CHAPTER III

RESEARCH METHODOLOGY

RESEARCH QUESTION

Primary Research Question.

If respiratory rate were a good indicator of pneumonia, what is the cut-off point considered as fast breathing in children under 5 years old with a minimum acceptable sensitivity of 80% (95% Confidence Interval 70%-90%) and specificity of 60% (95% Confidence Interval 50%-70%) in a tertiary care setting?

Secondary Research Questions :

1. Whether different cut-off values of respiratory rate as indicator of pneumonia have to be used in infants and children 1-4 years old?.
2. Whether severity or any complication of pneumonia affects the respiratory rate ?.
3. What are the clinical signs relating to radiological evidence of pneumonia in children under 5 years old?.
4. What is the etiology of pneumonia in children under 5 years old?.

HYPOTHESIS

Clinical signs,especially respiratory rate > 50/minute,is a good indicator of radiological evidence of pneumonia, giving an optimum combination of acceptable sensitivity and specificity defined by a ROC curve, and a likelihood ratio of a positive test greater than 2 (95% Confidence Interval 1.5-3).

Likelihood ratio of a positive test is defined as > 2 based on minimum acceptable sensitivity of 80% and specificity of60%.

		Gold standard +	Gold standard −	
Test	+	0.8	0.4	LR + = 0.8/0.4 = 2
	−	0.2	0.6	LR − = 0.2/0.6 = 0.33

ASSUMPTION

1.Prevalence of pneumonia in children under 5 years old in a tertiary care setting is approximately 20%.

2.A simple definition of fast breathing of > 50/minute is sufficient to predict pneumonia in children under 5 years old.

3.Among several clinical signs,chest indrawing (mainly subcostal) is a good indicator of pneumonia.

4.Intensive training and standard clinical procedures will minimized inter-observer variability.

5.Intra-observer variability in an experienced radiologist is minimal if the results are reviewed independently.

RESEARCH DESIGN

Design: cross-sectional,diagnostic test.

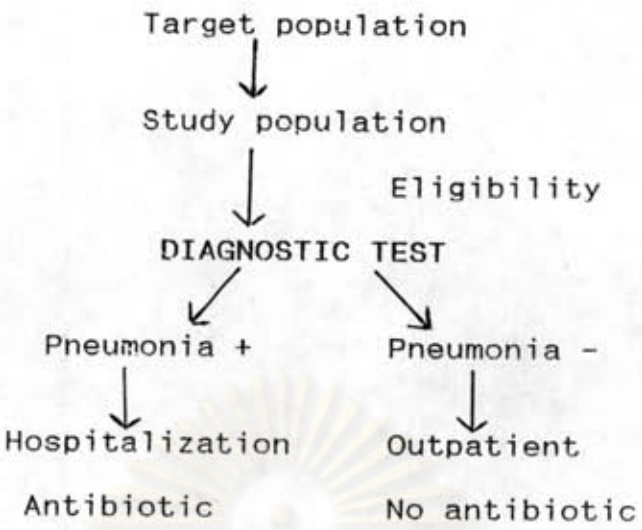
A diagnostic test is appropriate to test RR and several other clinical signs compared to the best available standard considered to be a gold standard for pneumonia : radiologically comfirmed pneumonia.

The gold standard should be properly performed and that the results are interpreted with a standard criteria.
Radiologically confirmed pneumonia is the gold standard,defined by diffuse alveolar infiltrates or frank consolidation, as this is mostly caused by bacterial infection (Caffey,1961 and Meschan, 1966).

Being a screening test,this diagnostic test should be able to detect the disease whenever it is present.So,the test should have a high sensitivity,but also a properly high specificity.

