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tachment 1.

Date 2nd December, 1991

ACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

incipal Investigator DR. MAHBUBUR RAHMAN

Trainee Investigator (if any) 69

plication No. 96-023

Supporting Agency (if Non-ICDDR,B)

tle of Study Surveillance and Associa-
udies of Antimicrobial Resistance in
ococcus Pneumoniae (sp) and Haemophilus
nzae (Hi) in Children.

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

rcle 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
(d) Sensitive questions Yes (No)
(e) Benefits to be derived (Yes) No
(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

5. Will signed consent form be required: ____
(a) From subjects ____ Yes No
(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).
✓ 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 olving the rights and welfare of subjects before making such change.

Mahbubur Rahman
Principal Investigator

Trainee

CHECK-LIST FOR SUBMISSION OF PROPOSALS TO THE RESEARCH REVIEW COMMITTEE (RRC)

[Please tick (✓) the appropriate box]

1. Has the proposal been reviewed, discussed and cleared at the Division level ?

   Yes ☑

   No ☐

   If 'No', please clarify the reasons: _____

2. Has the proposal been peer-reviewed externally ?

   Yes ☑

   No ☐

   If the answer is 'NO', please explain the reasons: _____

3. Has the proposal scope to address gender issues ?

   Yes ☐

   No ☑

   If the answer is 'YES', have these been adequately incorporated in the proposal. Please indicate: _____

4. Has a funding source been identified ?

   Yes ☑

   No ☐

   If the answer is 'YES', please indicate the name of the donor: The Government Of Bangladesh and The World Bank

5. Whether the proposal is a collaborative one ?

Yes [✓]

No [ ]

If the answer is 'YES', the type of collaboration, name and address of the institution and name of the collaborating investigator be indicated:

Dr. Samir Kumar Saha, Dr. Ruhul Amin
Dhaka Sishu Hospital

6. Has the budget been cleared by Finance Division ?

Yes [✓]

No [ ]

If the answer is 'NO', reasons thereof be indicated: _____

7. Does the study involve any procedure employing hazardous materials, or equipments ?

Yes [ ]

No [✓]

If 'YES', fill the necessary form.

December 2, 1996
Date

Mahbubur Rahman
Signature of the
Principal Investigator

SECTION 1 : RESEARCH PTOTOCOL

1.	Title of Protocol	:	Surveillance and Associated Studies of Antimicrobial Resistance in *Streptococcus pneumoniae* (sp) and *Haemophilus influenzae (Hi)* in Children.
2.	Principal Investigators:		Dr. Mahbubur Rahman, MBBS, MS, Ph.D Laboratory Sciences Division, ICDDR,B
		:	Dr. Nigar Shahid, MBBS, MPH Community Health Division, ICDDR,B
		:	Dr. Samir K. Saha, Ph.D Dhaka Shishu Hospital (DSH)
3.	Consultant		Dr. M.J. Albert, Ph.D, ICDDR,B
4.	Other Investigators	:	Dr. Shafiqul Alam Sarker, MBBS, MD ICDDR,B Dr. Ruhul Amin, FCPS, DSH
5.	Starting Date	:	1 January, 1997
6.	Date of completion	:	31 December, 1999
7.	Funding Source	:	Government of Bangladesh and World Bank
8.	Total Budget	:	US$ 120,000.00 (One hundred twenty thousand US Dollars only)
9.	Head of Programme	:	Dr. M.J. Albert Acting Division Director Laboratory Sciences Division ICDDR,B

SURVEILLANCE AND ASSOCIATED STUDIES OF ANTIMICROBIAL RESISTANCE IN S. PNEUMONIAE (Sp) AND H. INFLUENZAE (Hi) IN CHILDREN

ABSTRACT

Acute respiratory infection, primarily pneumonia, is the leading cause of mortality in children less than 5 years old in Bangladesh (ref), and in the developing world, in general (1). To decrease pneumonia mortality the World Health Organization has developed a system of case management whereby children with cough and difficult breathing are classified as having pneumonia based on easily discerned clinical signs and are emprically treated with an antimicrobial agent (2). Several agents--cotrimoxazole, amoxicillin, and procaine penicillin--are recommended by WHO for therapy because their spectrum of activity includes *S. pneumoniae* (Sp) and *H. influenzae* (Hi), which are the principle bacterial pathogens that cause pneumonia (3). In Bangladesh, cotrimoxazole is the agent recommended by the National ARI Control Programme.

The recent emergence of resistance to each of these antimicrobial agents by Sp and Hi threatens the success of the case management approach. In response, the WHO Programme for the Control of ARI developed a method of surveillance for antimicrobial resistance in these pathogens and has recommended that this be incorporated into National programs (4). In several countries that have conducted surveillance, the rates of cotrimoxazole resistance have ranged between 20% and 60% (5, J. Bell, personal communication). Nevertheless, the number of countries that have conducted

surveillance has been limited by cost and technical complexity. Several simplified methods of surveillance have been suggested but have never been adequately evaluated.

The purposes of the proposed study are to develop surveillance for resistance in Bangladesh based on WHO recommended methods (providing inportant data to the National ARI programme), and to evaluate simplified methods that could be applied in subsequent surveillance activities in Bangladesh and elsewhere. Finally, studies will be done to evaluate sources of antimicrobials, and mothers' knowledge and attitudes, and behaviours regarding antimicrobial use; these studies may provide information that would be helpful in decreasing total and inappropriate antimicrobial use, thus, slowing the spread of resistance.

GENERAL OBJECTIVES

1. Determine rates of antimicrobial resistance in Sp and Hi using the WHO recommended approach to surveillance, and assess whether surveillance methods can be simplified without significantly altering results.

2. Evaluate antimicrobial use patterns and source of antimicrobials, mothers' knowledge and attitudes and behaviours regarding antimicrobial use in the treatment of ARI.

SPECIFIC OBJECTIVES

1. Improve laboratory capacity for isolation, susceptibility testing, and serotyping of Sp and Hi, and determine rates of resistance for Sp and Hi using the WHO recommended approach to surveillance (NP culture of children with pneumonia enrolled throughout the pneumonia season).

2. Compare resistance rates and Sp serogroup distribution for children with pneumonia and those brought to clinic for other acute illnesses who do not have pneumonia.

