achment 1.

CE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B. 8/9/93

ncipal Investigator Anne Ronan

lication No. 93-028

le of Study Clinical Diagnosis of Acute Lower Respiratory Tract Infection in Children with Dehydrating Diarrhoea

Trainee Investigator (if any)

Supporting Agency (if Non-ICDDR,B)

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

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

Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects Yes (No)
(c) Minors or persons under guardianship (Yes) No

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)

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)

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 N/A
(d) Sensitive questions Yes No N/A
(e) Benefits to be derived Yes No N/A
(f) Right to refuse to participate or to withdraw from study (Yes) No
(g) Confidential handling of data Yes No N/A
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure Yes No N/A

5. Will signed consent form be required:
(a) From subjects Yes No N/A
(b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to project 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).
- ✓ Protocol (Required)
- ✓ Abstract Summary (Required)
- ✓ 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
- ✓ Informed consent form for parent or guardian
- Procedure for maintaining confidentiality
- ✓ 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.

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

Anne Ronan
Principal Investigator

Trainee

A-032056

RESEARCH PROTOCOL.

| | |
|---|---|
| TITLE | CLINICAL DIAGNOSIS OF PNEUMONIA IN CHILDREN WITH DEHYDRATING DIARRHOEA. |
| PRINCIPAL INVESTIGATOR | DR. ANNE RONAN |
| CO-INVESTIGATOR | DR. NAHRINA DEWAN |
| CONSULTANT | DR. MARK STEINHOFF |
| DURATION | 12 MONTHS |
| TOTAL DIRECT COST | $22,500 |
| SCIENTIFIC PROGRAMME HEAD | DR. DILIP MAHALANABIS, ASSOC. DIRECTOR, CLINICAL SCIENCES DIVISION, ICDDR,B. |

This protocol has been approved by the Clinical Sciences Division.

Signature
Associate Director
Clinical Sciences Division.

Date 25-6-93

# Clinical diagnosis of pneumonia in children with dehydrating diarrhoea.

- INTRODUCTION.

The diagnosis of pneumonia, one of the top killers of children in the world today, remains a matter of controversy in clinical practice, despite the intense efforts of the World Health Organization (WHO) to simplify and rationalise it. The main areas of confusion lie in the fact that children with infections of the respiratory tract often have concomitant problems such as diarrhoea, malnutrition, and malaria, and also that the perfect diagnostic tool for pneumonia does not yet exist, thereby giving us no yardstick by which to measure the accuracy of our clinical decisions. The basis of effective management of any disease is diagnosis, and this study attempts to clarify the diagnosis of pneumonia in children who have two of the commonest diagnoses in the world, diarrhoea and malnutrition.

- HYPOTHESIS:

1. The specificity of a diagnostic test for pneumonia in children, based on raised respiratory rates, is reduced by 20% or more in children with dehydrating diarrhoea.

- OBJECTIVES:

Primary objectives:

1. To prospectively measure the sensitivity and specificity of the respiratory rate cut off values, upon which the current WHO guidelines for diagnosis of pneumonia in children are based, in children with diarrhoea and dehydration.

2. To evaluate the use of pulse oximetry to determine the presence or absence of pneumonia in children with diarrhea and dehydration, especially those who are malnourished.

Secondary objectives:

3. To describe the presentation and respiratory symptomatology of children with diarrhoea and dehydration, and look for the findings that best predict the concurrent presence of pneumonia in this population.

4. To describe the short term outcome of the combination of diarrhoea and pneumonia in this population.

- RATIONALE /BACKGROUND:

1. The present guidelines for diagnosis and treatment of Acute Respiratory Infections (ARI) in children, outlined in a recent document by the World Health Organization (1), are published as a simple algorithm (APPENDIX 1). This algorithm is designed to help a community health worker, when faced with a child with cough or breathing difficulty, to differentiate between Upper Respiratory Tract Infections (URTI), which do not require antibiotic treatment, and pneumonia, or severe pneumonia, which do require antibiotic treatment, on the basis of raised respiratory rate (tachypnoea) corrected for age, and/or chest indrawing. These symptoms are present in pneumonia, probably due to decreased lung elasticity, and are often accompanied by hypoxia. If these symptoms are present, treatment with antibiotics or referral to hospital is recommended, depending on severity. The respiratory rates which predict pneumonia at different ages have been found by clinical studies on children with and without pneumonia (pneumonia being defined by a variety of "gold standards" of diagnosis such as chest X ray, and paediatrician's diagnosis with chest X ray) (2, 3, 4, 5). The respiratory rates separating pneumonia from non-pneumonia cases at different ages, adopted by the WHO for their algorithm, have a sensitivity of between 67% and 78%, and a specificity of approximately 80% in detection of pneumonia and severe pneumonia (1). The visual measurement of respiratory rate over one full minute has been recommended by the WHO, and validated as accurate and consistent in children with pneumonia, in experimental studies.(6)

2. The diagnosis of pneumonia in children with diarrhoea and dehydration is more difficult. Acidosis, a relatively common sequelae of dehydrating diarrhoea, is also known to cause tachypnoea, not due to decreased lung elasticity, but rather the increased plasma carbon dioxide levels produced by the blood buffer systems. Also, although it has not been formally documented in standard texts, the occurrence of lung crepitations in children with acidosis and dehydration, but not pneumonia, is often remarked on by medical staff working with dehydrated children. Only one report of this phenomenon exists in the medical literature since 1966 (7). All these may combine to make the diagnosis of pneumonia substantially more difficult in this population.

3. Where dehydration or acidosis is suspected clinically, trained medical staff sometimes feel they should ignore signs of tachypnoea or lung crepitations as markers of pneumonia, unless they are accompanied by chest x ray changes. Antibiotics may be delayed or withheld, and emergency treatment with infusions of bicarbonate, potentially dangerous in a child with pneumonia, may be given, if pneumonia is mistakenly diagnosed as acidosis. The safe fluid requirements for a child with dehydration and a child with pneumonia are very different. In a post mortem series of children hospitalised with diarrhoea, in the International Centre for Diarrhoeal Diseases Research of Bangladesh (ICDDR,B), Dhaka, pneumonia was found to be the cause of death in one third of cases. (8). Early appropriate management is essential in reducing mortality from pneumonia (1), so it is of some importance that the correct diagnosis be made as early as possible.

4. On the other hand, the potential for over treatment of pneumonia needs to be quantified. Less intensively trained community health workers, for whom the diagnostic guidelines are designed, would not be expected to differentiate between the two causes of fast breathing. The confusion with clinical signs of acidosis and pneumonia may result in the specificity of the WHO management algorithm being lower than that quoted. This would result in children in hospital having unnecessary X rays, and in both hospital and community, being overtreated with antibiotics.

This is particularly important since the use of inappropriate antibiotics during diarrhoea has been associated with the development of persistent diarrhoea and haemolytic uraemic syndrome, both conditions with high case fatality rates, and persistent salmonella carrier states. Also, antibiotics are often used for specific

diarrhoeal illnesses seen in this country, and little overlap between the treatment of pneumonia and diarrhoea exists now due to the emergence of drug resistance in diarrhoeal pathogens. This means that multiple antibiotics must be used.

5. In generating guidelines for diagnosis of pneumonia, a small amount of specificity has been sacrificed to obtain better sensitivity, with the rationale that some excess antibiotic treatment is preferable to missing cases (1). This is very reasonable, but the specificity needs to be re-evaluated in this group of children, and if found to be unacceptably low, it is possible that a more specific guideline for treatment of pneumonia in children with diarrhoea may be given which could help prevent undue multiple antibiotic use. This is in line with the current guidelines for health workers being developed by UNICEF, which recognises that children attending community health workers often have multiple problems.

6. The use of respiratory rate measurement is not recommended as a diagnostic test for pneumonia in children with severe malnutrition. As in very young children, the strength of the diaphragm and other respiratory muscles is reduced in the severely malnourished (9), and they may not be able to respond to the increased work of breathing in pneumonia by increasing their respiratory rates, as healthy children do. The WHO guidelines advocate treatment of any severely malnourished children with cough, at the community level, as "very severe" pneumonia, and referral immediately to hospital is recommended. There, it is supposed, the diagnosis will be made by chest X ray.