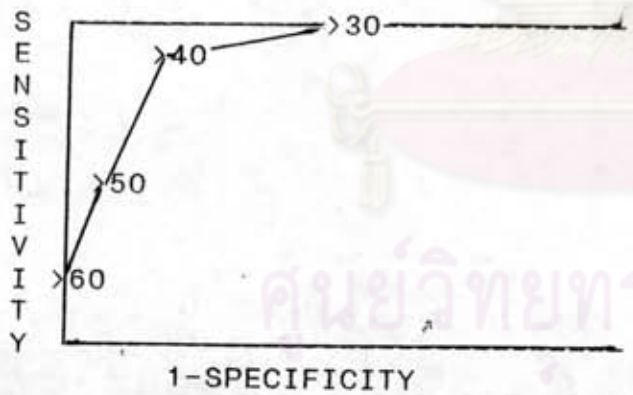
A receiver operating characteristics (ROC) curve which relates false-positive to true-positive at multiple cut-point can be constructed.It shows the various trade-off existing between proportions of false-positive and true-positive responses,to discriminate between disease and non-disease.

The diagnostic test and the gold standard should be independent.Each patient should undergo both test.The process should be blind to those who perform and interpret the diagnotic test and those who interpret the gold standard.If this independence is not maintained,expectation bias may occur and may result in a spurious increase in the sensitivity and specificity, and predictive values (Schechter,1991).
For each clinical sign, a 2 by 2 table could be constructed and all properties of a diagnostic test could be calculated.



Two by two tables could be drawn for each RR threshold.

		Radiological pneumonia +	-	
RR	+	a	b	Sensitivity (95% CI) Specificity (95% CI)
>50	-	c	d	LR + (95% CI) LR - (95% CI)



ROC curve for RR as indicator of pneumonia

Five ROC curves could be drawn:
A.Children less than 12 months old
B.Children 13-24 months old
C.Children 25-36 months old
D.Children 37-48 months old
E.Children > 48 months old

POPULATION

Target population :

In this study,the target population are children 0-4 years old.

Population sampled:

In this study they are children 0 - 4 years old visiting the Paediatric Outpatient Department Kariadi Hospital in Semarang, Indonesia who comply and satisfy the eligibility criteria. This Hospital is a university teaching hospital affiliated with the Faculty of Medicine Diponegoro University.

Selection Criteria

Eligible subject for the study are:

1. those 0-4 years old with any 2 of the complaints : cough,fever,fast or difficult breathing,
2. of less than 1 week duration.

The exclusion criteria are :

1.patients with stridor,

2.congenital heart disease (cyanotic or acyanotic)

3.heart failure

4.another condition requiring antibiotics

SAMPLE SIZE CALCULATION

Sample size formula for estimating sensitivity and specifity is

$$n = \frac{(Z\ \text{alpha}/2)^2\ P\ Q}{d^2}$$

Based on previous studies,we estimate that with a suitable cut-point for distinguishing between pneumonia and non - pneumonia

cases,it will be possible to have a test with 80% sensitivity.

So P = sensitivity ,set at 0.8 (95% CI 70-90%)

Q = 1 - P = 0.2

alpha = 0.05, so Z 0.025 = 1.96

d = 0.1 (allowable error)

$$n = \frac{1.96^2 (0.8)(0.2)}{0.1^2} = 62 \text{ (in diseased group, or a+c)}$$

If the prevalence is 20%,then

n in the non-diseased group = 62 x 4 = 248

And total sample size is 62 + 248 = 310

OPERATIONAL DEFINITION:

PNEUMONIA defined clinically as an illness resulting in 2 or more of the followings: cough,tachypnea,cyanosis,chest indrawing,rales (fine and medium).

CYANOSIS is blue discoloration of the skin and mucous membranes especially the tongue and inside of the lips.

CHEST INDRAWING is inward movement of the whole lower chest wall when the child breathes in.

THE GOLD STANDARD is radiologically confirmed pneumonia,either diffuse alveolar infiltrates, or frank consolidation .

OBSERVATION AND MEASUREMENT

An oral informed consent is obtained from each eligible child's parent or guardian.The investigator's explanation of the study included a description of the study,its goal,the various

examinations and treatment the child will receive,and the risk and benefit of the examination and treatment.