3. Determine whether resistance rates and Sp serogroup distribution are comparable for surveillance conducted throughout the pneumonia season and for a short (3 week) period during the pneumonia season ("rapid assessment").

4. Assess antimicrobial use in children before presenting to hospital and evaluate such use as a risk factor for carriage of antibiotic resistant Sp and Hi.

5. Characterize resistance rates and Sp serogroup and Hi capsular-type distribution for invasive isolates (blood and CSF).

6. Determine trends in antimicrobial resistance rates of Sp and Hi over two pneumonia seasons (years).

7. Assesss method of obtaining appropriate lower respiratory secretions for culture from children with pneumonia.

RATIONALE

This project addresses several important needs of the Bangladesh and the WHO ARI Control Programmes. Surveillance results will be useful to the Bangladesh Programme in determining whether resistance is a potential problem in pneumonia therapy, characterizing trends in resistance, and developing approaches to limiting the spread of resistance. These goals are particularly relevant to Bangladesh because some preliminary data suggest that resistance to cotrimoxazole, penicillin, and chloramphenicol are present in Sp and Hi isolates obtained from sterile site cultures (6, and unpublished data, S. Saha). The project also will contribute to developing the capacity of two Bangladeshi laboratories to act as sentinel labs for the SAARC region to isolate the pneumonia pathogens, test them for resistance, and to characterize strains by serotype.

This project will address important needs of the WHO ARI Control Programme as well. Goals of the programme addressed in this project include evaluating simplified methods of surveillance and

developing a feasible methodology to identify the possible etiology of pneumonia by collecting lower respiratory tract secretions from children. Data on pneumococcal and *H. influenzae* serotype distribution also will be helpful in evaluating the coverage of candidate conjugate Sp vaccine formulations, and estimating the potential impact of immunization with Sp or Hi conjugate vaccines.

ETHICAL IMPLICATIONS

Surveillance for resistance using NP swab cultures will not provide any benefit to the individual children who are cultured. However, these data will benefit all children in Bangladesh by providing information on the adequacy of the recommended empiric therapy for pneumonia. Obtaining a specimen of NP secretions using a small swab on a flexible wire shaft is associated with minor discomfort but no morbidity. We also will be obtaining an aspirate of lower respiratory secretions from some children with pneumonia by using a suction catheter introduced through the nares into the posterior pharynx, inducing a cough, and aspirating the sputum. Although there is greater discomfort associated with this approach, there is no associated morbidity and the results of microscopic evaluation and culture may assist in patient care. A previous study utilizing this procedure from The Gambia found potentially treatable causes of pneumonia (e.g., tuberculosis or infection with Gram negative bacteria) that would not have received appropriate therapy using

standard case management criteria (7). These specimens will be evaluated microscopically immediately after they are obtained and if such a pathogen is identified, specific therapy will be provided. However, this test cannot replace the use of an NP swab because the yield of this procedure for Sp and Hi has not been established and the ability to obtain an adequate specimen has not been determined. In addition, blood samples will be obtained for culture and a chest radiograph will be obtained where clinically indicated; culture results may directly assist in patient management by facilitating specific therapy for the pathogen identified.

BACKGROUND

Acute lower respiratory tract infections (ALRI) is the leading cause of death among young children in the developing world (1). Of an estimated total 12.4 million deaths occurring in 1990 among children under age five, 3.76 million (30%) are attributed to ALRI (World Health Organization [WHO], unpublished data). Although tracheobronchitis, bronchiolitis, and pneumonia each accounts for about one-third of ALRI cases, several studies suggest that pneumonia is responsible for most ALRI deaths. In three studies which reported the diagnosis in children who died from ALRI (8-10), a median of 89% of ALRI deaths were associated with pneumonia (range 71% to 100%). Consequently, reducing pneumonia mortality has been the focus of programmes to decrease the impact of ALRI in

children.

A case management strategy has been developed by WHO (2,3) and has become the primary approach used by national ARI control programmes to decrease pneumonia mortality. This strategy is based on diagnosis of pneumonia in children with cough or difficult breathing using easily discernable signs (tachypnea and chest indrawing), followed by empiric antimicrobial therapy. The success of this approach depends on selection of an antimicrobial agent that is effective against the pathogens most likely to cause fatal pneumonia. The bacterial etiologies of pneumonia have been determined in several studies based on results of lung aspirate and blood cultures, and by non-culture methods such as antigen detection and serology (7,11-19). Results of these studies indicate that *S. pneumoniae* (Sp) and *H. influenzae* (Hi) cause most bacterial pneumonia mortality; a recent review estimates that these pathogens account for almost 1 million and 500,000 annual deaths, respectively (Schwartz, unpublished data). While only limited data are available for Bangladesh, Sp was the leading bacterial pathogen identified in children with pneumonia hospitalized at ICDDR,B between 1986-88, causing 30% of episodes in which a bacterial pathogen was identified (20).

Cotrimoxazole, amoxicillin or procaine penicillin have been recommended as first line therapy for children with pneumonia and because of their activity against both Sp and Hi. Cotrimoxazole is

most widely used because of its lower cost and greater ease in dosing compared with the other first line agents, and is the drug recommended by the National ARI Control Programme in Bangladesh. Several studies have shown a substantial decrease in pneumonia and total child mortality with ARI case management.

However, the emergence of antimicrobial resistance threatens the success of the case management approach. Sp and Hi isolates resistant to each of the first line agents have been reported throughout the world (5,21-24). In 1991, the Centers for Disease Control (CDC) and WHO developed a manual of surveillance for antimicrobial resistance in Sp and Hi and recommended its use by National ARI Control Programmes (4). Surveillance was based on obtaining nasopharyngeal (NP) isolates of Sp and Hi from children with pneumonia who present to a participating facility during the peak pneumonia season and determining their susceptibilities. Based on these data and other factors, the National Programme would decide whether to continue using the current recommended empiric therapy or to change therapy.

Surveillance using these methods has been conducted in Pakistan, Thailand, Egypt, and Vietnam. In Pakistan, resistance to cotrimoxazole, the agent recommended for therapy, exceeded 50% overall (5). Data from the other three countries have not yet been completely analysed. During surveillance, however, several difficulties were identified with the recommended methods.