7. The accuracy of chest X ray, especially in malnourished children, as a "gold standard" for diagnosis of pneumonia, has been criticised (10, 11). It is at best a very subjective test, with wide intra-observer variability. In the very ill or malnourished, chest X ray may show no signs of consolidation, when post mortem findings are later unequivocal. In malnourished children also, the low body mass may lead to over penetrated and falsely negative X rays unless care is taken. The best diagnostic test we have had until recently is probably the combination of chest X ray and the examination findings of a doctor experienced in examining children. Even this combination has considerable potential for error.
The only true "gold standards" for diagnosis of pneumonia in children remain needle biopsy or aspirate of lung tissue, or post - mortem examination of lung tissue.

Both practical and ethical considerations preclude the use of these as investigative or diagnostic tools in most developing countries.

Now, however, arterial oxygen saturation, as measured by pulse oximetry, is being shown be of substantial value in this area. Studies in Peru and Kenya show that the presence of hypoxaemia in clinically diagnosed pneumonia in children, as measured by pulse oximetry, is a better predictor of outcome and death than chest X ray findings, and predicts the presence of X ray pneumonia in up to 75% of cases (12, 13).

8. Pulse Oximetry is a technique which utilises spectrophotometric principles to measure, continuously, and non-invasively, the oxygen saturation of arterial haemoglobin, via a small infra-red light-emitting probe attatched to the child's finger or toe. Pulse oximetry is a widely used and objective test which is cheaper and less invasive than X ray, has no known harmful effects, and should nowadays be included in a battery of tests for pneumonia diagnosis. Since the tachypnoea of acidosis is not associated with hypoxia, while the tachypnoea of pneumonia usually is, oximetry may provide an especially useful tool for diagnosis of tachypnoeic children with diarrhoea. It is reliable in children with anaemia and babies of very low body mass, (14, 15) and does not rely on any physiological response to infection such as fever, leucocytosis or inflammatory infiltrate, which may be lost in malnourished children. In this group especially, it should be of great value.

9. Diarrhoea and pneumonia are thought to occur together more frequently than would be expected by chance (8), and both occur very frequently in this population (16). A high case fatality rate is seen for the combination of the two illnesses (17). In areas where malaria is a common disease of childhood, the clinical diagnoses of malaria and pneumonia have been found to overlap considerably (18). Although diarrhoea is a much more common diagnosis in this area, no studies have been done to date to evaluate the effect of diarrhoeal disease on the clinical diagnosis of pneumonia.

10. At least one recent publication evaluating clinical signs of pneumonia using WHO criteria excluded children with dehydration, to avoid misdiagnosis (12). Diarrhoea is one of the commonest diseases of children in the world. The effect of this disease on the symptomatology of one of the leading killers of young children needs to be elucidated.

11. Severely malnourished children are at increased risk of death from pneumonia (19), and especially the combination of pneumonia and diarrhoea. In previous studies in ICDDR,B, Dhaka, children with malnutrition, of any degree, had almost twice the case fatality rate from the combination of pneumonia and diarrhoea than well nourished children (17). They constitute a major proportion of the children attending any health service in Bangladesh. The assessment of a less invasive diagnostic method which has the potential to be specifically helpful in malnourished children should not exclude them.

- STUDY DESIGN:

Prospective, clinic based, observational study.

- POPULATION:

The study population will consist of children attending the outpatient treatment centre of the Clinical Research and Service Centre (CRSC) of the International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR,B). This centre provides primary care for diarrhoeal diseases for at least 53,000 children per year, who are brought from Dhaka and the surrounding countryside. The children brought to the CRSC are representative of the target population, ie. Bangladeshi children who would be brought to primary care facilities all over the country. The CRSC also has readily available secondary care and diagnostic facilities.

From surveillance data from 1989 -1991, the proportion of children under 4 years of age attending the centre, with severe malnutrition was 16 %, or approximately 8,000 children per year.

From previous publications, the prevalence of pneumonia among children with diarrhoea appears to be at least 1-3 % in this country (16, 17). A preliminary survey of 100 children attending the CRSC, conducted over the months of June and July 1993, concurs with this, showing a minimum prevalence of cough or breathing difficulties of 12 %, and of pneumonia, 3 %.

Dehydration was present in 93 % of the children in this sample, 4 % of those having severe dehydration. All the children with breathing difficulties or cough were dehydrated (10 some dehydration, 2 severe).

- SAMPLE SIZE:

The quoted specificity of the current WHO criteria based on raised respiratory rate, is about 80% (1). To detect a difference of 20% or more in this specificity, with 90% power and 5% significance, using a one sided formula for proportion in a single sample, the sample needed is 42 children who do not have "gold standard" pneumonia (20). Our preliminary studies have shown us that approximately 25% of children with diarrhoea, who also have cough or breathing difficulty, will have X ray pneumonia, and 75 % do not have X ray pneumonia. Therefore we need to examine at least 56 children with cough or breathing difficulty, to find 42 who have not got X ray pneumonia.

We hope to include an equal number of children with "true" or X ray pneumonia, so from our pilot survey figures, we will need to examine 200 children with diarrhoea plus cough or breathing difficulty, to find 50 with pneumonia.

However, the pneumonia management algorithm produced by the WHO puts severely malnourished children (for definitions see APPENDIX 3) in a separate category, not to be diagnosed by measuring respiratory rates. Therefore the above sample size must exclude severely malnourished children, based as it is on the known specificity of the raised respiratory rates quoted by the WHO. Since we still wish to include severely malnourished children for the second objective, the evaluation of oximetry as a diagnostic technique in this population, and the third objective, to describe the respiratory symptomatology, we will include a subset of 100 children with severe malnutrition and cough or breathing difficulties, and analyse them separately in calculations of specificity.
This gives us a total of 300 children.

- INCLUSION CRITERIA:

Children aged 2 months to 4 years with diarrhoea plus cough or difficulty breathing, and dehydration as defined by the criteria in the current WHO diarrhoea management algorithm. (APPENDIX 2)
Since dehydration is not diagnosed by these criteria in severely malnourished children, as many of the signs of dehydration are normally present anyway, (dry

mucous membranes, reduced skin turgor, lethargy, irritability), the subset of severely malnourished children will be included regardless of these criteria, but on the presence of cough or breathing difficulty, and diarrhoea, alone.

- EXCLUSION CRITERIA:

Children with chronic respiratory, cardiac, renal or CNS disease;
Children with cough for more than 14 days ( Possible T.B.);

- METHODS:

- ENROLLMENT

The children will be enrolled over a period of at least eight months, a maximum of 4 children being enrolled per day or 60 children in any one month. The first four children who meet the entry criteria attending the CRSC between the hours of 8 am to 1 pm will be enrolled. This spread should ensure that children with a variety of different diarrhoeas and degrees of dehydration are seen, as this tends to vary with season..

- CONSENT

The guardian will be informed of the nature of the study and asked to sign a consent form, written in Bengali. (English translation is attached to this protocol for review). This consent form will be read to those who are not fully literate, and it will be made clear that they are under no obligation to participate if they have any concerns.

1. All children, who fit the inclusion and exclusion criteria, attending the Treatment Centre of the CRSC are screened from 8 am until 1 pm, by a specifically trained health assistant, for presence of cough or difficulty breathing.

2. The child will be seen immediately by one of the study paediatricians, before any rehydration is begun.

3. The respiratory rate is counted by the study paediatrician over one full minute, and again after 10 minutes with the child calm and not crying.

4. The child is classified as potentially having pneumonia if the respiratory rate is greater than or equal to 50/minute for children between 2 and 12 months of age, greater than or equal to 40/minute if the child is between 12 months and 3 years of age, or severe pneumonia if the child has chest indrawing. In this way, a diagnosis of "pneumonia" or "severe pneumonia" according to the WHO algorithm is made. If the child does not have a raised respiratory rate or chest indrawing, he/she is classified as having "no pneumonia". Children who fit the relevant criteria for "very severe disease" will be so classified.
(DATA FORM; EXAMINATION 1 / PRE REHYDRATION - WHO DIAGNOSIS 1)

5. The paediatrician will take a history ( DATA FORM ; HISTORY 1), from the mother or guardian, obtaining information about the symptoms of pneumonia and respiratory distress that they may have noticed, and the mother's perception of the relative severity of the child's diarrhoea and respiratory problems.