1.The RR of the child is counted by 2 trained senior nurse independently by observing either abdominal or chest wall movement in a child's naked chest for 60 seconds, twice in 2 minutes interval then average the count, while the child is calm, using an electronic timer.

The infant's state (awake,sleeping) is also recorded.

2.The child is then referred to a Paediatrician after taken its demographic data and personal charactheristics, its weight , height,arm circumference,and rectal temperature.

Clinical examination by the Paediatrician using a standard form including cyanosis,grunting,flaring,chest indrawing,dullness, decreased breath sounds,rales,or the presence of any complication.

The clinical diagnosis of pneumonia and further management are then made without knowledge of the test result.

3.Routine blood analysis and culture are then taken.

4.Each child undergoes chest radiography,whether or not there had been clinical evidence of pneumonia. A postero-anterior radiograph will be taken in the erect position,or if the patient's condition does not permit,an antero-posterior supine view is then taken.

Radiographs will be read by an experienced radiologist without knowledge of any patient's clinical findings,and he will make an independent review on 2 separate occasions of each patient.

5.Follow-up:all patients will be followed until at least 1 week.

1.Out-patients: repeat assessments are made by a Paediatrician on the third,seventh and tenth day on clinical signs or any complication;medications or other medical problems will be monitored.

A second blood analysis and chest roentgenogram are made only if indicated.

2.In-patients:daily assessment are made by a Paediatrician on clinical signs,any complication,or other medical problems.

Blood analysis and chest roentgenogram are made on the seventh day,or earlier if indicated.

DATA ANALYSIS

Diagnostic test for pneumonia will give the results of sensitivity,specificity and its confidence interval that allow more critical evaluation of point estimates describing the sensitivity and specificity.The width of this range of values defines the degree of precision of the sensitivity and specificity.A positive and negative predictive value can be calculated from the 2 by 2 table

		Gold standard +	Gold standard −
Test	+	a	b
	−	c	d

$$\text{sensitivity} = a / (a+c)$$

$$95\%\ CI = [a/(a+c)] \pm 1.96 \sqrt{[a/(a+c)].[c/(a+c)]/(a+c)}$$

$$\text{specificity} = d / (b+d)$$

$$95\%\ CI = [d/(b+d)] \pm 1.96 \sqrt{[d/(b+d)].[b/(b+d)]/(b+d)}$$

positive predictive value = a/(a+b)

negative predictive value = d/(c+d)

accuracy = (a+d)/(a+b+c+d)

prevalence = (a+c)/(a+b+c+d)

A receiver operating characteristics (ROC) curve , which relates false-positive to true-positive at multiple cut-points can be constructed to help determine the cut-point that gives the optimum combination of sensitivity and specificity.The decision criterion is systematically varied,for a given capacity to discriminate between positive and negative cases (Feinstein,1985). The ROC analysis provides an index of diagnostic accuracy that is independent of other decision factors and of prior probabilities.

A more powerful method of establishing a test's usefulness is to examine the associated likelihood ratio which allows estimates of the probability that disease is present at any level of diagnostic test result.The likelihood ratio combines sensitivity and specificity to describe the change in odds favoring disease given a particular test result.When a likelihood ratio exceeds 1,the odds favoring disease increase;when the likelihood ratio becomes less than 1,the odds favoring disease decrease;when the likelihood ratio approaches 1,the odds favoring disease do not change and the test is indeterminate. Since likelihood ratios refer to actual test results before disease status is known , they are more immediately useful to clinicians than sensitivity and specificity (Simel et al.,1991).

Likelihood ratio has three important properties:

1.It does not change with the prevalence of disease.

2.It can be calculated for multiple levels of outcome.

3.It allows assessing the impact of a test result on the odds that a patient will have the disease.

The likelihood confidence interval can be determined from the dual functions of sensitivity,and therefore can be used to guide sample size estimation.

LR + = sensitivity / (1-specificity)

$$95\%\ CI = \exp\left(\ln \frac{\text{sensitivity}}{1-\text{specificity}} \pm 1.96 \times \sqrt{\frac{1-\text{sensitivity}}{a} + \frac{\text{specificity}}{b}}\right)$$

LR - = (1-sensitivity) / specificity

$$95\%\ CI = \exp\left(\ln \frac{1-\text{sensitivity}}{\text{specificity}} \pm 1.96 \times \sqrt{\frac{\text{sensitivity}}{c} + \frac{1-\text{specificity}}{d}}\right)$$

Because a consequence of missing a case will result in withholding antibiotic treatment and close monitoring in the hospital,it may lead to complication or even death,we have to choose a value for the positivity criterion that minimizes the false negative rate.

While false positive will be identified during follow-up, giving antibiotic will not be harmful to them.

When a false negative result is undesirable,set the positivity criterion equal to a value toward the right on the ROC curve,so almost all patients with the disease are detected by the diagnostic test.

The accuracy of a test can be described as the area under the ROC curve,the larger the area,the better the test.

Inter-observer variability in the interpretative component of the test will be assessed by using Kappa test.

A comparative analysis on variables (age,sex,duration of illness, chest indrawing,cyanosis,rales) between those who have normal and fast breathing will be made.

The data were entered in a EPI 5.0 programme and later were converted to dBase III in an IBM PC computer and analysed with the use of Statistical Package for Social Sciences (SPSS/PC+,Chicago).

The sensitivities, specificities, likelihood ratios and its 95% Confidence Interval were calculated using Lotus 1-2-3.

ETHICAL CONSIDERATIONS

Since this study is conducted in children who are unable to understand or give consent,ethical issues should be emphasized.

1. The protocol of the study should be presented to an ethics review committee of Kariadi Hospital who will review and decides whether it meets the ethical standard.
2. Parent or guardian of the subjects are asked to consent to take part in the study.
   Each parent is adequately informed of the aims and method of the study,anticipated benefits and discomforts before enrollment.
3. The process of obtaining blood will be made minimally uncomfortable to the subject.Parents will be informed of this and permission will be obtained.
4. Some subject will have 2 chest roentgenograms.Sensitive areas will be covered with a thick lead rubber.

LIMITATIONS AND OBSTACLES

1. The pneumonia episodes detected represent only a fraction of the total incidence,since many children might have pneumonia which pass unnoticed by the parents,or death probably already occured before they were seen.
2. Only cultures of lung aspirates and blood culture can produce reliable bacteriological diagnosis.Due to strong ethical objection to the use of lung aspirates,the best information on the bacterial etiology of pneumonia will be obtained through blood culture,despite the fact that the sensitivity is somewhat lower.

   Rapid immunological techniques such as counter immunoelectrophoresis,latex agglutination or coagglutination, or ELISA are not yet entirely satisfactory and not always available.
3. No virological studies will be made,due to difficulties of obtaining nasopharyngeal aspirates,as well as virus isolation and antigen detection techniques.
4. This study will be conducted in a University Teaching Hospital. If the results will be applied to the community,we have to consider that :

   4.1.These tests may not be as sensitive in detecting less severe disease seen in the community.

   4.2.The prevalence of pneumonia in the community will be somewhat lower,resulting a lower positive predictive value in the community setting.

EXPECTED BENEFIT AND APPLICATION

1. A simple but reliable guideline for fast breathing in children under 5 years old will make ARI case management correctly applied in a community setting, even by a community health worker, as in some remote areas children are often seen by them.
2. The importance of one simple chest physical finding in distinguishing pnemonia from non-pneumonia cases will ensure proper management of ARI and decision which cases need to be referred to a higher level health facility.
3. Stressing the relationship between pneumonia to immunization, especially measles, with an achievement of more than 90% success in the Expanded Programme on Immunization (EPI) in Indonesia, a development of a locally effective case management on ARI, will further reduce infant and childhood mortality from 54/1000 live birth to 40/1000 live birth, and from 10.6/1000 to 8/1000 respectively, in the next Sixth Five Year Plan of Indonesia beginning April 1994.