Obtaining isolates only from children with pneumonia restricts the facilities that can participate in surveillanece to those that have large outpatient populations, where sufficient numbers of children can be enrolled. In addition, performing accurate susceptibility tests in developing country laboratories has proved to be difficult with results frequently differing from those obtained in international reference laboratories.

Other approaches to surveillance have been proposed to overcome these difficulties. Studies conducted in South Africa and the Central African Republic have compared resistance rates for isolates obtained from children with and without pneumonia; although no significant differences were identified, neither study had sufficient power to definitively show comparability of the two patient groups (A. Rowe, K. Klugman, unpublished data). These studies also collected all isolates during an intensive 2 week study period, which allowed a laboratory consultant to be on-site during the entire study. However, the comparability of data gathered during a short period and that obtained from throughout the entire pneumonia season is unclear.

Antimicrobial use will inevitably exert selective pressure for the development of antimicrobial resistance. Thus, over time, one would expect resistance rates to increase. Because the number of antimicrobial agents that are effective therapy for Sp and Hi, and which can be afforded in a developing country setting are limited,

decreasing the spread of antimicrobial resistance to retain effectiveness of treatment, is an important objective. Addressing this issue requires understanding the behaviours and beliefs of parents with respect to antimicrobial treatment for their children for ARI as well as other acute illness.

STUDY METHODS

We will address the study objectives in a two-year study conducted in several phases, each building on previous results. First year activities will be focused on building laboratory capcaity, obtaining data on rates and patterns of antimicrobial use and resistance, and evaluating surveillance methodology. Data from subsequent year will be used to identify trends in resistance, changes in serotype distribution.

Year 1

1. **Patient enrollment:**

A. Children between 2 months and 5 years old presenting to the Outpatient Departments at ICDDR,B and Shishu Hospital with pneumonia diagnosed by WHO case management criteria. Exclusion: Children who have been hospitalized within the previous 2 weeks.

B. Children between 2 months and 5 years old presenting to the same facilities for any acute illness who do not have pneumonia. Exclusion: Children who have been hospitalized

within the previous 2 weeks or who are being seen at clinic for follow-up, immunization, or a non-acute process (chronic illness or well child care).

C. Sampling: Children will be enrolled from the pneumonia and non-pneumonia groups in approximately a 2:1 ratio. Children with a chief complaint of ARI will be identified by a triage nurse. Based on existing records from Shishu hospital, approximately 2/3 of these children will meet WHO criteria for pneumonia per day. Study physicians will evaluate children for enrollment during routine clinic hours, alternating 2 children with pneumonia and 1 child with another acute illness or ARI without pneumonia, selected from the children from the queue based on the order of their presentation at the clinic. Children who meet eligibility criteria and whose parents provide informed consent will be enrolled. When a child evaluated by a study physician does not meet eligibility criteria (i.e., a child with ARI but no pneumonia) or does not consent to participate, the physician will select another child from the same enrollment category (pneumonia or non-pneumonia) for possible enrollment. During the rapid assessment period, children with ARI but no pneumonia will not be excluded from possible enrollment.

2. **Surveillance period:**

A. Children with and without pneumonia will be enrolled throughout the pneumonia season (approximately 4 months). Intensive patient enrollment, to assess a rapid surveillance methodology, will occur during a 3 week period beginning one month after onset of routine patient enrollment.

B. Blood and cerebrospinal fluid (CSF) Sp and Hi isolates from ICDDR,B and Shishu Hospital will be obtained throughout the year from children routinely cultured for suspected bacteremia or meningitis.

3. **Data and specimen collection:**

A. Physician evaluation: Study physicians will obtain informed consent for study participation, identifying and demographic data, a brief history of the current illness, and perform a clinical evaluation. Children with ARI will be assessed using the WHO case management algorithm. In addition, immediately after a child is enrolled, the physician also will place a urine collection bag on the child. He will also interview the child's caretaker (generally the mother) to obtain detailed information on care seeking for the current illness, prior medication use including antibiotics, and the caretaker's

general behaviours and beliefs with respect to use of antibiotics.

B. **Specimen collection:**

i) NP swab for culture will be obtained by passing a small swab on a flexible wire shaft through the nares of the child into the posterior nasopharynx. The specimen will be placed into Amies transport media and taken to the laboratory for culture

ii) Blood for culture will be obtained from pneumonia cases using standard methods, if clinically indicated

iii) Urine will be collected from a bag specimen and transported to the laboratory for testing of antimicrobial activity

iv) Lower respiratory tract secretions will be collected from children with pneumonia using the following method: Sputum will be collected by placing a small catheter through the nares into the posterior pharynx, inducing a cough, with aspiration of the expectorated material. The suction catheters will be placed in a sterile cup and transported to the laboratory. Microscopic examination, culture and criteria for determining specimen quality will be undertaken according to standard method.

v) A chest radiograph will be obtained if clinically indicated.

During the rapid assessment period, data collection will be limited to facilitate increased patient enrollment. A comparison of data and specimens collected during routine surveillance and during the rapid assessment period is shown in Table 1.

Table 1. Data and specimen collection during the routine surveillance and rapid assessment periods

	Routine Surveillance Period	Rapid assessment Period
Basic questionnaire	X	X
Extended questionnaire	X	
NP swab specimen	X	X
Urine specimen	X	X
Sputum specimen	X	
Blood specimen	(X)	(X)
Chest radiograph	(X)	(X)

(X) = If missed during routine clinical management for pneumonia cases only.

4. Laboratory studies

A. Nasopharyngeal swabs and blood specimens will be processed for:

i) Culture for *Streptococcus pneumoniae* (sp) and *H. influenzae* (Hi) by standard method.

ii) Test for antimicrobial susceptibility by modified Kirby-Baur method and MIC by E-test (4). E-test will be done for all isolates found resistant and intermediate by disc diffusion method. Following discs will be used to determine antimicrobial susceptibility.

For Sp: Cotrimoxazole, oxacillin, chloramphenicol, erythromycin

For Hi: Cotrimoxazole, ampicillin (and ß-lactamase production), chloramphenicol

A representative number (10%) of the isolates will be tested for antimicrobial susceptibility in a reference laboratory (Jan Bell's Laboratory, Monash Medical Centre, Melbourne, Victoria 3168, Australia).