6. The paediatrician will then examine the child (DATA FORM; EXAMINATION 1), noting vital signs and weight, assign a level of dehydration as outlined by the WHO (APPENDIX 2), and signs of pneumonia.

7. Arterial oxygen saturation will be measured using a portable pulse oximeter (model N - 10, Nellcor Inc. Hayward, California) with the child inhaling room air. This reading will be repeated three times over five minutes and the average taken of the readings. The results of the pulse oximetry will be recorded at that time.
(DATA FORM; EXAMINATION 1 / PRE REHYDRATION - OXYGEN SATURATION 1)

8. A postero-anterior chest X ray will be performed on all children, within 30 minutes of the examination and pulse oximetry measurements. The results of the chest X ray, as assessed by the paediatrician, will be recorded at that time. Rehydration will not be delayed.
(DATA FORM; EXAMINATION 1 / PRE REHYDRATION - CHEST X RAY 1.)

9. Using the clinical and chest X ray evidence, the paediatrician will attempt to make a clinical diagnosis of either pneumonia or no pneumonia at this point, and record the diagnosis.
(DATA FORM; EXAMINATION 1 / PRE REHYDRATION - PAEDIATRICIAN DIAGNOSIS 1.)

10. The usual path of assessment and treatment of diarrhoea in the CRSC is as follows:
The level of dehydration is assessed by a specifically trained and highly experienced triage nurse at the reception desk, and a decision made by him or her to
(a) discharge with advice on diet and rehydration;
(b) admit to the observation ward of the CRSC, and rehydrate with oral or intravenous fluids as thought appropriate by the triage nurse. Such patients are seen five times/day by one of the doctors working in the CRSC, and further treatment or admission to the inpatient wards is instituted if thought necessary by the doctor.
(c) refer to a physician immediately, in which case the child is usually admitted directly to the inpatient ward, and sometimes to the Special Care Unit.
It is our intention to interfere with this process as little as possible, and the duty doctors will assume responsibility for each study patient in the normal way. The only exceptions to this are that the study paediatrician will institute any treatment in a child who requires it, if there will be any delay in the child being seen by the duty doctor. The duty doctor will be told the results of the examination, chest X ray, and oximetry.

11. After a timed period of six hours of rehydration, the child is examined again by the same study paediatrician. Chest X ray is <u>not</u> repeated at this time.
(DATA FORM; EXAMINATION 2 / POST REHYDRATION)

12. The measurement of arterial oxygen saturation by pulse oximetry is also repeated in the same manner as before, and recorded at this time.
(DATA FORM; EXAMINATION 2 / POST REHYDRATION - OXYGEN SATURATION 2)

13. At this time, the respiratory rate is counted over one full minute, and repeated again after 10 minutes. On the basis of the average respiratory rate, a reassessment of the diagnosis of pneumonia according to the WHO algorithm is made.
(DATA FORM; EXAMINATION 2 / POST REHYDRATION - WHO DIAGNOSIS 2)

14. At the same time, the study paediatrician will reassess the diagnosis of pneumonia made using full clinical examination, and awareness of the previous X ray findings, and repeat a diagnosis of either pneumonia or no pneumonia.
(DATA FORM; EXAMINATION 2 / POST REHYDRATION - PAEDIATRICIAN DIAGNOSIS 2)

15. 48 hours after rehydration is started, the child is examined again by the same study paediatrician. Pulse oximetry is repeated in the same manner, and the results of both recorded.
(DATA FORM; EXAMINATION 3 / 48 HOURS - OXYGEN SATURATION 3)

16. The child will have a repeat chest X ray at 48 hour follow-up, if the following conditions are met;
- CHEST X RAY 1 was normal or equivocal, but the child still has signs of pneumonia at 48 hour follow-up.
- CHEST X RAY 1 was normal or equivocal, but the child has been treated as having pneumonia on clinical grounds.

A repeat chest x ray will not be performed for the purposes of the study, on a child who had an obviously abnormal CHEST X RAY 1, or who had a normal CHEST X RAY 1 and remains free of any clinical evidence of pneumonia at 48 hours.
The chest X ray will be assessed by the study paediatrician, and the results recorded at that time.
(DATA FORM; EXAMINATION 3/ 48 HOURS - CHEST X RAY 2)

17. At this time, the respiratory rate is counted over one full minute, and repeated again after 10 minutes. On the basis of the average respiratory rate, it is seen whether the child still fulfills the WHO criteria for pneumonia or not.
(DATA FORM; EXAMINATION 3 / 48 HOURS - WHO DIAGNOSIS 3)

18. At the same time, the study paediatrician will reassess the diagnosis made using full clinical examination, awareness of both X ray findings, and clinical course over the previous 48 hours, and make a retrospective final diagnosis of either pneumonia or no pneumonia.
{DATA FORM; EXAMINATION 3 / 48 HOURS - PAEDIATRICIAN DIAGNOSIS 3 (FINAL)}

19. If the child is well enough to be discharged at any time in this 48 hour period, they will be sent home and asked to return at 48 hours for follow-up. Money will be given (TK 50 ) if needed for transport costs.
No child will be kept in the CRSC purely for the purposes of the study.

20. Any investigations such as complete blood count, electrolytes, blood and stool culture, which have been done in the course of the stay in the CRSC will be recorded. (DATA FORM; INVESTIGATIONS.)
No investigations other than chest X ray and oximetry will be done purely for the purposes of the study.

21. The chest X rays will be assessed periodically by a paediatric radiologist, who is blinded to the results of the clinical findings or the paediatrician's interpretation of the X ray.
(DATA FORM: RADIOLOGIST'S X RAY REPORT)

22. The chest X rays will also be assessed independently and by a paediatrician other than the study paediatrician; who is also blinded to the results of the clinical examination and the other interpretations of the X rays.
(DATA FORM: INDEPENDENT PAEDIATRICIAN'S X RAY REPORT)

- OUTCOME

Outcomes of interest are;

1. Diagnosis of pneumonia using the current WHO criteria, before and after a six hour period of rehydration.
   (WHO DIAGNOSIS 1 AND 2)

2. Diagnosis of pneumonia made by a paediatrician using clinical examination before and after a six hour period of rehydration, aided by chest x ray taken at initial examination.
   (PAEDIATRICIAN DIAGNOSIS 1 AND 2)

3. Final retrospective diagnosis of pneumonia, using clinical course over the 48 hours of study, and the results of the X ray(s) as assessed by the paediatrician.
   (PAEDIATRICIAN DIAGNOSIS 3 - FINAL)

4. X ray diagnosis of pneumonia, defined as an alveolar or interstitial infiltrate on chest x ray, made by a radiologist.
   (RADIOLOGIST'S X RAY REPORT)

5. X ray diagnosis of pneumonia, defined as an alveolar or interstitial infiltrate on chest x ray, made by a paediatrician other than the study paediatricians.
   (INDEPENDANT PAEDIATRICIAN'S X RAY REPORT)

6. The oximetry readings at entry, post rehydration, and at follow up.
   (OXYGEN SATURATION 1, 2, AND 3)

7. Outcome at 48 hours, defined as clinically worse, unchanged, improved, or dead.

- ANALYSIS

All children will be classified according to the 'gold standard' diagnoses of;

(1) X ray pneumonia, as assessed by the independent radiologist.
(RADIOLOGIST'S X RAY REPORT)

(2) Paediatrician's final assessment of whether pneumonia was present or not.
(PAEDIATRICIAN DIAGNOSIS 3 - FINAL)

They will also be assigned a diagnosis of pneumonia or no pneumonia (URTI) according to the WHO algorithm also, before and after rehydration.
(WHO DIAGNOSIS 1 AND 2)

Two by two tables will be constructed to relate the findings of the WHO algorithm to the gold standard diagnoses, and sensitivity, specificity, and positive and negative predictive values will be calculated using standard formula.

