of age in rural Bangladesh".

The Research Review Committee met on Monday, the 22nd March 1993 to consider your protocol referred to above.

I am pleased to inform you that the protocol was approved.

However, the Committee observed that tropical Eosinophilia may also be looked into as a cause of wheezing bronchitis.

CC: Associate Director, CHD

DH:zbmb

APP 12

Response to Research Review Committee

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH
COMMUNITY HEALTH DIVISION
MCH-FP PROJECT
MATLAB

MEMORANDUM

To: Prof. D. Habte, Chairman RRC

From: Dr. S. Erny

Date: 10th April 1993

Re: Protocol No. 93-014:

Alteration following the Research Review Committee's recommendations

According to the recommendation given by the Research Review Committee, I have included a paragraph on the diagnostic procedure in case of suspected Tropical Pulmonary Eosinophilia.

(second paragraph under chapter 13.5.5 on page 11)

APP 13

Curriculum vitae of PI

SURNAME: Erny DATE OF BIRTH: 4 / 10 / 1963

FIRST NAME: Samuel PLACE OF BIRTH: Basel, Switzerland

NATIONALITY: Swiss

- SCHOOLS / COLLEGE / UNIVERSITY :

1970 - 1982 Schools and college in Basel, Switzerland

1982: Matriculation at Medical Faculty, University of Basel

1986: Course for Tropical Medicine and Public Health (3 months) at the Swiss Tropical Institute in Basel

1987: Diploma Course in Tropical Medicine and Hygiene (DTM & H) at the Liverpool School of Hygiene and Tropical Medicine

1988/89: Agogo Hospital, Agogo, Ashanti Akim, Ghana, West Africa: Rotations in general surgery (Swiss consultant), pediatrics (Dutch consultant), ophthalmology (British consultant), internal medicine and community health.

Komfo Anokye Teaching Hospital, Kumasi, Ghana: Rotation in Obstetrics and Gynecology.

1990: Final exams ("Staatsexamen") passed at University of Basel:

- JOBS:

1991: Alpine Children's Hospital, Davos, Switzerland (6 months)

from Oct. 1991: Research fellow at Community Health Division, Mother and Child Health - Family Planning Project (MCH-FP), Matlab, in the frame of the interinstitutional linkage between ICDDR,B and University of Basel, Switzerland