B. Urine: Test for antimicrobial activity by growth inhibition of a sensitive *Micrococcus sp.*

C. Lower respiratory tract secretions:

i) Microscopic examination to evaluate specimen quality depending on the number of epithelial cells and pus cells.

ii) Gram stain

iii) Ziehl-Nielson stain for acid-fast bacilli

iv) Culture for Sp, Hi, and other potential bacterial pathogens, including quantitation as 1+ to 4+.

D. Blood will be cultured using routine methods.

5. Sample size: In a study with multiple objectives, sample size is estimated based on the largest sample needed to accomplish any of the objectives. For the first year studies, this is the comparison between the different surveillance methods (i.e., evaluation of rapid assessment and children with and without pneumonia). If we assume a rate of resistance of 30% (based on preliminary data for cotrimoxazole resistance of sterile site isolates from Shishu Hospital), and consider a difference of greater than +/- 10% to be significant, then we would need to collect 476 and 238 isolates (assuming a 2:1 ratio between pneumonia and non-pneumonia patients or between overall surveillance and the rapid assessment period) for a

power of 80% in detecting this difference. Data from previous studies at ICDDR,B indicates that the yield of NP cultures is likely to be approximately 60%. Thus, almost 800 children with pneumonia, 400 children without pneumonia, and 400 children during the rapid assessment period would need to be enrolled. These estimates are presented in Table 2.

Table 2. Sample size estimates for evaluation of surveillance methods.

	# Isolates	# Specimens
Pneumonia (routine surv.)	476	793
No pneumonia	238	397
Rapid assessment period (+/- pneumonia)	238	397
Total	952	1,586

We anticipate that specimens are collected from Shishu Hospital 5 days per week and from ICDDR,B 4 days per week (with no specimen collection on Thursday or Friday at either facility and no collection on Saturday at ICDDR,B). If 10 and 5 specimens per work-day are collected from each hospital, respectively, in routine surveillance and the ratio of children with and without pneumonia is 2:1, then in 14 weeks of surveillance (17 weeks over 4 months), then 1,190 children would be cultured (793 with and 397 without pneumonia). Culturing an additional 397 children during the 3 week rapid assessment period would require enrolling an additional 19 children per day from Shishu Hospital and 9-10 children per day from ICDDR,B.

Given these sample sizes, the 95% confidence limits around a point estimate of resistance of 30% in children with pneumonia would be, approximately, +/- 3%.

The investigation of antimicrobial use practices of mothers is primarily descriptive. However, if 40% of all enrolled children had received antimicrobials before culture (estimated based on previous data from children with pneumonia presenting to ICDDR,B), with a sample size of 1,586 children, we would be able to detect an increase of 10% in the rate of resistance (from 30% to 40%) with a power of 98%, and an increase of 7% (from 30% to 37%) with a power of 80%.

Year 2

Objectives of the second year of the study include repeating surveillance for resistance and determining pneumococcal serogroup distribution and comparing resistance rates for Dhaka.

1. **Patient enrollment:**

Surveillance for resistance:

i) Surveillance in Dhaka: Children with pneumonia will be enrolled in surveillance from the outpatient clinics at

ICDDR,B and Shishu Hospital, as described above. If the study in Year 1 suggests that rates of resistance and serogroup distribution are similar for specimens obtained from children with pneumonia and those with other acute illnesses, the surveillance approach may be modified to include all children with acute illness.

ii) Surveillance period: Surveillance will be conducted during the peak pneumonia season (approximately 4 months) corresponding to the surveillance period during Year 1 of the study.

iii) Data and specimen collection: Surveillance in Dhaka: Procedures will be the same as during Year 1 except that the extended data on antibiotic use practices and beliefs, and the collection of lower respiratory tract secretions will be omitted.

iv) Laboratory studies: Laboratory studies will include culture of NP swab specimens (and blood for selected patients), and determination of antimicrobial activity in the urine for patients included in surveillance for resistance. Sp and Hi isolates obtained from NP and sterile site specimens will be tested for antimicrobial resistance and isolates will be serogrouped.

v) Sample size: The sample size for NP surveillance (500 children will generate approximately 300 Sp and Hi isolates.

DATA ANALYSIS AND STATISTICAL PLAN

Clinical study data will be entered into an Epi-info database at ICDDR,B. Laboratory data will initially be entered in a spreadsheet program (Excel or Lotus 1-2-3) at ICDDR,B using a specific format developed for surveillance of resistance. These files then will be converted into Epi-info and merged with the clinical database for analysis. Analysis could be done either in Epi-info or using files converted into SAS.

Resistance rates will be calculated for each pathogen and antimicrobial agent; in addition, the proportion of multiple drug resistance will be determined, defined as resistance to 3 or more classes of antimicrobials. These data will be reported by specific MICs as well as "sensitive" (S), "intermediate" (I), and "resistant" (R) using accepted National Committee for Clinical Laboratory Standards (NCCLS) criteria. Comparisons will be made between resistance rates for isolates from children with pneumonia and no pneumonia, for those who had and had not received antimicrobials before presentation to clinic, using a Chi-squared test with dichotomized data (S *versus* I and R). Similar calculations will be done to compare resistance rates for children

with pneumonia enrolled throughout the pneumonia season and those included in the rapid assessment period.

Different patient groups also will be compared for pneumococcal serogroup distribution. These will be done by a 2-by-10 Chi-squared test using the 9 conjugate vaccine serogroups and "other" groups. If a statistically significant result is obtained (p-value <0.05) then multiple 2-by-2 Chi-squared tests will be done to determine which serogroup(s) differ significantly from the others. Similar commparisons will be made for serogroup distribution of invasive and NP isolates, although the power to detect significant differences may be limited.

Culture and Gram stain results of adequate quality specimens will be described.

Data on maternal careseeking behaviuor, and antimicrobial use knowledge and practices will be described. Univariate and multivariate (logistic regression) analyses will be done to evaluate factors predictive of practices (e.g., level of education or socio-economic status as predictors for careseeking approach).