Those children classified as having "very severe disease", which will consist almost entirely of the severely malnourished children, will be analysed separately from the others in these calculations. If there is a substantial minority of children in this group for other reasons, eg. stridor, they will be separated and analysed separately also.

Subsequent exploratory analysis, which will include the severely malnourished group, may suggest other combinations of clinical signs which are easily recognisable by the mother or health workers, the use of which may improve the accuracy of the algorithm in children with diarrhoea. In particular, the effect of the period of rehydration on the diagnosis of pneumonia will be assessed, and the use of pulse oximetry in all children, including those who are severely malnourished, will be evaluated as a predictor of pneumonia and outcome.

- TIME SCALE

| | | |
|---|---|---|
| Training and piloting data forms and use of oximeter. | = | 1 month. |
| Enrolling 300 patients. | = | 9 months |
| Data entry and analysis. | = | 2 months. |
| TOTAL: | = | 12 MONTHS. |

- PERSONNEL.

Health Assistants -2 Study Paediatricians - 2
Paediatric Radiologist Independent Paediatrician for assessment of X ray.

- COST PROJECTION.

1. SALARIES (for 12 months).

| | |
|---|---|
| Dr. Anne Ronan 50% | $12,000 |
| Dr. Nahrina Dewan 25% | $ 1,800 |
| Health assistants (2) 100% | $ 1,800 |
| TOTAL | $15,600 |

2. EQUIPMENT.

| | |
|---|---|
| Nellcor model N - 10 portable battery operated pulse oximeter. plus 2 boxes of sensors | $3,500 |

3. INVESTIGATIONS.

| | |
|---|---|
| Approximately 500 chest x rays and reporting of same by radiologist. | $1,250 |

4. OTHER.

| | |
|---|---|
| Office supplies /printing | $ 500 |
| Local transport cost for doctors | $ 200 |
| Patient transport cost (200 of the patients at TK 50 each) | $ 250 |
| Data Analysis | $ 500 |
| Telex / Fax | $ 200 |
| Non stock items | $ 500 |

TOTAL DIRECT COST = $22,500

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# CONSENT FORM

Doctors in this hospital are doing a study of children with diarrhoea and cough or difficulty breathing to see how many of them really have pneumonia.
We would like your child to be part of that study.
If you agree to this, we will ask you some questions, and examine your child in the same way a doctor usually does, today and two days later. We ask you to come back to the hospital in two days time with your child for a check up if you are discharged before then.
We will also do a chest X ray on your child, to look for pneumonia. If this X ray does not definitely show pneumonia, but the doctor is still worried that your child may have pneumonia, we will do another chest X ray 2 days later.
We will also examine your child with a device to measure how well his lungs are working. This device does not hurt at all, only takes a few minutes to use, and will not harm your child in any way. We use this device every time we examine your child.
If we find that your child has pneumonia or any other disease that needs treatment, they will be treated fully, even if you do not agree to them being in the study. Your child will get the same treatment and be looked after by the same doctors, whether or not your child is in the study.
We will not take any blood tests for the study, but the other doctors caring for your child may need to do blood tests if they think that your child needs them.

I understand the purpose of the study and agree that my child

_____

becomes part of that study for 2 days. I understand that this in no way changes the treatment that my child will get in this hospital, and that if I refuse it will not harm my child in any way.

Signed _____ Date_____

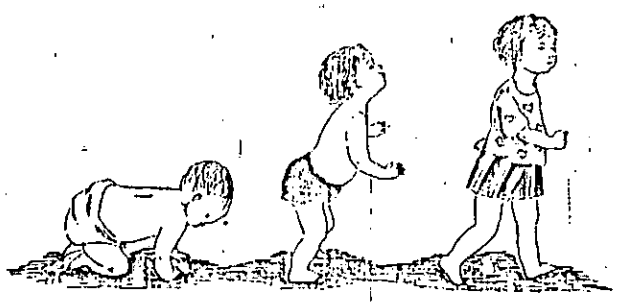
Principal Investigator

Witness _____

APPENDIX 1: WHO ALGORITHM FOR THE MANAGEMENT OF ACUTE RESPIRATORY TRACT INFECTIONS IN CHILDREN AGED 2 MONTHS - 4 YEARS.

MANAGEMENT OF THE CHILD AGED 2 MONTHS - 4 YEARS WITH COUGH OR DIFFICULT BREATHING

| | |
|---|---|
| SIGNS: | • Not able to drink,<br>• Convulsions,<br>• Abnormally sleepy or difficult to wake,<br>• Stridor in calm child, or<br>• Severe malnutrition. |
| CLASSIFY AS: | VERY SEVERE DISEASE |
| TREATMENT: | ▸ Refer URGENTLY to hospital.<br>▸ Give first dose of an antibiotic.<br>▸ Treat fever, if present.<br>▸ Treat wheezing, if present.<br>▸ If cerebral malaria is possible, give an antimalarial. |



| | | | |
|---|---|---|---|
| SIGNS: | • Chest indrawing.<br>(If also recurrent wheezing, go directly to ▸ *Treat Wheezing*) | • No chest indrawing, and<br>• Fast breathing<br>(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<br>• No fast breathing<br>(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.<br>▸ Give first dose of an antibiotic.<br>▸ Treat fever, if present.<br>▸ Treat wheezing, if present.<br>(If referral is not feasible, treat with an antibiotic and follow closely.) | ▸ Advise mother to give home care.<br>▸ Give an antibiotic.<br>▸ Treat fever, if present.<br>▸ Treat wheezing, if present.<br>▸ 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.<br>▸ Assess and treat ear problem or sore throat, if present (see chart).<br>▸ Assess and treat other problems.<br>▸ Advise mother to give home care.<br>▸ Treat fever, if present.<br>▸ Treat wheezing, if present. |

Reassess in 2 days a child who is taking an antibiotic for pneumonia:

| | WORSE | THE SAME | IMPROVING |
|---|---|---|---|
| SIGNS: | • Not able to drink.<br>• Has chest indrawing.<br>• Has other danger signs. | | • Breathing slower.<br>• Less fever.<br>• Eating better. |
| TREATMENT: | ▸ Refer URGENTLY to hospital. | ▸ Change antibiotic or Refer. | ▸ Finish 5 days of antibiotic. |

APPENDIX 2: CURRENT WHO GUIDELINES FOR DIAGNOSIS OF DEHYDRATION IN CHILDREN

| | No Dehydration | Some Dehydration | Severe Dehydration |
|---|---|---|---|
| General Condition ** | Alert | Restless, Irritable | Floppy, Lethargic, Unconscious |
| Eyes | Normal | Sunken | Dry, Sunken |
| Tears | Present | Absent | Absent |
| Tongue | Moist | Dry | Very Dry |
| Thirst ** | Normal | Present | Unable To Drink |
| Skin Turgor ** | Normal | Slow return | Very slow return |

Each level of dehydration is diagnosed by having any two signs present, one of which must be from the three signs marked by a **.

## APPENDIX 3: DEFINITION OF PEDIATRIC CLINICAL SIGNS

Suggested Guidelines for Investigators and Observers

Mark C. Steinhoff, MD
Center for Immunization Research
Johns Hopkins University

well child has normal activity and a normal appetite (food intake) and none of the spiratory or GI signs listed below.

inorrhea* - fluid or mucus observed to exit from nostril (note before nasal wash procedure).

aryngitis* - unequivocal pharyngeal erythema ± exudate with tender cervical nodes.

ough* - more than 2 episodes of coughing in 15-minute timed observation, describe number of episodes, character and quality (dry or productive/wet; or barking, croupy); if cough present by history, determine if interfered with sleep or if associated with vomiting.

heeze - a sustained musical sound, heard in expiration, with prolonged expiratory phase of respiration. Must be heard by 2 observers over a 15-minute period.

drawing - Inward movement of the lower part of the child's chest on inspiration.

ded - use American Thoracic Society classification
lmonary (attached) to describe crackles or rhonchi.
unds

itis Media - abnormal appearing tympanic membrane, with decreased mobility on pneumatoscopy, confirmed by second observer, if possible; or use tympanometer to measure compliance. Note clinical diagnosis and prescribed treatment.

arrhea - ≥ 3 abnormal stools (conform to shape of container)/24 hours.

miting - ≥ 1 vomiting episode/24 hours.

ver - > 38.1°C (100.5°F) rectal temperature, repeat at 15 minutes to confirm.

lust be present on 2 consecutive days to meet illness criteria.