MONITORING, QUALITY CONTROL, AND PREPARATION OF REPORTS

Clinical activities will be supervised by investigators at ICDDR,B (S.A.S.) and Shishu Hospital (R.A.). These activities include

patient enrollment, assessment of pneumonia using case management criteria, specimen collection, and completion of study forms. Feedback will be given to study physicians and research assistants as problems are identified.

Quality control of laboratory procedures will be done on an ongoing basis. These include evaluation of the quality of the media used for bacterial isolation and susceptibility testing and of susceptibility test results. Disk diffusion and MIC (E-test) results will be compared and the proportion of discreptant results determined. If this rate exceeds accepted standards, both methods will be evaluated to determine potential sources of error. Overall supervision of laboratory activities will be the responsibility of S.K.S. and M.R., at Shishu Hospital and ICDDR,B, respectively.

M.R. and N.S.S. will have overall responsibility for assuring the quality of all study activities from the initiation of project activities and field testing to data entry and analysis. They also will be responsible for preparing reports of study results for the National ARI Control Programme, participating institutions, and donor agencies, as well as preparing manuscripts for publication collaboratively with the co-investigators and consultants.

INVESTIGATORS

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24. Gratten M, Naraqi S, Hansman D. High prevalence of penicillin insensitive pneumococci in Port Moresby, Papua, New Guinea. Lancet 1980;2:192-95.

ersonnel, ICDDR,B

Description	Total Cost	Year 1	Year 2
. Mahbubur Rahman	4,426.66	2,213.33	2,213.33
. Nigar Shahid	4,260.00	2,130.00	2,130.00
. Shafiqul A. Sarker(40%,40%,20%)	1,957.60	978.80	978.80
enior Research Assistant	6,150.00	3,075.00	3,075.00
ontractual Medical Res. Associate	7,024.40	3,512.20	3,512.20
fice and data processing assistant	4,464.00	1,488.00	2,976.00
stem analyst	1,380.00	920.00	460.00
nior Research Assistant/Sr. Lab Attendant	3,219.52	1,609.76	1,609.76

Dhaka Shishu Hospital

. Samir K. Saha	5,333.34	2,666.67	2,666.67
. Ruhul Amin	1,200.00	600.00	600.00
ysician (Research)	5,268.30	2,634.15	2,634.15
nior Research Assistant	4,097.56	2,048.78	2,048.78
nior Research Assistant	2,926.84	1,463.42	1,463.42
Personnel Sub-total =	**51,708.22**	**25,340.11**	**26,368.11**

Laboratory Supplies

Description	Total Cost	Year 1	Year 2
Aimes Transport media	42.38	21.19	21.19
Trypticase soy broth	44.02	22.01	22.01
Columbia agar base	1,364.31	836.19	528.12
Blood agar base	880.20	528.12	352.08
Vitox	637.50	387.50	250.00
Sheep blood	5,450.00	3,512.50	1,937.50
Rabbit blood	684.00	420.00	264.00
Bacitracin	87.34	43.67	43.67
Gentamicin	31.60	15.80	15.80
Mueller-Hinton agar	704.16	430.32	273.84
Mueller Hinton broth	89.66	44.83	44.83
Antisera (S.pnemoniae & H.Influenzae	10,000.00	10,000.00	
IAD	44.40	22.20	22.20
SPS	18.00	9.00	9.00
Saponin (White)	170.56	85.28	85.28
Skim milk	18.52	9.26	9.26
X-factor discs	254.28	156.48	97.80
V-factor discs	254.28	156.48	97.80
XV-factor discs	254.28	156.48	97.80
Optochin discs	141.81	88.02	53.79
Ampicillin (10 mcg)	76.54	47.84	28.70
Oxacillin (1 mcg)	66.97	38.27	28.70
Chloramphenicol (30 mcg)	143.52	86.11	57.41
Cotrimoxazole (25 mcg)	143.52	86.11	57.41
Erythromycin (15 mcg)	78.97	58.27	20.70
ET strips	11,316.00	6,954.00	4,362.00
Cefinase discs	1,995.00	1,230.00	765.00
Petridishes	3,306.00	2,044.50	1,261.50
Borosilicate tubes	187.50	112.50	75.00
Media dispenser	600.00	600.00	
Cryotubes	476.00	289.00	187.00
Ultra freerer (40 C) chest/ Laminar Flowhood)	4,200.00	4,200.00	
Computer	3,800.00	3,800.00	
Refrigerator/Balance	800.00	800.00	
Microwave	500.00	500.00	
Sub-total	**48,861.32**	**37,791.93**	**11,069.39**

Collection

Description	Total Cost	Year 1	Year 2
lexible wire swabs	200.00	200.00	
crew capped tubes (3-5ml)	102.00	102.00	
UC bags	5,000.00	5,000.00	
terile plastic vials (50 ml)	300.00	300.00	
uction catheters	500.00	500.00	
0 ml syringes	40.00	40.00	
ace marks	12.00	12.00	
Sub-total	**6,154.00**	**6,154.00**	**0.00**

Transport

Description	Total Cost	Year 1	Year 2
pecimens	800.00	375.00	425.00
ersonnel	500.00	-	500.00
aboratory staff	500.00	-	500.00
2 (ARI VS non-ARI)	100.00	-	100.00
Sub-total	**1,900.00**	**375.00**	**1,525.00**

nternational travel	3,000.00	1,500.00	1,500.00
rinting and Publication	500.00	500.00	-
erox	500.00	500.00	
Sub-total	**4,000.00**	**2,500.00**	**1,500.00**
Total	**112,623.54**	**72,161.04**	**40,462.50**

Miscellaneous (5% of total)	**5,631.18**	**3,608.05**	**2,023.13**
Communication (2% of total)	**2,252.47**	**1,443.22**	**809.25**
Grand total	**120,507.19**	**77,212.31**	**43,294.88**

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র, বাংলাদেশ

ও

ঢাকা শিশু হাসপাতাল

ARI

সম্মতিপত্র

(প্রধান গবেষক অথবা অংশগ্রহণকারী অন্যান্য ডাক্তারেরা শিশু রোগীর মাতাপিতা অথবা অভিভাবককে এই সম্মতিপত্রটি পড়ে শুনাবেন এবং ব্যাখ্যা করে বলবেন)।

আপনার শিশু শ্বাসনালী সংক্রামক রোগে আক্রান্ত হয়েছে এবং তাকে এই উদরাময় গবেষণাকেন্দ্রে / ঢাকা শিশু হাসপাতালে ভর্তি হতে নিয়ে এসেছেন। সুচিকিৎসা দিয়ে আপনার শিশুকে সম্পূর্ণ সুস্থ করে তুলতে আমরা সাহায্য করবো। আমাদের দেশের শিশুদের শ্বাসনালী সংক্রান্ত রোগের প্রধান কারণগুলো খুঁজে বের করার জন্য আমরা একটি গবেষণা কার্য চালাচ্ছি। আপনাকে স্বইচ্ছায় আপনার শিশুকে নিয়ে আমাদের এই গবেষণায় সাহায্য করতে অনুরোধ করছি।

আপনার শিশুর নাকে ও গলার ভিতর একটি কাঠির আগায় সামান্য তুলা জড়িয়ে মুছে কিছু শ্লেষ্মা নেবো। এতে হয়ত তার সামান্য অস্বস্তি লাগতে পারে, কিন্তু কোন ক্ষতি হবে না। এর সঙ্গে পায়ের গোড়ালী অথবা সুবিধামত শরীরের যে কোন স্থান থেকে ১ সি,সি, (1 c.c) পরিমাণ রক্ত নেবো পরীক্ষা করার জন্য। আপনার শিশুর বুকের একটি এক্সরে ও নেবো। এসবগুলোই নিয়মমাফিক ও নিরাপদ সুলভ পরীক্ষা। যারা এই গবেষণায় অংশ গ্রহন করছেন এবং যারা করছেন না তাদের সকলকেই একই রকম ঔষধপত্র ও একই রকম পরিচর্যা দেয়া হবে।

ডাক্তার বা গবেষকের এবং মাতাপিতা বা অভিভাবকের সই দিতে হবে। যদি মাতাপিতা বা অভিভাবক নিরক্ষর হোন তবে টিপসই দিতে হবে।

গবেষক অথবা ডাক্তারের সই

মাতাপিতা অথবা অভিভাবকের সই

তারিখ:-

নিরক্ষর হলে টিপসই

Use of Forms in the Protocol

1) Hospital Form will be used for pneumonia cases.

2) ARI Form No. 2 will be used for control and non-pneumonia ARI cases.

3) Bacteriology Lab Report Form will be used for culture of nasophayngeal swabs.

4) Blood culture form for culturing blood.

HOSPITAL FORM NO : 1 CODE : SAMPLE ON : DD/MM/YY HOURS

INTERVIEWER NAME : _____

PATIENT'S IDENTIFICATION & ENVIRONMENT

1. NAME OF PATIENT: _____

2. ADDRESS : _____

_____

_____

3. STUDY NUMBER : RI

4. HOSP NUMBER :

5. SEX : M F

6. AGE : Y M D

7. RELIGION : M H C OTH

8. D/ADMISSION : DD/MM/YY

9. EDUCATION : 1=Illiterate 2=Primary 3=Secondary 4=H.Secondary 5=University — FATHER / MOTHER

10. EDUCATION

11. OCCUPATION : 1=Serv 2=Busi 3=Peas 4=Labour 5=Others 6=J/Less — FATHER

12. OCCUPATION : 1=Housewife 2=Working 3=Student — MOTHER

13. # OF CHILDRENS OF SAME MOTHER

14. FAMILY MEMBER :

15. FAMILY INCOME PER MONTH : 1= Upto 500 2= 501-1000 3= 1001-2000 4= 2001-4000 5= Above 4000

16. # SMOKER IN FAMILY :

17. # PERSON IN FAMILY WITH CRONIC COUGH (MORE THAN THREE MONTH/YEAR)

18. FUEL TO COOK : 1=Gas 2=Elec 3=Kero 4=Wood 5=Othr

19. COOK PLAC : 1=Kito 2=B.Rm 3=Open 4=Vara 5=Othr

20. NUM OF ROOMS IN HOUSE

21. NUM OF ROOMS IN HOUSE FOR SLEEP

PAST MEDICAL HISTORY

EARLY FEEDING — 1=Breast 4=Other 2=Bottle 9=U/Kn 3=Mixed

1. | 1 | 2 | 3 | 4 | 9 |

IMMUNIZATION — 0=No 1=Yes 9=U/Kn

	0	1	9
2. BCG			
3. DPT 1st dose			
4. DPT 2nd dose			
5. DPT 3rd dose			
6. DPT 4th dose			
7. POLIO 1st dose			
8. POLIO 2nd dose			
9. POLIO 3rd dose			
10. MEASLES			

11. HOSPITALIZED FOR ARI DURING PAST YEAR ? — 0.No 1.Yes 9.Unknown | 0 | 1 | 9 |

IF YES (Rel Info) _____

_____

_____

_____

_____

PRESENT ILLNESS HISTORY

	DURATION (DAYS)
12. FEVER	
13. RUNNING OR BLOCKED NOSE	
14. COUGH	
15. RAPID BREATHING	
16. HOARSENESS	
17. REFUSAL OF FOOD	
18. EAR PAIN	
19. EAR DISCHARGE	
20. VOMITING	
21. DIARRHOEA	
22. DIFFICULTY IN SWALLOWING	
23. STRIDOR	
24. WHEEZING	
25. FOR HOW MANY DAYS HAS THE CHILD BEEN ILL	