# CLINICAL CLASSIFICATION OF INFECTIOUS RESPIRATORY SYNDROMES

Center for Immunization Research
Johns Hopkins University

Suggested Guidelines for Investigators

See attached descriptions and definitions of specific signs and symptoms

**ld (URI):** Excessive nasal discharge (rhinorrhea), and nasal obstruction, sneezing; often associated with pharyngitis, tracheobronchitis, or fever.

**aryngitis:** Sore throat, painful swallowing, pharyngeal erythema ± exudate, may have tender enlarged cervical nodes.

**oup:** (also laryngotracheobronchitis) Barking cough, with hoarseness, inspiratory stridor. URI often present.

**onchitis:** (also tracheobronchitis) Cough and coarse airway sounds, without laryngeal obstruction (hoarseness, stridor) or wheezing, often associated with fever, URI and pharyngitis.

**onchiolitis:** First episode of expiratory wheezing in infants < 2 years old with cough, URI, fever and tachypnea. Often epidemic, may be associated with pneumonia.

**eumonia:** New alveolar consolidation on radiograph with cough and crackles (crepitations). Fever, rapid respiratory rate, dyspnea and subcostal retractions are common. Pneumonia may be associated with any of the above syndromes, but if present, should be the main diagnosis.

**afted by:** Mark C. Steinhoff, MD

**apted from:**
F.W. Denny, J Pediatr 1986;108:635-646
S.D.M. Court, Post Grad Med J 1973;49:771-776
K. McConnochie, Am J Dis Child 1983;137:11-13

## RECOMMENDED CLASSIFICATION OF AUSCULTATORY PULMONARY SOUNDS

| Acoustic Characteristics | American Thoracic Society Nomenclature | Common Synonyms |
|---|---|---|
| Discontinuous, interrupted explosive sounds, Loud, low in pitch | **Coarse crackle** | Coarse rale |
| Discontinuous, interrupted explosive sounds Less loud than above, shorter duration; higher in pitch than coarse | **Fine crackle** | Fine rale, crepitation |
| Continuous sounds, high pitched; a hissing sound | **Wheeze** | Sibilant rhonchus |
| Continuous sounds, low pitched; a snoring sound | **Rhonchus** | Sonorous rhonchus |

Modified from Loudon and Murphy, Am Rev Respir Dis 1984;130:663-673

## CLASSIFICATION OF NUTRITIONAL STATUS.

Mild Malnutrition: Weight for age ≤ 2 standard deviations below the National Centre for Health Statistics (NCHS) median.

Moderate Malnutrition: Weight for age ≤3 standard deviations below the NCHS median.

Severe Malnutrition: Weight for age ≤ 4 standard deviations below the NCHS median, or presence of nutritional oedema.

# DATA FORM

## Check List

Cough, < 15 Days OR Difficulty Breathing? YES ☐

Diarrhoea ? YES ☐

Dehydration? OR Weight for age ≤ 4 sd below NCHS median (from tables) YES ☐

Chronic Illness ? NO ☐

History Of Asthma ? NO ☐

**ONLY ADMIT PATIENT TO STUDY IF ALL BOXES ARE TICKED YES OR NO AS APPROPRIATE.**

---

(1) Study No ☐☐☐

Name _____

(2) Age ☐☐ Mths

(3) Sex(2 = Female,1 = Male) ☐

(4) Observation Centre No. ☐☐☐☐☐☐☐

(5) Hospital No. ☐☐☐☐☐☐

(6) Date Admitted To Study. Day / Month / Year ☐☐/☐☐/☐☐

(7) Time Rehydration Begun ☐☐.☐☐ Hrs

(8) Time of First Examination ☐☐.☐☐ Hrs

Study No _____ Name _____

HISTORY 2 = Yes 1 = No

(9) Cough ☐ (10) Duration ☐☐☐ Hrs

(11) Difficulty Breathing ☐ (12) Duration ☐☐☐ Hrs

(13) Noisy Breathing ☐ (14) Duration ☐☐☐ Hrs

(15) Fast Breathing ☐ (16) Duration ☐☐☐ Hrs

(17) Colour Change ☐ (18) Blueness ☐

(19) Unable To Drink ☐ (20) Hard To Waken/ Abnormally sleepy ☐

(21) Convulsion ☐ (22) Fever ☐

(23) Type Of Diarrhoea ☐ (24) Duration Of Diarrhoea ☐☐☐ Hrs
1 = Loose
2 = Watery
3 = Mucoid
4 = Bloody +/– mucus

(25) Breast fed ☐
4 = Fully
3 = Partially
2 = Not Breast Fed Now
1 = Never Breast Fed

(26) Antibiotics Taken Outside ☐
3 = Yes (Name _____)
2 = Maybe
1 = No

(27) Mother's Perception Of Main Problem? ☐
1 = Diarrhoea
2 = Cough/Breathing Difficulty/Blueness
3 = Both
4 = Other

Study No _____ Name _____

EXAMINATION.(1) / PRE REHYDRATION

(28) Respiratory Rate (A) ☐☐☐/Min

(29) Respiratory Rate (B) 10 Mins Later. ☐☐☐/Min.

(30) Weight ☐☐.☐Kg (31) Ht ☐☐☐.☐Cm

(32) Oedema ☐ 2 = Yes 1 = No

(33) Xerophthalmia ☐ 2 = Yes 1 = No

(34) Pulse ☐☐☐/Min (35)Temp.(pr) ☐☐.☐ $^{o}C$

(36)Oxygen Saturation (a) ☐☐☐%

(37)Oxygen Saturation (b) ☐☐☐%

(38)Oxygen Saturation (c) ☐☐☐%

(39)AVERAGE OXYGEN SATURATION (1) ☐☐☐% (CALCULATED)

## LEVEL OF DEHYDRATION

(40) General Condition ** ☐
3 = Floppy, Lethargic
2 = Restless, Irritable
1 = Alert

(41) Eyes ☐
3 = Dry, Sunken
2 = Sunken
1 = Normal

(42) Tears ☐
2 = Absent
1 = Present

(43) Tongue ☐
3 = Very Dry
2 = Dry
1 = Moist

(44) Thirst ** ☐
3 = Unable to Drink
2 = More than Normal
1 = Normal

(45) Skin Turgor ** ☐
3 = Very Slow Return
2 = Slow Return
1 = Normal

(46) Level of Dehydration ☐ 3 = Severe, 2 = Some, 1 = None

(47) Rehydration given ☐ 3 = Iv 2 = Oral 1 = None

Study No _____ Name _____

EXAMINATION (1)

| | | |
|---|---|---|
| (48) Cyanosis | 2 = Yes | 1 = No |
| (49) Chest Indrawing | 2 = Yes | 1 = No |
| (50) Nasal Flare | 2 = Yes | 1 = No |
| (51) Grunting | 2 = Yes | 1 = No |
| (52) Crepitations | 2 = Yes | 1 = No |
| (53) Wheeze | 2 = Yes | 1 = No |
| (54) Bronchial Breathing (not R upper zone) | 2 = Yes | 1 = No |
| (55) Decreased Air Entry | 2 = Yes | 1 = No |
| (56) Abdominal Rigidity | 2 = Yes | 1 = No |
| (57) Mental Status After Exam. | 3 = Alert. | 2 = Lethargic<br>1 = Unrousable |

(58) Describe CXR Findings _____

(59) CHEST X RAY (1)
- 3 = Consistent With Pneumonia
- 2 = Unable To Rule Out Pneumonia
- 1 = No Sign Of Pneumonia

(60) WHO DIAGNOSIS (1).
- 4 = Very Severe Disease
- 3 = Severe Pneumonia
- 2 = Pneumonia
- 1 = No Pneumonia

(61) PAEDIATRICIAN DIAGNOSIS (1).
- 3 = Definite Pneumonia
- 2 = Unsure but treat as Pneumonia
- 1 = Not Pneumonia

Study No_____ Name_____

EXAMINATION (2) / POST REHYDRATION

(62) Time Of Second Examination □□.□□ Hrs

(63) Resp.Rate(A) □□□ /Min.

(64) Resp.Rate (B) □□□ /Min.

(65) Weight. □□.□ Kg

(66) Pulse □□□ /Min (67) Temp.(pr) □□.□ °C

(68) Oxygen Saturation (a) □□□ %

(69) Oxygen Saturation (b) □□□ %

(70) Oxygen Saturation (c) □□□ %

(71) AVERAGE OXYGEN SATURATION (2) □□□ % (CALCULATED)

(72) Degree Of Dehydration □ 3 = Severe 2 = Some 1 = None

(73) Cyanosis □ 2 = Yes 1 = No

(74) Chest Indrawing □ 2 = Yes 1 = No

(75) Nasal Flare □ 2 = Yes 1 = No

(76) Grunting □ 2 = Yes 1 = No

(77) Crepitations □ 2 = Yes 1 = No

(78) Wheeze □ 2 = Yes 1 = No

(79) Bronchial Breathing (not R upper zone) □ 2 = Yes 1 = No

(80) Decreased Air Entry □ 2 = Yes 1 = No

(81) Abdominal Rigidity □ 2 = Yes 1 = No

(82) Mental Status After Exam. □ 3 = Alert. 2 = Lethargic 1 = Unrousable

Study No. _____ Name_____

(83) Antibiotic Started For Pneumonia
3 = Yes, IV
2 = Yes, Oral
1 = No

(84) Antibiotic Started For Diarrhoea
2 = Yes
1 = No

(85) Antibiotic Started For Other Reason
2 = Yes
1 = No

(86) Name Antibiotic(s) _____

(87) Oxygen Given in last 4 hours
2 = Yes
1 = No

(88) WHO DIAGNOSIS (2).
4 = Very Severe Disease
3 = Severe Pneumonia
2 = Pneumonia
1 = No Pneumonia

(89) PAEDIATRICIAN DIAGNOSIS (2).
3 = Definite Pneumonia
2 = Unsure but treat as Pneumonia
1 = Not Pneumonia

Study No_____ Name_____

EXAMINATION (3) / 48 HOURS

(90) Resp.Rate(A) ☐☐☐/Min.

(91) Resp. Rate (B) ☐☐☐/Min.

(92) Weight. ☐☐.☐Kg

(93) Pulse ☐☐☐/Min (94) Temp.(pr) ☐☐.☐ $^{o}$C.

(95)Oxygen Saturation (a) ☐☐☐%

(96)Oxygen Saturation (b) ☐☐☐%

(97)Oxygen Saturation (c) ☐☐☐%

(98)AVERAGE OXYGEN SATURATION (3) ☐☐☐% (CALCULATED)

(99) Degree Of Dehydration ☐ 3 = Severe 2 = Some 1 = None

(100) Cyanosis ☐ 2 = Yes 1 = No

(101) Chest Indrawing ☐ 2 = Yes 1 = No

(102) Nasal Flare ☐ 2 = Yes 1 = No

(103) Grunting ☐ 2 = Yes 1 = No

(104) Crepitations ☐ 2 = Yes 1 = No

(105) Wheeze ☐ 2 = Yes 1 = No

(106) Bronchial Breathing (not R upper zone) ☐ 2 = Yes 1 = No

(107) Decreased Air Entry ☐ 2 = Yes 1 = No

(108) Abdominal Rigidity ☐ 2 = Yes 1 = No

(109) Mental Status After Exam. ☐ 3 = Alert. 2 = Lethargic 1 = Unrousable

Study No. _____ Name _____

(110) Antibiotic Started For Pneumonia between 6 and 48 hours? ☐
3 = Yes, IV
2 = Yes, Oral
1 = No

(111) Antibiotic Started For Diarrhoea between 6 and 48 hours ☐
2 = Yes
1 = No

(112) Antibiotic Started For Other Reason between 6 and 48 hours ☐
2 = Yes
1 = No

(113) Name Antibiotic(s) _____

(114) Oxygen Given between 6 and 48 hours ☐
2 = Yes
1 = No

(115) Describe CXR Findings _____

(116) CHEST X RAY (2) ☐
3 = Consistent With Pneumonia
2 = Unable To Rule Out Pneumonia
1 = No Sign Of Pneumonia
0 = Not Done

(117) WHO DIAGNOSIS (3): ☐
4 = Very Severe Disease
3 = Severe Pneumonia
2 = Pneumonia
1 = No pneumonia

(118) PAEDIATRICIAN DIAGNOSIS (3). ☐
3 = Definite Pneumonia
2 = Unsure but treat as Pneumonia
1 = Not Pneumonia

(119) OUTCOME ☐
4 = Improved Clinically
3 = Unchanged
2 = Worsened Clinically
1 = Dead

**Investigations On Admission.**

**Study No.**_____ **Name** _____

(120) Hct ☐☐ %

(121) Total WCC ☐☐.☐

(122) Polymorphs ☐☐ %

(123) Bands ☐☐ %

(124) Stool Culture ☐☐
1 = Vibrio Cholerae
2 = Vibrio Non 01
3 = Shigella dysenteriae
4 = Shigella flexnerae
5 = Other shigella spp. (Specify_____)
6 = Other Organism Found (Specify_____)
7 = No Organism Found
8 = No R/S Or Stool Culture Done

(125) Blood Cultures ☐
( At any time during the previous 48 hours)
3 = Positive (Specify_____)
2 = No Growth
1 = Not Done

(126) Sodium ☐☐☐.☐ Mmol/ L

(127) Potassium ☐.☐ Mmol/ L

(128) Chloride ☐☐☐.☐ Mmol/ L

(129) TotalCO2 ☐☐.☐ Mmol/ L

(130) Creatinine ☐☐☐ Micromol/ L

(131) Glucose ☐☐☐ Mg/Dl

---

3 = Definite pneumonia
2 = Possible Pneumonia
1 = No Pneumonia

(132) RADIOLOGIST'S X RAY REPORT ☐

(132) INDEPENDENT PAEDIATRICIAN'S X RAY REPORT ☐

Reviewer – 1



Title: Clinical diagnosis of acute lower respiratory tract infection in children with dehydrating diarrhoea.

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

| | Rank Score | | | |
|---|---|---|---|---|
| | High | Medium | Low | |
| Quality of Project | | ✓ | | |
| Adequacy of Project Design | | ✓ | ✓ | form design is good, however |
| Suitability of Methodology | | ✓ | | |
| Feasibility within time period | | | | |
| Appropriateness of budget | - | - | - | |
| Potential value of field of knowledge | | | | |

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☑ underestimated

Review 1

Protocol Clinical diagnoses of ALRI in children with dehydrating diarrhoea.

Comment The protocol is difficult to follow beacuse of its unorderly presentation. I have drawn up a study flow chart which corresponds to a viable study organisation. This flowchart may not be what the proposer intends, but serves as a basis for discussion of the issues involved. These are as follows:

(i) Screening by health assistant for cough or breathing difficulty puts much study reliance on the lowest qualified person. As a safeguard, should a random ( or systematic) 4% of screen negative children be invited for WHO(1) assessment by health worker (HW) as a check on the performance of the initial screen?

(ii) WHO (1) Health worker now applies WHO criteria. Is it the HW's responsibility to apply exclusion criteria or does HW assess all screen positives, and leave it to paediatrician (who examines next) to evaluate exclusion criteria?

(iii) PAED (1) Does study paediatrician examine all screen-positive children, or only those who are both scree and WHO(1) positive? I have drawn up the flowchart on the former assumption: because the study can then also establish whether (and how many) ALRI cases are missed by WHO (1) which are identified by study paediatrician. If the suggested flowchart entails too many examinations for the study paediatrician, then at least a random X% of the WHO(1)-negative, screen positive children should undergo paediatric assessment (say..... 25%.. power considerations will properly determine X%)

Do all children examined by the padeiatrician undergo chest X-ray. The protocol appears to suggest this and the flowchart so indicates. Certainly this should be the case.

Digression : Treatment decisions: It is unclear from the protocol when correction of dehydration is instituted - apparently after the first paediatric exam, - in relation to the timing of first examination by Paediatrician and in relation to first X-ray. These matters must be clarified if study organizatioin is to proceed smoothly. Also, from the protocol it appears that treatment decisions will be taken by the duty doctor who receives a copy of (confirm) the study paediatrician's findings and the chest X-ray. How quickly does this become available ? There may need to be allowance on the off-study forms for radiological review of X-rays, this independent assessment differing perhaps from the duty radiologists/ doctor's interpretation at the time (see form 5).

CORRECTION OF DEHYDRATION Again there is need to clarify when correction is instituted in relation to timing of 1st study paediatric exam and by whom.

WHO (2) WHO criteria are again applied after correction of dehydration in moderate/severely dehydrated children. Since the protocol does not include the WHO algorithm as an appendix it should!), it is unclear to me whether WHO recommends waiting until after correction of dehydration before application of its criteria. The point seems to be to compare WHO findings before and after correction of dehydration. It would therefore, be important to have the same observer (HW) apply WHO criteria before and after, so that inter-HW differences in interpretation/application of WHO criteria do not confound the comparison of interest.

PAED (2) Study paediatrician repeats clinical exam on rehydrated children.

XRAY (2) Is the X-ray repeated also for all rehydrated children? (unclear from protocol: shown on flowchart as repeated).

48 hours follow-up WHO criteria are applied for the 3rd time by same HW and study paediatrician examiners (Note: non-dehydrated children omitted all examinations (2) on flow chart).

EVIDENCE OF ALRI X-ray is repeated in children in whom the study paediatrician finds evidence of ALRI i.e. continued evidence despite treatment or de novo evidence in untreated children.

OFF STUDY The 'gold standard' for diagnosis of ALRI at admissioin to be based on paediatrician examinations (1) ± (2) if applicable + X-ray (1) read by indep, radiologist + X-ray (2) if applicable, plus for children who did not receive antibiotics of pneumonia in first 48 hours, paediatric exam (3) + X-ray (3) if applicable. For other children who did receive anti-pneumonia therapy paid (3) + X-ray (3) are inadmissible because assessed post-treatment.

Analysis

1. Thus for each child is established a final diagnosis of pneumonia as : Yes, unsure, No, And for each child its initial dehydration status mild, moderate, severe is known. Of interest are three: a) Proportion of pneumonias correctly identified by WHO (1); by WHO (2); by PAED (1); by PAED (2); by X-ray (1); by X-ray (2) - according to initial delayed status. b) Proportion of not pneumonias wrongly classified as pneumonia by WHO (1); by WHO (2); by PAED (1); by PAED (2); by X-ray (1) by X-ray (2) - according to initial dehyd. status. c) For dehydrated children, crosstabulations (also by dehydration status)=pneumonia?

| (A) WHO (i) criteria met | | | (B) PAED(1) Initial diagnoses | | | | |
|---|---|---|---|---|---|---|---|
| Post rehydration WHO(2) criteria | Yes | No | Post-rehydration Paed (2): updated diagnosis | Yes | Unsure | No | |

| (C) X-ray (1) = Pneumonia ? Initial diagnosis | | | | |
|---|---|---|---|---|
| Post-rehydration X-ray (2): updated diagnosis | Yes | Unsure | No | |
| | | | | Yes |
| | | | | Unsure |
| | | | | No |

Explaratory analyses subsequently may suggest other signs which improve upon WHO criteria and which are easily recognisable by mother or HW.

Study Size On $p^3$ objective is given as to investigate effect of dehydration and acidosis on the specificity of WHO criteria (i.e. tachypooea) for diagnosing pneumonia (see also Hypothesis: specificity reduced by 20% or more if dehydration)

Sensitivity = % of true positives WHO test positive
Specificity = % true negatives WHO test negative

In Dhaka, it is assumed that 3% of children with diarrhoea have pneumonia. However, presumably the % is higher amongst diarrhoea children who also have cough or breathing difficulty, viz those eligible for this study. What % of diarrhoea children have cough or breathing difficulty? Let us assume a proportion C.

Thus out of 1300 self-referrals
$1300_C$ eligible for study, of whom
$4^2$ have pneumonia

WHO (1) criteria claim 67-68% sensitivity, say 70% so that out of the 4 pneumonias per 1300 self-referrals, 29 met WHO (1) criteria. Specificity of 80% is claimed, so that of 1300 - 42 cases who have diarrhoea and cough/breathing difficulty but not pneumonia, 80% shall fail WHO (1) criteria and 20% will falsely test positive - 0.2 x 1300 x c -8

Thus WHO criteria met by 29 pneumonias

{ 0.2 x 1300 x c } - 8 non-pneumonias

The alternative hypotheses is that in dehydrated children, specificity is reduced from 80% to 60%. In this case, WHO criteria met by 29 pneumonias

{ 0.4 x 1300 x c } - 8 non-pneumonias

The applicant has not estimated the proportion C of children with diarrhoea who also have cough/breathing difficulty. This proportion may differ according to dehydration status.

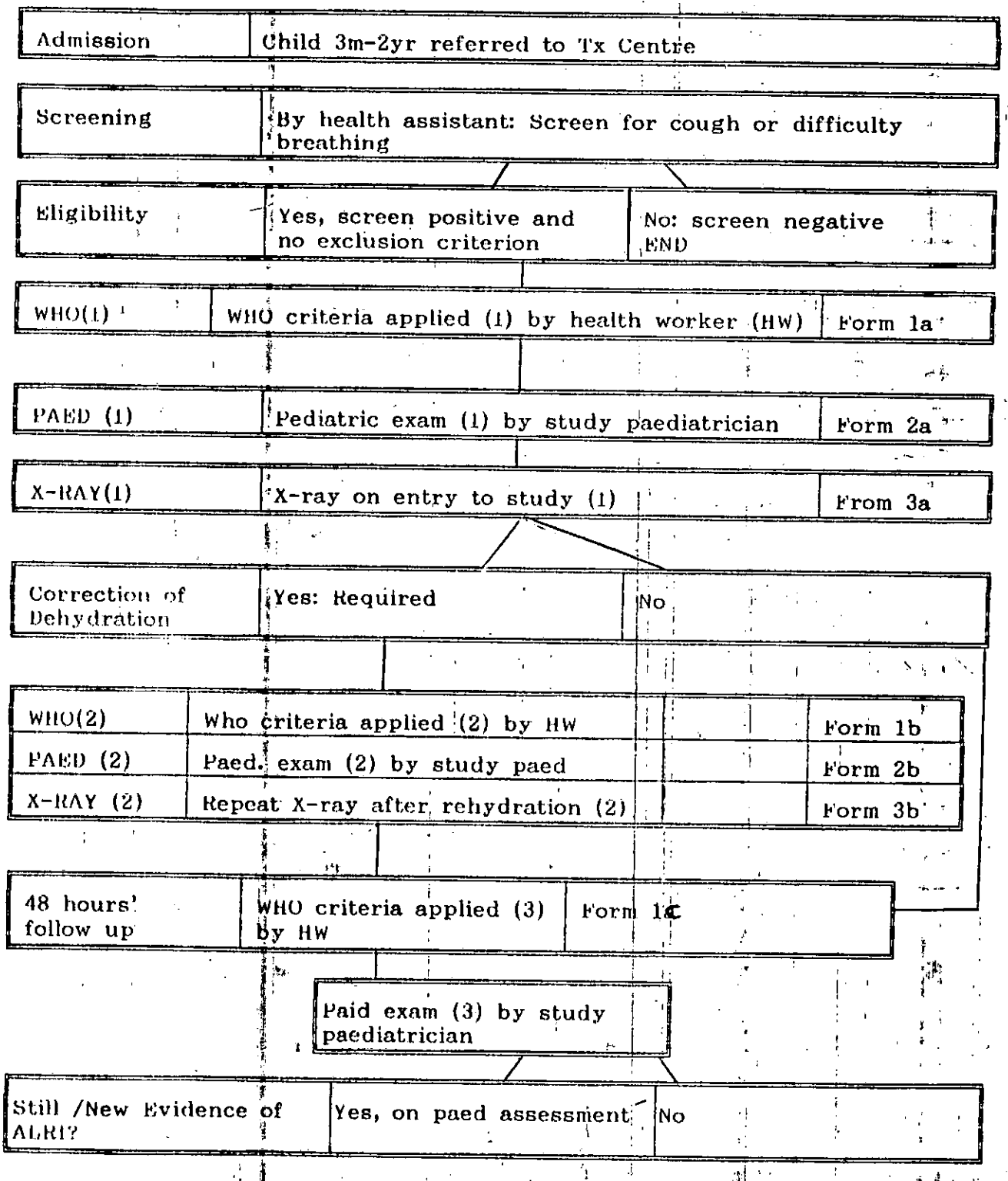
Moreover, sample size calculation for a single sample is not appropriate because speciticity will be compared between study parents who have mild v. moderate v severe dehydration. Now has the applicant provided information on the % of children 3m -2 yrs with diarrhoea and cough/breathing difficulty who have mild v. moderate, v. severe dehydration. When the above background data have been ascertained, sample size calculations should be redone. Also, the applicant should reconsider whether studying a quota of mild/moderate/severe dehydration cases (as seems to be implied) is sensible and appropriate to objectives and operationally feasible.

Forms Comment penned on copies attached. General poiints are

(a) Avoid calculations
(b) WHO criteria to appear on form as reminder
(c) Separate forms for different assessors
(d) Examinatioins to be printed in some order and location from form to form
(e) Consider colour coding of forms

Generalization Since history is being taken and paediatric examination done anyway in diarrhoea cases with mild/mod/severe dehydration plus cough/breathing difficulty, ensure that history/signs cover those of other major complications beisdes pneumonia ( ? meningitis) which might otherwise be missed or which via exploratory analysis could lead to a BANGLA Diarrhoea Baby check (for other complications, pneumonia being one).

Study Flow chart



| | | |
|---|---|---|
| X-Ray (3) | Repeat X-ray at 48 hours (3) | Form 3c |

| | | |
|---|---|---|
| OFF-STUDY | Summary of ALRI diagnoses by WHO (1+2) paed (1+2) final (3) | Form 4 |
| | Radiological review of X-rays (1),(2),(3): final | Form 5 |

Review - 2



Title: Clinical diagnosis of acute lower respiratory tract infection in children with dehydrating diarrhoea.

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

| | Rank Score | | |
|---|---|---|---|
| | High | Medium | Low |
| Quality of Project | | ✓ | |
| Adequacy of Project Design | | ✓ | |
| Suitability of Methodology | | | ✓ |
| Feasibility within time period | ✓ | | |
| Appropriateness of budget | ✓ | | |
| Potential value of field of knowledge | | ✓ | |

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☐

I have reviewed the protocol "Clinical diagnosis of acute lower respiratory tract infection in children with dehydrating diarrhoea"

The protocol concerns an important issue and is therefore worthy of careful consideration.

The design of the study is confusing.

The study is referred to as 'Case and Controls' and sometimes like a clinical trial which is confusing.

It is proposed to study children with diarrhoea, dehydration and cough plus fasting breathing and persistent elevated rate.

To obtain an estimate of specificity of the WHO criteria as proposed, one needs to study subjects with diarrhoea, couth plus difficult breathing. This will include those with and without elevated respiratory rates.

Sensitivity and specifity may vary across the spectrum of a clinical illness. Therefore, in the proposed study, these should be determined independently, fulfilling trial size requirements for each one, in the following groups:

"Diarrhoea, no dehydration (obvious) cough or difficult breathing
diarrhoea, dehydration, cough or difficult breathing

What is the gold standard is not clearly stated. In all likelihood, x-ray chest may be appropriate.

It is advisable to have two radiologists read the X-rays independently and without access to clinical data, and in case of disagreement, a third radiologist may be asked to do so. This, agreement by at least 2 radiologist would be the basis of gold standard.

The X-ray chest examination and the clinical date should be obtained within 30 minutes of each other.

Clinical data may be obtained in the dehydrated group before, and post rehydration such that the WHO criteria are evaluated at both phases of illness.

Overall, I think it is a useful study, deserves to be carried out but the protocol needs extensive modification.

Response to comments of Reviewer 1.

1. The reviewer comments that the presentation is "unorderly" and therefore hard to understand. The protocol has been substantially rewritten to make the organisation and flow of the study clearer.

2. The reviewer comments (i) that the initial screening by the health worker puts a great reliance on the lowest qualified person, and suggests a second check by a paediatrician. Having trialled the protocol with a health worker of the standard available in the hospital, I have no worries about their competence in this screening. Many mothers will answer positively about symptoms on repeated questioning, and I do not think that having a "second round" of screening will necessarily help to make the process more like the questioning carried out by a health worker in a community clinic, which is what it aims to imitate.

3. Points (ii) and (iii) are due to confusion over the flow of the study examinations. I have clarified this in the revised protocol.

4. "Digression: Treatment decisions". I have clarified the timing and progression of these decisions in the protocol. There is no duty radiologist; the paediatrician's interpretation is made as soon as the x ray is developed, which normally takes about 30 minutes.

5. "Correction of dehydration". I think this is now clear in the protocol.

6. " X ray (2). The reviewer is mistaken- there is no X ray done immediately after rehydration on any child. This has been clarified.

7. "Off Study". The reviewer states that the final examination and X ray are inadmissible in children who have received antibiotics. I do not agree with this. Antibiotics will not remove the signs of pneumonia in two days, and the final paediatric assessment is not to diagnose pneumonia at that moment exactly, but rather to form a final, retrospective decision as to whether the child had pneumonia or not on admission, based on clinical progression over the two days, response to treatment, as well as clinical findings at the 48 hour examination.

8. Sample Size: a pilot survey has clarified the proportions of children with diarrhoea who have cough, and the proportion of these who have pneumonia. The sample size has been revised according to those proportions. The comment about the feasibility of finding three groups of children with dehydration at different levels, each of the required sample size, was valid, and the protocol now no longer requires these three groups.

9. "Forms". All comments have been incorporated, except the colour coding, which is not feasible.

10. The comments about researching a Bangla Baby Check are not appropriate to the scope of this protocol.

Response to Reviewer 2.

1. Again the reviewer says that the study is confusing. I have rewritten the protocol substantially to clarify the flow of events.

2. The comment about cases and controls refers to a typing error in one line which has been removed.

3. The reviewer states that the study needs to look at groups of children with and without dehydration. I have no scientific grounds to believe that children with diarrhoea and no dehydration will have any symptoms which will confound the diagnosis of pneumonia, and therefore do not intend to study them.

4. The reviewer seems to be confused as to what is the Gold Standard for diagnosis of pneumonia. I think this is clearly stated, and reviewer (1) does not seem to have had difficulty with this, so I have not changed it.

5. The reviewer suggests that it would be better to have two radiologists to review the x rays. I feel that from previous studies, "blind" radiologist review, although definitely the only really independent, unbiased diagnostic test for pneumonia, is very subjective, and this is why we must have a variety of gold standards involving both interpretation of a test, and also clinical judgment of someone experienced in examining children. Involving another radiologist trained in reading x rays will only reiterate the fact, already well proven, that two radiologists very often will not agree on the same x ray. Given the difficulty in finding a second paediatric radiologist here, I feel that it is not justified by the theoretical benefit. An independent, well qualified paediatrician will be easier to use and will give almost as good a back up diagnosis.

6. The chest X ray and the clinical data will be collected within 30 minutes of each other.