26. MEDICATION RECEIVED IN PAST WEEK ? 0=No 1=Yes 9=U/kn | 0 | 1 | 9 |

IF YES (What Medi)_____

_____

HOSPITAL FORM NO : 3 PHYSICAL EXAMINATION STUDY NO : RI _ _ _ _

1. WEIGHT : -KG-- .-GRM-

2. HEIGHT (CM) :

3. TEMPERATURE °F : (RECTAL)

4. HEART RATE/MIN :

5. RESP RATE/MIN :

6. NASAL DISCH ARG: 0=None 2=Puru 1=Clear 3=B.St — 0 1 2 3

7. TONSL &PHAR YNX: 0=Norm 2=Pus 1=Red 3=Red+Pus — 0 1 2 3

8. EAR DRUMS: 0=Norm 2=Dischr 1=Red 3=N/Exam — 0 1 2 3

9. GEN AFPEA RNC: 1=Alert 3=Drowsy 2=R/Less 4=Comatose — 1 2 3 4

10. CERVI GLAND: 0=Normal 3=N/Examin 1=Enlar not tender 2=Enlarged tender — 0 1 2 3

11. SKIN RASH: 0=None 2=Vesicu 1=Morbil 3=Others — 0 1 2 3

12. NUTRI TIO N: 0=Norm 2=Kwasio 1=Maras 3=MasKw — 0 1 2 3

0 1 9 = = =

A P U
B R N
S E
E S K
N E N
T N O
T W
N

13. HOARSENESS 0 1 9

14. CYANOSIS 0 1 9

15. NASAL FLARING 0 1 9

16. CHEST INDRAWING 0 1 9

17. WHEEZING 0 1 9

18. STRIDOR 0 1 9

19. GRUNTING 0 1 9

20. EYE: 0=Norm 3=C.ulc 1=Opac 4=Blind 2=B. spot — 0 1 2 3 4

21. BREAT SOUND: 0=Vesi 3=Abse 1=Bron 4=Othr 2=D.Ves — 0 1 2 3 4

22. CREPE TATIO N: 0=None 2=Coarse 1=F.Cr 9=Unknown — 0 1 2 9

23. HEART SOUND: 0=Norm 2=B/Card 1=T/card 3=Others — 0 1 2 3

24. DEHYD RATIO N: 0=None 2=Moder 1=Mild 3=Severe — 0 1 2 3

25. OTHER SIGN : _____

26. ADMIS DIAGN: 0=B/Pn 3=Cru 1=L/Pn 4=ALB 2=AcBr 5=Oth — 0 1 2 3 4 5

27. ADD ILLNESS: _____

CLINICAL LAB FORM

- BLOOD EXAMINATION -

1. HCT :
2. HAEMOGLOBIN (%):
3. TOT LEUCO COUNT:
   A. NEUTROPHIL % :
   B. LYMPHOCYTE % :
   C. MONOCYTE % :
   D. EOSINOPHIL % :
   E. BASOPHIL % :

4. X-RAY EXAM :

LEFT	0	1	2	3	4

RIGHT	0	1	2	3	4

0=Normal 3=Dif Con
1=Seg Con 4=Hil Adm
2=Lob Con

SPECIMEN INFORMATION

5. THROAT SPECIMEN (BACTERIA) PICKED	Y	N
6. NASO-PH SPECIMEN (VIRUS) PICKED	Y	N
7. NASO-PH SPECIMEN FROZEN	Y	N
8. THROAT SPECIMEN FROZEN	Y	N
9. URINE SPECIMEN FROZEN	Y	N
10. BLOOD CULTURE DRAWN	Y	N
11. BLOOD FOR HCT/Hb% DRAWN	Y	N
12. BLOOD FOR TOT AND DIFF WBC DRAWN	Y	N
13. X-RAY CHEST DONE	Y	N
14. OTHER SPECIMEN OBTAINED	Y	N

COMMENTS ON OTHER INVESTIGATION

STUDY NO : RI _ _ _ _

DIAGNOSIS, TREATMENT & DISCHARGE

1. DATE OF ADMIS : .-DD/MM/YY--. | | | | | | |_|_|_|_|_|_|

2. DATE OF DISC : .-DD/MM/YY--. | | | | | | |_|_|_|_|_|_|

3. |DISC| 1=T/Recov 3=Dead
   |STAT| 2=P/Recov 4=Other
   |_US_| 9=U/Known

1	2	3	4	9

4. DISC DIAGNOSIS :

1	2	3	4	5	6	7

1=Broncho-pneumonia 2=Lobar pneumonia 3=Croup
4=Acute-bronchitis 5=Acute-laryngotrachites
6=Acute-epiglottis 7=Others

5. OTH ASSOC DIAG : _____

6. ANTIBIOTIC USE / DURATION

	1	2	3	4	5	6	7	8	9
	Pen	Ery	Amp	Clx	Cot	Chl	Gen	Oth	Oth

7. OTH INFO OF ANTIBIOTICS : _____

8. OXYGEN : 0=No 1=Yes 9=U/Kn

0	1	9

9. HUMIDIFICATION :

0	1	9

10. TRACHEOSTOMY :

0	1	9

11. I.V. FLUID : 0=None 2=D/Aqu 1=N/Sal 3=Oth

0	1	2	3

12. OTH MEDICATION : _____

HOSPITAL COURSE

DAY	TEMPERATURE (MAX)	RESPI RATE (MAX)	PULSE RATE (MAX)
1st	_____ ° _	_____	_____
2nd	_____ ° _	_____	_____
3rd	_____ ° _	_____	_____
4th	_____ ° _	_____	_____
5th	_____ ° _	_____	_____
6th	_____ ° _	_____	_____
7th	_____ ° _	_____	_____

SUMMARY OF HOSPITALIZATION

_____

_____

_____

_____

_____

_____

HOSPITAL FORM NO - 6

STUDY NO : RI _ _ _ _ _

CLINICAL LAB RESULTS

CULTURE	ORGANISM ISOLATED		
1. STOOL / RS			
2. URINE			
3. BLOOD			
4. THROAT SWAB			

5. Sodium _____

6. Potasium _____

7. Chloride _____

8. TCO2 _____

9. Creatinine _____

10. Glucose _____

ARI - FORM II

CODE : [ ][ ] SAMPLE ON : DD/MM/YY [ ][ ]/[ ][ ]/[ ][ ] HOURS [ ][ ]:[ ][ ]

INTERVIEWER NAME : _____

PATIENT'S IDENTIFICATION & ENVIRONMENT

1. NAME OF PATIENT: _____

2. ADDRESS : _____

_____

_____

3. MATCHED WITH STUDY NO : RI [ ][ ][ ][ ]

4. HOSP NUMBER : [ ][ ][ ][ ][ ][ ][ ]

5. SEX : [M] [F]

6. AGE : Y [ ][ ] M [ ][ ] D [ ][ ]

7. RELIGION : [M] [H] [C] [OTH]

8. D/ADMISSION : DD/MM/YY [ ][ ]/[ ][ ]/[ ][ ]

9. EDUCATION
10. EDUCATION

1=Illiterate
2=Primary
3=Secondary
4=H.Secondary
5=University

FATHER [1] [2] [3] [4] [5]

MOTHER [1] [2] [3] [4] [5]

OCCUPATION
1=Serv 4=Labour
2=Busi 5=Others
3=Cas 6=J/Less

FATHER [1] [2] [3] [4] [5] [6]

12. OCCUPATION
1=Housewife
2=Working
3=Student

MOTHER [1] [2] [3]

13. # OF CHILDRENS OF SAME MOTHER [ ][ ]

14. FAMILY MEMBER : [ ][ ]

15. FAMILY INCOME PER MONTH
1= Upto 500
2= 501-1000
3= 1001-2000
4= 2001-4000
5= Above 4000

[1] [2] [3] [4] [5]

16. # SMOKER IN FAMILY : [ ][ ]

17. # PERSON IN FAMILY WITH CRONIC COUGH (MORE THAN THREE MONTH/YEAR) [ ][ ]

18. FUEL TO COOK
1=Gas 4=Wood
2=Elec 5=Othr
3=Kero

[1] [2] [3] [4] [5]

19. COOK PLAC
1=Kito 4=Vara
2=B.Rm 5=Othr
3=Open

[1] [2] [3] [4] [5]

20. NUM OF ROOMS IN HOUSE [ ][ ]

21. NUM OF ROOMS IN HOUSE FOR SLEEP [ ][ ]

MATCHED WITH STUDY NO : RI _ _ _ _

PAST MEDICAL HISTORY

1. EARLY FEEDING — 1=Breast 2=Bottle 3=Mixed 4=Other 9=U/Kn | 1 | 2 | 3 | 4 | 9 |

IMMUNIZATION (0=No 1=Yes 9=U/Kn)

	0	1	9
2. BCG			
3. DPT 1st dose			
4. DPT 2nd dose			
5. DPT 3rd dose			
6. DPT 4th dose			
7. POLIO 1st dose			
8. POLIO 2nd dose			
9. POLIO 3rd dose			
10. MEASLES			

11. HOSPITALIZED FOR ARI DURING PAST YEAR ? 0.No 1.Yes 9.Unknown | 0 | 1 | 9 |

IF YES (Rel Info) _____

_____

12. REASON FOR ATTENDING INSTITUTION | 1 | 2 | 3 | 4 |

1=Diarrhoea 2=Surgical Problem 3=Immunization 4=Others _____

1. HOSPITAL NUMBER : | | | | | | |

2. CLINICAL INFORMATION : _____

3. SPECIMEN NAME : | TS | BI | UR | CSF | NA | PF | LPA | OTH |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

4. COLLECTED ON : MM/DD/YY | | | | | | HOUR | | | |

5. SCREENING OF PLATES

	BLOOD AGAR					CHOCOLATE AGAR				
	24 Hr	48 Hr	1Q	2Q	3Q	4Q	24 Hr	48 Hr	1Q	2Q	3Q	4Q

6. SUSPECTED COLONIES

(a) Gram Stain Result: | C+ | C- | b+ | b- | Oth |

(b) Sut Culture : | Y | N | BA | CA |

GRAM POSITIVE COCCI

IN-CLUSTER						IN-CHAIN		IN-PAIR			
Catalase-test		Coagulase-test				Bactracin disc		Optacin -disc		Bile-salt-solubility	
		Slide-Method		Tube-Method							
P	N	P	N	P	N	S	R	S	R	S	R

GRAM NEGATIVE COCCO BACILLI

Factor V,X,XV			Porpyrin test		β-lacta -mase	
V	X	XV	P	N	P	N

OTHER GRAM NEGATIVE BACILLUS : | P | N |

GRAM NEGATIVE COCCI : | P | N |

STRAIN STORED : | o -70 C | Lyp | o -20 C |

SIG _____ MM/DD/YY | | | | | | HOUR | | | |

FINAL RESULT	ORGANISM	Antibiotic Susceptibility				
		Pen	Ery	Oxa	SXT	Chlo
	St pneumonae					
	H.Influenzae					
	Staph aureus					
	Strep pyogens					

BLOOD CULTURE

DAY	DATE	G.Stain Result	Culture	Diagnosis	
D-1					
D-					
D-7					
D-					
D-10					

FINAL DIAGNOSIS	ORGANISM	ANTIBIOTIC SUSCEPTIBILITY								
		Pen	Ery	Oxa	Sxt	Chl	Amp	...	...	...
	St pneumoniae									
	H influenzae									
	Straph aureus									
	Strep pyogens									

Reviewer No. 1

Title: "Surveillance and associated studies of antimicrobial resistance in streptococcus pneumonia (sp) and Haemophilus infleunzae(Hi) in children"

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 do not support the application ☐

Name of Referee:

Signature:
Position:

Institutio

Detailed Comments

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel thay are justified.

(Use additional pages if necessary)

Title:

PI:

Reviewer:

My only concern pertains to the adequacy of methods used to assess antimicrobial susceptibility of Sp and Hi. Susceptibility testing of both of these organisms is technically demanding. Without careful application of standard methods, it is difficult to acheive reliable results. No detail was provided regarding the specific AST methods to be applied. Also, an attempt should be made to prepare and retain stock cultures of the isolates characterized in this study. It may be prudent to have a representative sample of these isolates tested in a reference laboratory as a means of confirming results.

Reviewer No. 2

Title: "Surveillance and associated studies of antimicrobial resistance in streptococcus pneumonia (sp) and Haemophilus infleunzae(Hi) in children"

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		✓ MAY NEED MORE FUNDS	
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☑ INTERNATIONAL IAR AND GPI COLLABORATION WOULD BE BENEFICIAL

b) with qualification ☐

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

I do not support the application ☐

Name of Referee:

Signature:.....Date: ....
Position:

Institution:

Detailed Comments

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel thay are justified.

(Use additional pages if necessary)

Title:

PI:

Reviewer: