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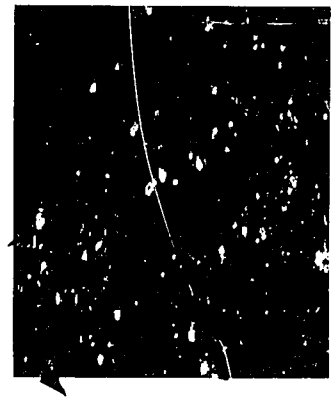

Workshop Report

ALRI & Child Survival in Developing Countries

Understanding the Current Status and Directions for the 1990s

The Johns Hopkins University
Institute for International Programs

Acute Lower Respiratory Infection & Child Survival in Developing Countries

Understanding the Current Status and Directions for the 1990s

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Edited by
Anne Gadomski, M.D., M.P.H.
Technical Advisor

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CONTENTS

PREFACE v

INTRODUCTION vii

Overview of Ongoing Research Activities and Plans

Summary of AID activities 1
PAMELA JOHNSON

Summary of WHO activities 11
MICHAEL MERSON

Summary of UNICEF activities 15
NYI NYI

Epidemiology of ALRI: State of the Art

Nosology and standards for ARI studies in children in developing countries 21
MARK STEINHOFF

BOSTID study on acute respiratory tract infections 29
PATRICIA CHARACHE

Overview of pneumonia in early infancy 39
STEPHEN BERMAN

Hierarchy of risk factors: feasibility and status of primary prevention 53
ROBERT BREIMAN

Available and potential vaccines for control of lower respiratory tract infections in developing countries 63
NEAL HALSEY

The BOSTID research program: future research needs 73
FLOYD DENNY AND JUDITH BALE

Discussion Summary 81

Community-based ALRI Treatment

Review of ALRI intervention studies: effect on mortality 85
ROBERT BLACK

Clinical signs predictive of pneumonia in children 89
STEPHEN REDD

Practical issues of ARI program implementation 99
NILS DAULAIRE

The therapeutic significance of the presence of wheezing in acute lower respiratory infection 105
ROBERT WELLIVER

Usage of antimicrobial agents and development of resistance to them 111
THOMAS O'BRIEN

Discussion Summary 117

Operations Research in ALRI Programs

Implementing ALRI programs: an operations research framework 121
JAMES HEIBY

Systems analysis and operations research in service delivery for ALRI 129
STEWART BLUMENFELD

Discussion Summary 141

Behavioral Aspects of ALRI Research and Programming

Behavioral aspects of acute respiratory infection in children 145
GRETEL PELTO AND CARL KENDALL

Mothers' perception of ALRI: a case study in Lesotho 153
RUTH WILSON AND ITUMELENG KIMANE

Behavioral research in the development of ALRI communication strategies 161
JUDITH GRAEFF

Field perspectives on implementation of an ALRI communications program in Honduras 173
PATRICIO BARRIGA

Discussion Summary 181

Cost and Cost-Effectiveness in ARI Programming

Cost and cost-effectiveness issues for ARI case management 185
LOGAN BRENZEL

Potential savings through reduction of inappropriate use of pharmaceuticals in the treatment of ARI 193
SALLY STANSFIELD

AGENDA 201

PARTICIPANTS 203

PREFACE

There is little disagreement that acute lower respiratory tract infections (ALRI) are a major source of mortality in young LDC children. It has been estimated that about 4 million children die each year due to ALRI, and that ALRI is responsible for approximately 25-30 percent of deaths in children under five years of age.

Numerous countries around the world have initiated ALRI activities to address this large problem, ranging from small scale studies to limited national programs. The scientific and empirical bases for programmatic responses to ALRI are evolving rapidly. However, many biological and behavioral issues critical to developing effective ALRI services are not fully understood.

For all these reasons, in August 1989 A.I.D. called together leading experts in the field to review the major technical issues surrounding diagnosis and treatment of ALRI and to discuss their programmatic implications.

The ALRI workshop participants represented a wide range of expertise. The workshop was not intended to produce a consensus statement or a set of specific recommendations. Rather, this volume presents a current summary of the state-of-the-art that appropriately identifies the difficult obstacles as well as the encouraging developments in this important field.

I hope that you will find this summary both useful and thought-provoking.

Ann Van Dusen, Ph.D.
Acting Director
Office of Health
Bureau for Science and Technology
Agency for International Development

INTRODUCTION[1]

Anne M. Gadomski, M.D., M.P.H.
The Johns Hopkins University and the
University of Maryland

BACKGROUND

This workshop focused on the following convergence of needs from both the research and the program implementation perspective: what are the lessons learned from current research and programs, what are the gaps in knowledge, and what immediate action is needed in the areas of implementation, service delivery and research. The intention of the workshop was to bring a multi-disciplinary perspective to these issues, and attempt to tie diverse themes together. The papers included in this proceedings present different perspectives on the topic of acute lower respiratory infections in developing countries in order to facilitate the next step of weaving these themes together.

In part, the agenda yielded to the question "what can be done now ?" This pressure to do something fairly immediate about ALRI mortality resulted in a greater emphasis on the curative intervention, i.e. case management of ALRI with antibiotics, rather than on preventive measures. Case management can be viewed as a stop gap, curative intervention that is subject to diminution by replacement mortality. This emphasis should not detract from the importance of preventive measures, particularly development of vaccines, nutritional intervention and low technology approaches to domestic smoke reduction. Past experience with other direct interventions suggests the need for more multi-disciplinary approaches that are less selective and have a broader potential impact. The challenge to health planners is integrating ALRI interventions with other services.

OVERVIEW OF THE PROCEEDINGS

International Health Agency Activities in ALRI

The first set of papers from the Agency for International Development (AID), the World Health Organization (WHO), and United Nations Children's Fund (UNICEF) describes the activities of these agencies in ALRI. AID has funded several, broadly distributed efforts both from the program and research perspectives that deal with ALRI. WHO has

[1] This introduction is derived in part from: Gadomski A. "Acute Respiratory Infections In Developing Countries: Programs and Priorities" presented at the American Public Health Association meetings, October 25, 1989.

greatly intensified its ARI national program development, training, and research efforts over the past year. New case management training materials should be available from WHO in early 1990. UNICEF is in the process of supporting the development and evaluation of national ARI program in Bolivia, The Gambia and Thailand. The implementation experiences of these three countries should provide many valuable lessons to other countries as they establish their own ARI programs.

Epidemiology of ALRI - State of the Art

Terminology within the acute respiratory infection (ARI) field can be misleading, so the first paper by Mark Steinhoff addresses the nosology of ARI. There is a need for those involved in the ARI field to speak the same language and use standardized definitions. While this is critical for comparing research results, it will also be important in comparing the effectiveness of ARI programs. Patricia Charache's paper describing the BOSTID studies underscores the importance of not only standardizing definitions of ARI, but also standardizing definitions of exposure to risk factors, study design elements and laboratory procedures in ARI research.

This proceedings adopts the following simple abbreviations. ARI is an inclusive term that covers both upper (URI) and lower tract infections (LRI). URI's, like the common cold, are very frequent, and do not contribute directly to childhood mortality. Acute lower respiratory infection (ALRI) includes pneumonia, bronchiolitis, tracheolaryngitis (croup), and bronchitis. ALRI is one of the chief causes of mortality in developing countries, so it was the focus of this workshop.

Twenty-five to thirty percent of the estimated 15 million deaths among children under five years of age occurring each year are attributed to ALRI. Pneumonia accounts for the majority of these [1]. The incidence of ARI is similar in developed and developing countries, with estimates that range from 2 to 7 respiratory illnesses per child per year. Infants, particularly those less than six months old, are at significantly greater risk of dying from ALRI, and progressing more rapidly to death than older children. Stephen Berman in his paper on ALRI in the first three months of life describes the reasons for this greater susceptibility in younger age groups and outlines the state-of-the-art in terms of research efforts in this age group.

The severity and case-fatality of ALRI is greater among young children, particularly infants, in developing countries. As discussed by Robert Breiman, this is due in part to the predominance of certain risk factors, poor access to effective health care, and co-morbidities, such as malnutrition and low birth weight, in developing settings. Conversely, ARI contributes to childhood malnutrition, especially via the cumulative impact of repeated episodes. Nutritional intake can be diminished during an ARI episode [2]. Fever associated with ARI also depletes nutritional stores by increasing the metabolic rate, and contributing

to anorexia. Therefore, ARI can fuel the vicious cycle of repeated infection and increased malnutrition.

Other risk factors, such as overcrowding and indoor air pollution, may vary in their relative importance depending on regional differences. Many of these factors are also associated with socio-economic status and level of education. This makes it difficult to isolate the effect that may be attributed to each of these independently. However, inferences on the negative effect of domestic smoke may be made based on the data linking passive smoking with an increased incidence of respiratory infections in infants in developed countries [3]. Additionally, domestic smoke in developing countries may be more toxic than exhaled tobacco smoke, due to a higher respirable particulate concentration and a greater variety of pollutants, such as hydrocarbons [4].

Given this array of risk factors, the long-term and short-term approach to ALRI control has to be multi-disciplinary, and involve preventative as well as curative interventions. A comprehensive program would have to address nutritional status, immunization status, low birth weight prevention, and environmental interventions to reduce domestic smoke, such as vents, windows and/ or smokeless stoves, in addition to antibiotic treatment. Neal Halsey provides a succinct update on the role of immunization in ARI control as well as the potential for future ARI vaccines. Finally, Floyd Denny and Judith Bale outline the future BOSTID research priorities that were recently discussed by the National Research Council Committee on ARI and that bring together the major themes of the papers presented in this section.

Community-Based ALRI Treatment

The objective of case management is to provide the right child with the right drug early in the course of disease. Community health workers (CHWs) are guided by a treatment algorithm for deciding which children with respiratory symptoms merit antibiotic therapy. The WHO ARI algorithm, upon which the case management approach is based, initiated the demystification of ARI, and could liberate ALRI from a sort of therapeutic vacuum at the village level. As a treatment algorithm, it has been simple and feasible. Prior studies of case management implemented by village health workers have suggested that CHWs can be trained to administer antibiotics safely, and effectively, if well supervised [5].

Several studies attempting to determine the effectiveness of case management were recently reviewed by WHO [6], and these are summarized by Robert Black. In some studies, case management appeared to have a significant impact, in others less so. Antibiotics are efficacious (they do work) in the treatment of pneumonia, however their effectiveness (whether they can work under field conditions) is modified by the quality of implementation as well as by community acceptance. The ARI program depends not only on correct case recognition, timely management and referral by the CHW but also on

antibiotic administration, supportive care and continued assessment by the caretaker at home.

The case management approach depends on the clinical yield of certain signs and symptoms used in the algorithm to "capture" the child with pneumonia, and to guide treatment. Steven Redd reviews the studies that have examined the utility of the signs and symptoms to identify the child with pneumonia. This has been a difficult area of study because of problems that arise with biases due to subject selection (case mix or spectrum bias) as well as how the diagnosis of pneumonia is made [7]. The WHO entry criteria and the management guidelines are currently undergoing revision and expansion to accommodate recent research findings pertaining to this algorithm [8,9,10]. These revisions most likely will include 1) a change in terminology from ARI to pneumonia, 2) a separate algorithm for infants less than two month olds, 3) use of separate RR cutoffs for different age groups to improve the sensitivity and specificity of the entry criteria, 4) addition of follow-up in two days of children treated for presumptive pneumonia, and 5) revised algorithm for children with wheezing.

Effectiveness of the case management approach is also determined by program coverage, supply logistics and the existing health infrastructure for referral, training and supervision. The managerial side of a community-based ALRI program in Jumla, Nepal is well described by Nils Daulaire, who outlines the conditions necessary for an ARI program to be effective. His list of conditions nicely underscores the importance of considering, not only the supply side, but also the demand side of an ARI intervention. Traditionally, much more attention had been given to the former, as if the simple provision of technology at the doorstep of the community were sufficient to have an impact on child health. The discussion summary, as well as the Behavioral Sciences section, reflects the emphasis that is increasingly being placed on the community side of the equation to better understand issues of program effectiveness, acceptability, and sustainability. Certainly, ARI programmers can gain a great deal from critical examination of the implementation experiences of other direct interventions, such as malaria and diarrheal disease control [11,12]. Integration and coordination with other services, particularly immunization, would augment the impact of the ARI program, while reducing duplication of services and providing more comprehensive primary health care.

Active case finding (going house to house on a regular basis to find children who meet the algorithm criteria) was employed in the Jumla ARI Intervention Trial. This could be a costly and labor intensive approach. It is likely that the case management strategy will have to also rely on passive case finding, i.e. self-referral by caretakers to the CHW. This mode of intervention will require ethnographic and other behavioral science input in order to construct effective communication and educational strategies for the area to be served. These strategies are described later in the Behavioral Science section.

Wheezing, a common finding in children due to bronchiolitis, asthma or broncho-pneumonia, presents a diagnostic and therapeutic dilemma in both developed and developing country settings. Robert Welliver discusses the therapeutics of wheezing children, drawing on the limited amount of data available in both developed and developing country settings. Bronchiolitis is the most common acute lower respiratory tract infection requiring hospitalization in the first year of life in developed countries [13]. It is associated with a 2% case mortality rate in normal children and 15-50% mortality rate in children with congenital heart disease or immunocompromise. It is probably an under-appreciated source of morbidity and mortality in developing countries, due to under-reporting or mis-classification. Significant controversy exists about the role of bronch- dilators, steroids, mist, and antiviral agents in the treatment of acute bronchiolitis [14,15,16], which makes decisions about standard treatment algorithms difficult. Clearly, this is an area in which research is needed to clarify management.

Antibiotics are the key technology involved in the case management strategy. Thomas O'Brien paints a rather sobering picture of growing global antibiotic resistance that threatens the efficacy of ALRI interventions. Recent surveys, described by Sally Stansfield in the cost-effectiveness section, have begun to document the extensive overuse of antibiotics. Antibiotics can be purchased without a prescription in many countries of the developing world. The demand for antibiotics is high because they have a good reputation, they yield visible results, and have a good track record dating back perhaps to the Yaws Control Program.

Inadequate dosage as well as abbreviated courses of antibiotics taken compound the overuse problem, and all of these contribute to the development of antibiotic resistance. H.influenza and to a lesser extent S. pneumoniae are becoming increasingly resistant to the penicillin drugs. The spread of antibiotic resistance can be quite efficient. For example, a single plasmid transferred among strains of H. influenza resulted in multiple resistance to ampicillin, tetracycline, and chloramphenicol [17]. The development of antibiotic resistance may necessitate the substitution of currently widely available penicillins and cotrimazole with more expensive, second line antibiotics. This resulting situation could be analogous to the development of both vector and parasite resistance in the malaria programs in the 1970's. As yet, it is unclear at what level of antibiotic resistance should policy changes be made.

Operations Research in ALRI Programs

The supply side of the intervention continues to be critically examined in this section. James Heiby describes the operations research framework within which the activities of service delivery can be disaggregated, and problems within the system can be identified and solved. The following basic questions can be approached in a systematic, objective fashion: what are health workers doing, how well are they doing it, what are the outcomes,

and how can the quality of services be measured, and improved? Specific technologies, such as timers with audible cues [2], could be evaluated using operations research methodology. Additionally, little is known about the outcome of children who are referred, and the determinants of such outcomes. Operations research can be conducted in the context of large scale programs to determine what process variables correlate best with a good outcome.

Functions of the CHW, supervisor and the health information system are further discussed and analyzed by Stewart Blumenfeld in his paper and in the discussion. The importance of providing higher level support to CHWs as well as attending to details of supply logistics and modes of referral cannot be underscored enough, and has been the subject of several recent reviews [18,19,20]. Capacities for community-based ALRI treatment should not be developed in isolation; rather the upgrading of supporting health facilities should take place in parallel or in advance of instituting community-based ARI case management.

The design of health information systems is an important element of an effective program. Because an average 40% of the CHWs working time is spent on collecting data (that is frequently not utilized) [21], such bureaucratic responsibilities may divert the CHWs time away from direct patient contact. In the discussion summary, Nils Daulaire describes the minimum of information that CHWs were required to collect in the Jumla ARI Intervention Trial. This description is a good example of how a balance between data collection and utility can be achieved, and how indicators can be used to monitor a program on a monthly basis.

Behavioral Aspects of ALRI Research and Programming

The household management of ARI is currently an active area of investigation, the framework for which is clearly circumscribed by Gretel Pelto and Carl Kendall. These authors draw helpful parallels between biomedical and emic/folk theories that help bridge conceptual gaps between the supply and demand perspectives on ARI control. Other dichotomies arise in the discussion of the behavioral aspects: community vs health system management of ARI, mother vs health worker perception and recognition of ARI, anthropologic vs biomedical templates for research and program planning. While drawing the parallels is helpful in conceptualizing the problems that arise in the interface of "opposites", the discussion revolved around how to achieve a better fit between cultural templates, between explanatory models and between service providers and recipients.

The case management approach depends on timely recognition and treatment of ALRI. What this really means is that the mother must be both a diagnostician as well as a

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[2] Such timers may facilitate the counting of RR's because the CHW does not have to have his/her eyes in two different places (i.e., on the chest and on the timer) at the same time.

primary caretaker. The importance of female education as a determinant of these roles cannot be over-emphasized[22]. Self-referral means that the mother recognizes and responds quickly to certain signs and symptoms (S&S) that indicate that the child has severe disease. Ruth Wilson presents a case study done in Lesotho on what ARI disease and S&S mothers recognize, and if they respond differently to certain ones. She describes the local terms employed for ARI, and relates these to the entry criteria that the treatment algorithm depends on. This study is a good example of the richness that exists in cultural ARI nosology and household management. The challenge is to link this knowledge to effective programming.

The specific determinants of local health seeking behavior need to be considered in program planning. Children commonly die from pneumonia because they come too late for treatment or because they do not come at all. Why does this happen? How do cost (both in time and money), confidence in curative power, proximity, and custom interact and modify the management decisions that the mother makes? Traditional healers were consulted as frequently as the dispensary or health center and more frequently than the village health worker in the ARI study done in Bagamoyo district in Tanzania [23]. Unlike the clinic setting, these workers may be accessible, affordable, responsive, and culturally sensitive. Regional differences in health seeking patterns should be expected. In contrast to Tanzania, a study of Jakarta urban poor revealed that the majority of respiratory illnesses are treated at home [24].

Ethnographic and anthropologic field work should be conducted prior to the intervention, in order to incorporate relevant traditional beliefs, local language and practices in the design of the program, including the communication component of the program. Judith Graeff describes the HEALTHCOM experience in the development of communication programs, and how these programs rely on well designed benavioral research. The importance of face to face communication with health workers and health worker training are identified as key elements in the success of a communication program in Honduras, which is later described from the field perspective by Patricio Barriga. In the implementation of this communication program, Barriga identifies obstacles that arose secondary to lack of coordination between public and private sectors, as well as among international health agencies, and underscores the need for a cooperative multi-disciplinary intersectoral effort.

Cost and Cost-Effectiveness in ARI Programming

Whether or not case management will lead to rational use of antibiotics, and therefore yield the much hoped for reduction in ALRI-specific mortality and concurrent economic benefits from less drug misuse, has yet to be determined. Like epidemiologic studies on ALRI etiology and risk factors, a standardized approach to studying the cost-effectiveness of ARI case management will be necessary. Logan Brenzel outlines the approach to the

costing and appropriate application of cost-effectiveness analysis in ARI programming. Of all the topics presented in this proceedings, the cost of an ARI program has the inauspicious distinction of having the least data available upon which to comment.

The use of drugs, including antibiotics and the numerous cough and cold elixirs to treat ARI, presents an economic problem. Sally Stansfield describes the magnitude of this problem, and presents compelling data on drug use. Overuse occurs at both the health provider and household levels. Even the well informed health provider may find it difficult not to yield to a caretaker's expectation that his/her child needs an antibiotic. At the household level, administration of left-over or shared antibiotics is commonly tried before taking the child to a health provider. Stansfield outlines the potential interventions to reduce inappropriate drug use in ARI treatment.

The various cold and cough elixirs that are so widely available often contain ineffectual and, at times harmful ingredients, which are also expensive. The discussion summary outlines various positions on whether or not an ARI program should provide a "safe" cough/cold mixtures. Cough is a protective reflex that serves in ALRI to aid in the clearance of mucous, cellular debris and pathogens from the lower respiratory tract. Should money be spent to suppress coughs? Cases can be made for and against. What is lacking in the argument are estimates on the extent to which these drugs consume scarce household resources, diverting them away from food and other essentials. Such data will be needed in order to address this problem and develop alternative strategies, such as a communications campaign, to counter the promotional activities of pharmaceutical companies.

In conclusion, primary health care programs designed to address child survival in developing countries can no longer ignore the problem of pneumonia mortality or LRI morbidity in these settings. At the same time, the relative novelty of the case management approach dictates that careful attention be paid to monitoring and evaluating this intervention, in order to efficiently address the operational problems that will inevitably arise.

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Summary of Current AID Funded Activities Related to Acute Respiratory Infection

Presented by Pamela Johnson, Ph.D.
Child Survival Coordinator
Agency for International Development

AID's child survival strategy is focused on delivering the most effective known technologies, and supporting field programs with technical expertise and results-oriented research. Thus far, this strategy has emphasized two technologies known to prevent the leading causes of death as the core of the child survival initiative: oral rehydration therapy and immunization. Up to this point, ARI has not been a major focus of the Agency's central activities, although directly and indirectly the Agency funds a number of ARI-related activities. Reports to AID's Health and Child Survival Information system indicate that in FY 1987, 57 projects or subprojects in 25 countries had some ARI involvement. In 1988, 63 projects in 25 countries reported ARI activities. Among those field projects in FY 87 (bilateral and PVO) that provided information on ARI activities, 61% reported a case management component, 61% had a training component, and 50% reported activities in health education or communications. 25% of field projects reported a research component; many have incorporated a strong evaluation component. (See "Summary of Ongoing Projects Reporting an Acute Respiratory Infection Component, ISTI, April 1989, following this paper.)

Major bilateral projects with ARI components include those in Egypt and Nepal. In Nepal, USAID has supported research studies of ARI case management and treatment in the Jumla and Gorka districts. In Jumla, the program includes active case detection and treatment of severe ARI in children under five. The impact of active house to house sur-veillance for ARI cases every two weeks and treatment of cases identified via this sur-veillance is currently being analyzed. Although preliminary analysis suggested a mortality differential the first year, subsequent analysis has not borne this out. The reasons for this lack of impact may be related to limited coverage of the intervention, as 75% of the mortality was never seen by health system. Most of the cases were identified by the home visits, with a small percentage of cases brought to health system for care.

In Egypt, a 20 million US dollar ARI component of the much larger Child Survival Project is in the planning and development stage. This project plans to address various aspects of ARI-related epidemiology, operations research, clinical management, training and diagnostic/treatment improvements. Many of these investigations will take place in the context of monitoring and evaluating the National ARI program currently being planned by the Egyptian Ministry of Health.

Currently, there are also a number of centrally-funded projects that are related to ARI research and programming. The Office of the Science Advisor funded an eight year program with the Board on Science and Technology in Development (BOSTID) in 1981 on the etiology and epidemiology of ARI. This research program is well known for its focus on the quality control of laboratory procedures and comparability of data obtained from diverse settings. Initial results from 11 of the 12 country studies were presented in October 1988. These studies include community based studies to determine the incidence of ARI, studies of outpatient populations to determine the clinical epidemiology and etiology of ARI, and studies of hospitalized children with ARI patients to determine the cause of severe and fatal ARI. They confirm that streptococcus pneumoniae and hemophilus influenza type B are the most significant bacterial causes of severe ARI. Respiratory syncytial virus (RSV) and parainfluenza were the most commonly observed viral pathogens. In general, about half of cases could have etiology established in these studies. Important problems with the sensitivity of both bacterial and viral diagnostic procedures have been identified through this research effort. As concomitant diarrhea and ARI are not infrequent, a hospital based etiologic study of ARI in children was recently completed by David Sack in Bangladesh. This study revealed that the spectrum of causation, i.e. respiratory syncytial virus (RSV) and the usual bacterial pathogens, was not different in these children.

The Office of the Science Advisor has also funded three studies to develop serologic and rapid diagnostic techniques for tuberculosis. One of these studies will also investigate the immunoregulation in tuberculosis. A study of the potential use of Bordetella pertussis invasive adenylate cyclase in the development of an acellular vaccine was also supported by the Office for Science Advisor through the US-Israel Cooperative Research Program.

The Office of Health has funded a number of studies focused primarily on operations research, case management, epidemiological assessment, diagnostic and evaluation tools, communications support, and vaccine development. These involve the following organizations and countries:

- Demographic and Health Surveys (DHS) have provided preliminary information on the prevalence of cough or difficulty breathing as well as kinds and sources of treatment for ARI. In Liberia, for example this question yielded 31% for children

under five, with the highest percentage, 52%, found in infants between 6 -11 months of age. Treatment of these children included a cough syrup in 62%, an indigenous therapy in 14%, and antibiotics in 2%. DHS data has been helpful in detecting regional variations in the prevalence and treatment of ARI. The DHS II questionnaire will combine these questions to aid in the estimation of the prevalence of children with cough and rapid or difficulty breathing. It will also include questions on treatment of ARI. In Bolivia, verbal autopsy questions were incorporated as part of the DHS I survey in order to estimate the levels of ARI-related mortality.

- Primary Health Care Operations Research (PRICOR) is focused upon systems analysis (observational studies) followed by operations research targeted at the problems identified by systems analysis. The later aspect of this research strategy allows for proactive investigations designed to improve the effectiveness of the program. Current ARI-related activities include the following:

    1. In Bogota, Colombia, a private corporation (Santa Fe de Bogota) was funded to carry out a descriptive study of ARI service delivery by community volunteers. The operational difficulties identified included inadequate training in case management, volunteers not up-to-date on new MOH norms for ARI management, liberal use of medications without prescription, little attempt to educate mothers during home visits. Operational studies focused on training and health service delivery were then undertaken to address these problems. The results of these studies inspired the MOH to look at quality of care in the public sector, and address similar operational problems.

    2. In the Philippines, a systems analysis of EPI, GM and CDD as well as ARI service delivery (with a focus on case management and its supervision) was achieved by direct observation of service provider's and their supervisors by independent observers. A total of 370 managed ARI cases were observed. This systems analysis identified quality of care shortcomings, such as inadequate counseling of mothers about medication use, and also demonstrated that field supervisors were unaware of health worker performance. For example, supervisors thought that mothers were counseled to monitor the child 66% of the time, whereas the health workers were observed to do so 1% of the time. These studies have led to the formulation of a series of operation research studies that will examine the details of service delivery and supervision of several child survival interventions.

3. In Indonesia, a systems analysis, i.e. quality of care assessment done by the Ministry of Health and the Western Consortium for Public Health, was completed via a questionnaire administered to MD's on cases of ARI. Six studies designed to examine the availability and use of antibiotics and the appropriate diagnosis and management of ARI by mothers and kaders have been completed. One of these studies documented that antibiotic treatment of mild ARI is not effective in preventing clinical progression, and this result will be published in an Indonesian medical journal. Another of these studies found that a letter from the provincial health officer ordering that antibiotics not be used for treatment of mild ARI was effective in reducing antibiotic use.

4. The Primary Health Care Thesaurus for ARI (volume one and volume two) includes an extensive list of ARI service delivery activities and corresponding quantitative indicators used in systems analysis. This listing focuses on the peripheral service workers. The use of these basic indicators could facilitate the monitoring and evaluating their programs. For example, specific components of a program, such as patient counseling in ARI, can be examined and evaluated by program managers using the specific indicators described in the thesaurus.

- HEALTHCOM, a project implemented by the Academy for Educational Development, has completed the development of a communication strategy for ARI intervention in Honduras. Based on ARI ethnographic and behavioral studies, radio communications, training procedures and incentives for health workers and mothers were developed in order to implement an integrated communication and behavior change approach to ARI control. Face to face demonstrations by health workers were shown to be effective in improving mothers' ability to care for children with ARI. In the Philippines, an observational study of mothers in urban clinic setting has been conducted in order to determine whether mothers are able to judge the severity of ARI using WHO diagnostic signs and symptoms. This study is currently in the analysis phase, and will contribute relevant baseline data to the Department of Health's (DOH) policy formulation in ARI control.

- A Technical Information on Population for the Private Sector (TIPPS) project in Peru has investigated the health status of children under five years of age, and services utilization of a mining community in Peru. A review of pharmacy records revealed that every patient under five years of age seen at the private clinic was

prescribed a minimum of two pharmaceuticals. For upper or lower respiratory infections, the mean number of medications prescribed was 3.7, which includes antibiotics, decongestants, expectorants and analgesics. The mean wholesale cost of these medications for this age group in one year accounts for one third of the total annual expenditure for the clinic's pharmacy. One recommendation from this study was that physicians be trained to reduce their prescription of antibiotics by using the WHO/PAHO norms for treating ARI.

- Diagnostic Technology for Community Health (DIATECH), a project implemented by PATH, is developing simple ARI diagnostic tools for use in isolated areas by non-medical field personnel. A recent workshop of DIATECH investigators discussed progress in the development of tuberculosis, respiratory syncytial virus, influenza, pneumococcus immunoassays and other diagnostic tests. The development of rapid diagnostics at this point is faced with the task of addressing the complexity and variety of antigens associated with ARI pathogens, so there are currently no tests ready for field testing at this point.

- Child Survival Action Program: Johns Hopkins University, via the Institute for International Programs and the Child Survival Fellows Program, has developed and tested verbal autopsy procedures and other evaluation techniques that include ARI. In addition, a child survival fellow (Krishna Bose) developed a protocol for ARI treatment program in India for a PVO (CARE).

- Verbal autopsy is a method currently under active investigation that may allow for estimation of mortality levels. A validation of verbal autopsy with hospital records, in addition to a study of material recall of ARI episodes with validation through hospital records of cases, has been completed in Cebu, the Philippines. These studies provided some of the required methodology and baseline data for TIER III evaluation of child survival activities in Cebu. This program evaluation is currently monitoring the level of ARI, diarrhea and measles childhood morbidity and mortality in this area of the Philippines. Other validation studies of the verbal autopsy approach, in which verbal autopsy histories were correlated with hospital based diagnoses and causes of death, have been completed in Bangladesh and are ongoing in Kenya. In Bangladesh, levels and causes of childhood morbidity which included ARI were determined as part of the truncated five year maternal history, and the survey is in the analysis phase. In Kenya, malaria may be a key confounder of ARI classification and reporting. Determining the validity of the verbal autopsy approach in a malarious area will be important in defining the utility of this approach in such areas.

- The MORVITA project in Indonesia will assess the impact of community-based vitamin A supplementation on the incidence and severity of ARI as well as

diarrheal disease. This double blind field trial of vitamin A is starting August 1989 and is being conducted by Gadjah Mada University in collaboration with Johns Hopkins University. As a pilot for this study, an ethnography of ARI in Central Java is currently being conducted.

- Pulse oximetry, a non-invasive technique for determining the oxygen saturation of blood, may be a useful tool in the evaluation of children with ARI. A pilot study by Johns Hopkins University was done in an inner city Baltimore emergency room to determine the correlation of signs and symptoms with radiologic diagnosis of pneumonia and with pulse oximetry. The clinical signs and symptoms of these children were compared to both radiologic diagnosis of pneumonia and to oxygen saturation as measured by pulse oximetry. The WHO criteria were specifically compared to radiologic diagnosis of pneumonia and to oxygen saturation, and were found to predict low oxygen saturation better than radiologic pneumonia.

- Technology for Primary Health Care (PRITECH) has supported a review of technical issues, and provides technical assistance in programmatic issues relevant to ARI. A PRITECH study in Indonesia documented prescription patterns for ARI and other conditions, revealing inadequate dosage and excessive use of antibiotics, associated with high costs. Resources for Child Health (REACH) has provided technical assistance in program areas related to ARI, particularly in financing.

- Vaccine Development - AID is working with a range of US institutions and counterparts in developing countries to develop and test new and improved vaccines. Through an agreement with the Department of Health and Human Services, AID is sponsoring a variety of activities to stimulate the development and testing of new vaccines. ARI-related vaccines have been given high priority. Because measles disease accounts for a considerable proportion of severe or fatal ARI, development of a measles immunization that is effective earlier in infancy would potentially contribute substantially to ARI control. Recent results from AID funded studies being carried out by researchers from the Centers of Disease Control and The Johns Hopkins University working with colleagues in Mexico and Haiti suggest that the Edmonston-Zagreb measles vaccine can protect children under nine months of age. As a prelude to a field trial of a conjugate pneumococcal vaccine, a community based 18 month surveillance of pneumococcal disease in infants and children in the Gambia is currently being planned. In addition, the Medical Research Council in the Gambia is currently establishing a field surveillance for a field trial for Hemophilus influenza type b vaccine immunogenicity study.

USAID Health Information System
Center for International Health Information, ISTI, April 1989

SUMMARY OF ONGOING PROJECTS REPORTING AN ACUTE RESPIRATORY INFECTION (ARI) COMPONENT

Source: Health Projects Database; 1987 and 1988 Health and Child Survival Questionnaires

	COUNTRY	TITLE	PROJECT NUMBER	BILATERAL REGIONAL OR CENTRAL SUPPORT	IMPLEMENTING AGENT	TYPE OF ORGANIZATION	RESEARCH ACTIVITY IN ARI	GEOGRAPHIC SCOPE OF THE PROJECT NATIONWIDE SUBNATIONAL OR GLOBAL
AFRICA								
	Kenya	Child Survival Grant to AMREF	9380519	CENTRAL	African Medical Research and Educational Foundation	PVO/U	YES	SUBNATIONAL
	Kenya	Child Survival Grant to WVRD	9380527	CENTRAL	World Vision Relief and Development	PVO/U		SUBNATIONAL
	Lesotho	Africa Child Survival Initiative - CCCD	6980421	REGIONAL	Centers for Disease Control	USG	YES	NATIONWIDE
	Lesotho	Communication for Child Survival-HEALTHCOM	9311018	CENTRAL	Ministry of Health	HCG		NATIONWIDE
	Malawi	Health Institutions Development	6120211	BILATERAL	Howard University	UNC		NATIONWIDE
	Malawi	Child Survival Grant to SCF	9380524	CENTRAL	Save the Children Federation	PVO/U		SUBNATIONAL
	Mali	Integrated Family Health Services	6880227	BILATERAL	Ministry of Health	PVO/U,HCG		SUBNATIONAL
	Mauritania	Rural Health Services	6820230	BILATERAL	John Snow	PVC		NATIONWIDE
	Nigeria	Africa Child Survival Initiative - CCCD	6980421	REGIONAL	Centers for Disease Control, UNICEF	USG, NGO/M	YES	NATIONWIDE
	Sudan	Rural Health Support	6500030	BILATERAL	African Medical Research and Educational Foundation	PVO/U		SUBNATIONAL
	Swaziland	Primary Health Care	6450220	BILATERAL	Management Sciences for Health, Charles R. Drew University	NGO/U,UNC		NATIONWIDE
	Swaziland	Africa Child Survival Initiative - CCCD	6980421	REGIONAL	Centers for Disease Control	USG	YES	NATIONWIDE
	Togo	Health Sector Support for Child Survival	6930228	BILATERAL	Ministry of Health	PVC,HCG		NATIONWIDE
	Uganda	Child Survival Grant to MIHV	9380513	CENTRAL	Minnesota International Health Volunteers			SUBNATIONAL
	Zaire	Basic Rural Health II	6600107	BILATERAL	Government of Zaire	HCG		SUBNATIONAL
	Zaire	Kimbanguist Hospital Assistance	6600122	BILATERAL	Hadassah/USA	PVO/U		SUBNATIONAL
	Zaire	Primary Health Care in Operations Research	9365920	CENTRAL	Center for Human Services	NGO/U	YES	SUBNATIONAL
	Zimbabwe	Child Survival Grant to WVRD	9380505	CENTRAL	World Vision Relief and Development	PVO/U		SUBNATIONAL
Asia/Near East								
	ANE Regional	West Bank/Gaza: Life Cycle Health Education	3980159	REGIONAL	Catholic Relief Services	PVO/U		SUBNATIONAL
	Bangladesh	Urban Volunteer Program	3880073	BILATERAL	International Centre for Diarrhoeal Disease Research,Bangladesh	NGO/M, UNC	YES	SUBNATIONAL
	Bangladesh	Child Survival Grant to SCF	9380502	CENTRAL	Save the Children Federation	PVO/U		SUBNATIONAL
	Bangladesh	Child Survival Grant to WVRD	9380505	CENTRAL	World Vision Relief and Development	PVO/U		
	Burma	Quality Care for Child Survival	4820013	BILATERAL				NATIONWIDE
	Egypt	Cost Recovery Program for Health	2630170	BILATERAL	Ministry of Health	HCG		NATIONWIDE
	Egypt	Child Survival	2630203	BILATERAL	Atlanta University	UNC	YES	NATIONWIDE
	India	Development and Mangement Training	3860487	BILATERAL	Ministry of Finance	HCG		NATIONWIDE
	India	Program for Advancement of Commercial Technology	3860496	BILATERAL	Infosys Consultants Private, LTD.	PVC		SUBNATIONAL
	India	Child Survival Health Support	3860504	BILATERAL	Ministry of Health, UNICEF	HCG,NGO/M		NATIONWIDE
	India	Child Survival Fellow: Technical Assistance to CARE	9365951	CENTRAL	Johns Hopkins University	UNC		
	Indonesia	Comprehensive Health Improvment Program	4970325	BILATERAL	Ministry of Health	HCG		SUBNATIONAL
	Indonesia	Vitamin A Intervention Program	9310045	CENTRAL	Helen Keller International	PVO/U	YES	
	Indonesia	Primary Health Care in Operations Research	9365920	CENTRAL	Center for Human Services	NGO/U	YES	SUBNATIONAL
	Indonesia	CSAP Support - American Medical Association	9365951	CENTRAL	American Medical Association	PVO/U		SUBNATIONAL
	Jordan	Primary Health Care Nursing Development	2780270	BILATERAL	PRAGMA, John Short	PVC	YES	NATIONWIDE
	Nepal	Integrated Rural Health/Family Planning Services	3670135	BILATERAL	John Snow	PVC	YES	NATIONWIDE
	Nepal	PVO Co-Financing	3670144	BILATERAL	Save the Children Federation	PVO/U		SUBNATIONAL

USAID Health Information System
Center for International Health Information, ISTI, April 1989

SUMMARY OF ONGOING PROJECTS REPORTING AN ACUTE RESPIRATORY INFECTION (ARI) COMPONENT
Source: Health Projects Database, 1987 and 1988 Health and Child Survival Questionnaires

COUNTRY	TITLE	PROJECT NUMBER	BILATERAL REGIONAL OR CENTRAL SUPPORT	IMPLEMENTING AGENT	TYPE OF ORGANIZATION	RESEARCH ACTIVITY IN ARI	GEOGRAPHIC SCOPE OF THE PROJECT NATIONWIDE SUBNATIONAL OR GLOBAL
Pakistan	Primary Health Care	3910475	BILATERAL	Ministry of Health	HCG		NATIONWIDE
Pakistan	Child Survival	3910496	BILATERAL	Ministry of Health	HCG	YES	NATIONWIDE
Pakistan	Child Survival Grant to Aga Khan	9380530	CENTRAL	AGA KHAN Foundation/USA	PVO/U		SUBNATIONAL
Philippines	Communication for Child Survival - HEALTHCOM	9311018	CENTRAL	Academy for Educational Development	NGO/U	YES	SUBNATIONAL
Philippines	Primary Health Care in Operations Research	9365920	CENTRAL	Center for Human Services	NGO/U	YES	SUBNATIONAL
Philippines	Metro Cebu Evaluation	9365951	CENTRAL	Johns Hopkins University	UNC	YES	SUBNATIONAL
Yemen	Tihama Primary Health Care	2790065	BILATERAL	Management Sciences for Health	NGO/U		SUBNATIONAL
Latin America & The Caribbean							
Belize	Child Survival Support	5050037	BILATERAL	CARE, Project HOPE	PVO/U		NATIONWIDE
Bolivia	Self-Financing Primary Health Care	5110569	BILATERAL	Management Sciences for Health	NGO/U		SUBNATIONAL
Bolivia	PVO ORT and Child Growth Monitoring	5110590	BILATERAL	Catholic Relief Services	PVO/U	YES	SUBNATIONAL
Bolivia	Community and Child Health	5110594	BILATERAL	Ministry of Social Welfare and Public Health	HCG	YES	SUBNATIONAL
Bolivia	Child Survival Network	5110601	BILATERAL	Multiple	PVO/U,L		NATIONWIDE
Bolivia	Child Survival Grant to SCF	9380502	CENTRAL	Save the Children Federation	PVO/U		SUBNATIONAL
Bolivia	Child Survival Grant to PCI	9380521	CENTRAL	Project Concern International	PVO/U		SUBNATIONAL
Bolivia	Child Survival to PLAN	9380522	CENTRAL	Foster Parents Plan	PVO/U	YES	SUBNATIONAL
Bolivia	Child Survival Grant to SCF	9380535	CENTRAL	Save the Children Federation	PVO/U		SUBNATIONAL
Colombia	Primary Health Care Operations Research II	5980616	REGIONAL	Center for Human Services	NGO/U	YES	SUBNATIONAL
Colombia	ORT Assistance	5980616	REGIONAL	Foundation for Higher Education	PVO/L		SUBNATIONAL
Colombia	FES - Fund for CS and Health Related Projects	5980616	REGIONAL	Foundation for Higher Education	PVO/L		SUBNATIONAL
Colombia	Colombian Expansion/Child Survival	5980616	REGIONAL	National Association of Partners of the Americas	NGO/U		SUBNATIONAL
Colombia	Child Survival and Health Training Program	5980616	REGIONAL	Fulbright Commission	NGO/U		NATIONWIDE
Dom. Republic	Child Survival	5170239	BILATERAL	Save the Children Federation	PVO/U	YES	SUBNATIONAL
Ecuador	Integrated Rural Health Delivery Systems	5180015	BILATERAL	Birch & Davis	PVC	YES	NATIONWIDE
El Salvador	Health and Jobs for Displaced Families	5190281	BILATERAL	Multiple	PVO/U,HCG,PVO/L		NATIONWIDE
El Salvador	Population Dynamics	5190210	BILATERAL	Multiple	HCG, PVO/L	YES	
El Salvador	Health Services Support	5190308	BILATERAL	Ministry of Health	HCG	YES	
Guatemala	Expansion of Family Planning Services	5200288	BILATERAL	Ministry of Health	HCG		NATIONWIDE
Guatemala	Immunization/Child Survival	5200339	BILATERAL	Management Sciences for Health, Academy for Educational Development	NGO/U	YES	NATIONWIDE
Guatemala	Child Survival Grant to Project HOPE	9380507	CENTRAL	Project HOPE	PVO/U		SUBNATIONAL
Guatemala	Child Survival Grant to PCI	9380521	CENTRAL	Project Concern International	PVO/U		SUBNATIONAL
Haiti	Mobilizing Mothers for Child Survival	5210194	BILATERAL	Centres Four le Developpment et la Sante	PVO/L		SUBNATIONAL
Haiti	Vitamin A Intervention Program	9310045	CENTRAL	Helen Keller International	PVO/U		NATIONWIDE
Haiti	CSAP Support: Child Survival Fellow	9365951	CENTRAL	Johns Hopkins University	UNC	YES	
Haiti	Vitamin A Intervention Program	9380284	CENTRAL	Eye Care International	PVO/U		SUBNATIONAL
Honduras	Health Sector I	5220153	BILATERAL	Ministry of Health	HCG	YES	NATIONWIDE
Honduras	Health Sector II	5220216	BILATERAL	Management Sciences for Health	NGO/U	YES	NATIONWIDE
Honduras	Community Health Self Motivating Activity	5220303	BILATERAL	Center for Studies and Promotion of Development	PVO/L	YES	
Honduras	Communication for Child Survival-HEALTHCOM	9311018	CENTRAL	Academy for Educational Development	NGO/U	YES	NATIONWIDE
Honduras	Child Survival Grant to Project HOPE	9380507	CENTRAL	Project HOPE	PVO/U		SUBNATIONAL

USAID Health Information System
Center for International Health Information, ISTI, April 1989

SUMMARY OF ONGOING PROJECTS REPORTING AN ACUTE RESPIRATORY INFECTION (ARI) COMPONENT
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COUNTRY	TITLE	PROJECT NUMBER	BILATERAL REGIONAL OR CENTRAL SUPPORT	IMPLEMENTING AGENT	TYPE OF ORGANIZATION	RESEARCH ACTIVITY IN ARI	GEOGRAPHIC SCOPE OF THE PROJECT NATIONWIDE SUBNATIONAL OR GLOBAL
Peru	Central Selva Resource Mangement	5270240	BILATERAL	Ministry of the Presidency	HCG	YES	SUBNATIONAL
Peru	Expanded Feeding Program	5270247	BILATERAL	Adventist Development and Relief Agency/OFASA	PVO/L		SUBNATIONAL
Peru	Child Survival Action Program	5270285	BILATERAL	Ministry of Health	HCG	YES	NATIONWIDE
Peru	Peruvian PVO Health Promotion Network	5270294	BILATERAL	Seton Institute for International Development	PVO/U		SUBNATIONAL
Peru	Reduction in Child Mortality	5270311	BILATERAL	PRISMA	PVO/L	YES	SUBNATIONAL
Peru	Ninos Child Survival Journal	5270316	BILATERAL	PRISMA	PVO/L	YES	NATIONWIDE
Peru	Central Selva Resource Mangement Phase II	5270321	BILATERAL	Ministry of Health	HCG		SUBNATIONAL
Peru	Integrated Food Nutrition and Child Survival Program	5270323	BILATERAL	PRISMA	PVO/L		NATIONWIDE
RCCAP	ORT, Growth Monitoring and Nutrition Education	5960115	REGIONAL	Institute of Nutrition in Central America and Panama	NGO/M		NATIONWIDE
Worldwide							
ST/H	Demographic and Health Surveys	9363023	CENTRAL	Westinghouse Institute for Resource Development	PVC		GLOBAL
ST/H	Primary Health Care Operations Research	9365920	CENTRAL	Center for Human Services	NGO/U	YES	GLOBAL
ST/H	MEDEX Support	9365932	CENTRAL	University of Hawaii School of Medicine	UNC	YES	GLOBAL
ST/H	Diagnostic Technology for Community Health	9365935	CENTRAL	Program for Appropriate Technology in Health	PVO/U	YES	GLOBAL
ST/H	ORT HELP:Peace Corps	9365939	CENTRAL	Peace Corps	USG		GLOBAL
ST/H	CSAP Support: Child Survival Fellow	9355951	CENTRAL	Johns Hopkins University	UNC	YES	GLOBAL

ACRONYMS FOR TYPE OF ORGANIZATION

USG	U.S. Government Agency
HCG	Host Country Government
UNC	University Contract, Grant or Coopertive Agreement
PVO/U	U.S. Private Voluntary Organization
PVO/L	Local Private Voluntary Organization
NGO/U	U.S. Non-Governmental Agency
NGO/M	Multilateral Non-Governmental Agency
PVC	Private Sector Contract (For-Profit)

WHO Activities in Acute Respiratory Infection

Presented by Michael Merson, M.D.
Director, CDD
World Health Organization

I. Introduction

The acute respiratory infections (ARI) are responsible for about 4 million childhood deaths annually. About 15-20% of these deaths (up to 25% in some countries) are a consequence of pertussis and measles and thus can be prevented by immunization through national EPI programmes. The remaining 80% are due to other causes, mostly pneumonia, and these deaths can only be prevented by proper treatment. Therefore, the main objective of the ARI Programme is to reduce mortality from acute lower respiratory infections, especially pneumonia, in children. Important secondary objectives are to reduce (a) the severity and complications of acute upper respiratory tract infections; (b) the inappropriate use of antibiotics and other drugs for treatment of ARI; and (c) the incidence of pneumonia.

2. Programme strategy

The central strategy of the programme is case management. Carefully conducted laboratory studies have shown that bacteria are responsible for 2/3 to 3/4 of pneumonia cases in children in developing countries, and that the same two bacteria are isolated from 85% of community acquired pneumonia cases, namely Streptococcus pneumoniae and Hemophilus influenzae. There are safe, inexpensive, oral antibiotics that are effective against these two agents and can be used for standard treatment of pneumonia at first level health facilities and at community level. WHO has developed a simple protocol for use in the management of all cases presenting to first-level health facilities with cough or difficult breathing. The core of the protocol is the identification of two objective signs of pneumonia -- fast breathing and chest indrawing -- among children presenting with cough or difficult breathing. A number of intervention studies in developing countries have

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provided epidemiological and clinical evidence that under ideal conditions pneumonia mortality in children can be reduced, using the WHO protocol, by 30 to 60 percent.

3. Programme activities

Within its health services component, the Programme has since 1986 provided materials to assist ministries of health initiate national ARI control programmes. These include guidelines on case management for outpatient services, small hospitals and community-based health workers; training modules in case management for first level supervisors; and audiovisual aids for training of health workers and health education of caretakers. As of December 1988, 41 countries have prepared technical guidelines, 33 have prepared plans of operations and 23 had begun to implement their ARI programme.

During 1989, the Programme is completing a revision of its guidelines on case management. They include a simplified terminology for classification of ARI, improved guidelines for assessment and treatment of pneumonia in young infancy when many pneumonia deaths occur, expanded entry criteria for pneumonia assessment to include difficult breathing, improved management of wheezing, and more emphasis on the reassessment of a child with pneumonia. Expanded information on oxygen therapy, use of bronchodilators and supportive care has also been provided for children hospitalized with severe pneumonia. The Programme is also preparing a standard ARI Treatment Chart, revising its treatment manual and case management modules, preparing review papers on the use of antimicrobial, cough and cold remedies and bronchodilators in treatment of ARI, and providing support for establishment of ARI Treatment Units (ATUs) in 7 countries to gain initial experience in conducting clinical management courses. A Programme Managers' Course is also under preparation and will be field-tested. Specifications have been drawn up for two essential instruments in case management: one minute timers, essential to count the respiratory rate, and oxygen concentrators, suited for small hospitals in developing countries. Development of two monitoring and evaluation instruments will soon be initiated: a household survey to measure ARI morbidity and treatment practices and a health facility survey to measure ARI clinical practices in health facilities. A manual describing procedures for surveillance of antimicrobial resistance for the major bacterial agents of pneumonia is also being prepared.

In 1990 there will be a great expansion of programme activities at country level, as the full range of WHO technical, managerial and training materials become available. The Programme's targets are that, by 1995, 88 countries with infant mortality greater than 40/1000 will have national programmes, 50% of the population in these countries will have access to a trained, regularly supplied source of antimicrobial, and 50,000 facility-based staff will have been appropriately trained in ARI case management.

In the research component, the Programme during 1989 has defined priority topics for

research support, identified possible institutes and researchers to undertake the needed research and prepared protocol guidelines for specific studies. Research priorities were selected in the areas of clinical, behavioral, health systems, and disease prevention research. Support for 30-40 projects will be initiated during the second half of 1989 and 1990.

For example, studies will be conducted to determine the predictive value of signs of pneumonia in young infancy, and to examine improved criteria for diagnosing pneumonia and severe pneumonia in older children. Behavioral studies will be initiated to learn more about caretakers' perceptions of signs of pneumonia, treatment practices at home, and compliance with treatment regimes. Health systems research will assess the cost and effectiveness of the case management strategy when implemented in selected national ARI programmes. The Programme hopes to also support the first field trial in a developing country (the Gambia) to determine the efficacy in infants of one or two of the newly available Haemophilus influenzae type b vaccines. The goal of all this research is to improve the case management strategy and to develop new tools for prevention of pneumonia, e.g. vaccines. Small task forces will be organized in a number of areas to help guide this research.

UNICEF Statement to USAID Workshop on Control of Acute Respiratory Infections

Presented by Dr. Nyi Nyi
Director
UNICEF Programme Division

At the last meeting of the WHO/UNICEF Joint Committee on Health Policy, a series of goals and strategies were adopted to improve the situation of children in the 1990s. One of these was the reduction by 25 percent in the deaths due to acute respiratory infections in children under five years of age.

Acute respiratory infections rank among the most common diseases of children the world over. Everywhere they represent either the first or the second cause of visits to health services by young children. The situation, however, is far more serious in developing than in developed countries. While the annual incidence of pneumonia, the most severe manifestation of acute respiratory infection, is 3 to 4 percent in children under 5 years of age in developed countries, it ranges from 10 to 20 percent in the developing countries, reaching levels as high as 80 percent in populations with a high prevalence of malnutrition and low birth weight.

Furthermore, in most developing countries, pneumonia is associated with high case fatality and mortality rates. Of the estimated 15 million deaths occurring each year in children under 5 years of age, 25-30 percent are due to acute respiratory infections, and the vast majority of these are caused by pneumonia. Thus, in absolute numbers pneumonia accounts for about 4 million childhood deaths annually.

In UNICEF's Medium-Term Plan for the Period 1988-1992 controlling ARI deaths among young children is cited as a major programme thrust in the reduction of infant and child mortality. In each of the regional strategies, ARI is described as a major child health problem. The Americas and the Middle East and North Africa regions give particular emphasis to ARI control efforts, citing specific countries in which this is a key cause of infant and young child mortality.

But despite the importance of ARI, the urgency of other priorities has made it difficult to

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provide adequate attention and support at the headquarters level. Nonetheless, a WHO/UNICEF joint statement on ARI was developed in 1986 and given wide distribution throughout the UNICEF network. Since that time, we have kept field offices informed of new developments and policy recommendations. In May 1987, we took a further step and selected three countries for special support in the development of national ARI programmes: Bolivia, Gambia, and Thailand. In these countries, emphasis is on overcoming managerial and attitudinal obstacles to adopting a broad-based, case management approach and to including ARI as a main component of the country programme. Efforts in these three countries will provide valuable lessons and experience as our involvement in national ARI programmes in other parts of the world steadily increases.

Thus far, wide differences in the health systems of these countries has resulted in the development of three different adaptations of a generally similar approach. They all share, however, the basic objective of reducing deaths from pneumonia among young children and a strategy rooted in correct case management of ARI cases. In each country detailed field methods will be developed in a few selected experimental areas for rapid extension to a national programme.

In Gambia, the Ministry of Health has already established a national control of ARI programme as part of primary health care services. Initial efforts include strengthening skills and services within health facilities, as well as the training of village health workers in the recognition and treatment of pneumonia with oral penicillin. A programme team, including representatives of UNICEF and WHO as well as outside experts, visited Gambia in October 1988 to help revise the Plan of Action and make recommendations concerning further development of the programme during the next three years. In brief, the team recommended significant changes in the existing treatment protocol, to bring it closer to the current recommendations from WHO. During the first year, the focus will be on training all health workers in the recognition and treatment of pneumonia. The first line of treatment to be used by village health workers has been changed to cotrimoxazole because it is much more effective in treating the organisms that cause pneumonia than penicillin. Referral health center and hospital care will also be improved with a full range of antibiotics. Emphasis will also be placed on improving supervision, especially of village health workers by community health nurses, and the functioning of the health information system. During the second year, the major effort will be to extend coverage from the trial districts to all Gambian children and to improve the quality/effectiveness of the programme as a whole. A comprehensive review of the programme will take place in the third year, to highlight lessons learned about the professional feasibility of involving health facility staff, village health workers and the community -- on a national scale -- in the recognition and treatment of pneumonia in children.

While the primary responsibility for developing these activities rests at the country level, UNICEF Headquarters will continue to provide special technical support and assistance

during the next few years.

The programme team that visited Bolivia in February this year -- which also included members from UNICEF and PAHO -- found a somewhat different situation. The government has been extremely interested in developing an effective ARI programme because pneumonia is the first cause of death, especially on the altiplano. A programme manager has been appointed. Previous programmes had been based on using penicillin injections with much diversion of the drugs from peripheral health centers and hospitals. Babies die before reaching the hospitals. The team recommended a phased approach. During the first phase, the focus will be on developing and testing clear, nationally-accepted norms for case management and on initiating training and service delivery in four geographically distinct areas of the country. This will provide an opportunity to test a number of operational factors, e.g. training, supervisory and logistics systems. In the second phase, services will be extended to other areas, training centers will be established and information systems will be further improved.

One of the major challenges in Bolivia is to strengthen services at first and second levels of referral while at the same time taking advantage of the well-developed network of community health volunteers under the "Comites Populares." This network reaches the three quarters of the population (mostly Aymara and Quechua) who are unserved by the formal system. These volunteers serve as the main first line providers for coverage in EPI and CDD. Integrating them into the national ARI programme was viewed by the programme team as a pre-condition for achieving coverage and long term sustainability.

A national steering committee has been designated to further develop the ARI programme along the lines outlined above. UNICEF and WHO will be providing consultants as well as other types of support during various stages of this process. Detailed plans will be developed in the next few months.

In Thailand, a national ARI programme has existed for some time but has also had problems in implementation. The challenge now is to bring the plans into line with the new WHO case management protocol, improve its effectiveness, extend coverage, and involve village level health workers in a meaningful way.

In 1988 a pilot project was started in 13 provinces in which the major activity was the teaching of case management to health center and hospital staff. The project will test whether doctors, nurses, and subdistrict health staff can clearly distinguish between mild, moderate, and severe cases of ARI and provide standardized care using the simple criteria in the present WHO protocol. The project is also testing how much should be taught to village volunteers.

The involvement of these community volunteers requires careful study, as many pedia-

tricians and doctors in Thailand view childhood pneumonia as a problem in which care of moderate and severe cases should be restricted to hospitals and doctors. To convince them, local data are needed to show that long-term reductions in deaths due to ARI among young children depends on early diagnosis and treatment of acute bacterial pneumonia by trained non-medical health personnel who are readily accessible to the population they serve.

To further develop the programme, a technical committee of 22 leading national experts has been appointed. A meeting will be held in early September 1989, to prepare a revised national plan of action. Consultants will be provided by WHO and UNICEF. Urgent needs are: 1) to revise the existing case management protocol to include, among other things, changing the diagnostic criterion of starting treatment only after 3 days of fever (since many deaths in babies occur before 3 days); 2) to focus more on childhood pneumonia than on other ARI infections; and 3) to promote the appropriate use and sequencing of antibiotics (i.e., cotrimoxazole as the first line treatment with other antibiotics for referral care). UNICEF and WHO will remain closely involved in all aspects of this programme.

We have already learned a considerable amount about the development of ARI programmes, both from these three efforts as well as from experiences in several other countries. We will be issuing a program directive to field offices later this month, providing broad guidelines for UNICEF assistance to national ARI efforts. These include, among other items:

- Careful attention to the development of technically-sound norms for treatment. Experience has shown us that the norms developed by ministries of health require discussion and careful study.

- Promotion of the case management approach for ARI, including intensive training for both health workers at first level referral facilities and -- where appropriate -- for community health workers in various settings.

- Promotion of projects on a limited scale in selected areas to test operational strategies. Once the effectiveness of these strategies has been established and refined, broader national programmes are appropriate.

- Provision of appropriate drugs in reasonable quantities. The heart of ARI programmes is, after all, getting the <u>right</u> drug to the <u>right</u> child at the <u>right</u> time. UNICEF agrees with the WHO position that it is inappropriate to create demand before services and drugs have been supplied to meet that demand.

- Development of sound communication strategies that are fully integrated into national programmes and supportive of reliable well-established services.

Although a good start has been made, we have much work ahead of us in this area. We look forward to learning from the many experts gathered here, especially concerning the role of community health workers, innovative schemes for the provision and financing of appropriate drugs to health workers and facilities that distribute them; and the extent to which prevention of ARI is an appropriate and feasible aspect of national programmes at this point.

Nosology and Standards for ARI Studies

Mark C. Steinhoff, M.D.
The Johns Hopkins University

It is appropriate to begin this workshop with a clarification of definitions and classification because the field of investigation of acute pulmonary disease in children has been plagued with difficulties of classification. Whereas diagnosis applies to decisions about an individual patient, nosology is the naming and classification of diseases. Nosology is the taxonomy of disease, a subject which attracts little attention. However the classification of illness is clearly of first importance, since it precedes the organized gathering of data, the analysis of differences and similarities, and the achievement of deeper understanding.

In this discussion I will first describe the process of gathering data that leads to a respiratory diagnosis. I describe the wide variety of classification systems and point out some of their problems, and I suggest a number of approaches toward solutions.

It may be useful to review the diagnostic process before we discuss the details of classification. Diagnosis is based on the analysis of symptoms and signs followed by recourse to laboratory tests, including radiography in the case of pulmonary disease. Since the perception of symptoms and signs is a human activity, biases, differences of opinion, and outright error may be common. Thus, standards and references for signs and symptoms become even more important.

Consider the use of the stethoscope, introduced by Laennec in 1819. He both devised the instrument and first described auscultatory findings. He used the French term "rale", meaning rattle, to describe the findings on chest auscultation in his writings, but he used the term "rhonchus", with his patients and therefrom began 170 years of confusion (1). The terms were variously translated into English and until recently, were not defined unambiguously. Table 1 (pg. 26) shows the terms used by Laennec and the recent official definitions of auscultatory findings adopted by the American Thoracic Society. This kind of standardization is necessary for clear communications regarding signs and symptoms. Even with standard definitions, variation in perception will occur between observers. One approach to the quantification of inter-observer variation is the kappa statistic, which ranges from a value of 1 for perfect agreement on the presence or absence of a finding to 0 for complete disagreement. Table 2 gives examples from selected investigations of inter-observer variation in the perception of rales (crackles) and wheezing, two common signs that are used for diagnostic and therapeutic decisions (2-4). Note that the kappa values

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are in the range of 0.30 to 0.40 (thought to represent moderate to good agreement), and not nearly as high as one would like. Note also that the kappa values for the signs in children are lower than in adults.

Radiography, if available, provides a permanent record, and the opportunity for an unbiased evaluation. However, radiographic interpretation is notorious for its observer variability (5). There is also no widely agreed upon classification for radiologic findings. In our clinical studies, we have been using Swischuk's classification scheme to describe radiographic findings, although we do not use it to predict etiology (6). Heulitt and co-workers have published a classification scheme that includes a notion of severity, without validation (7). A severely ill child could have minimal radiologic findings, and a child with major radiologic findings could be only mildly ill. We understand that Dr. Kirkpatrick has been working with the ARI group at WHO to produce a radiologic standard suitable for use in multicentered studies.

A series of nosologic schemes for lower respiratory tract infection and examples for each one are presented in Table 3. The ideal system would be an a classification by microbial etiology with an anatomic specification. However, given the difficulty of the accurate assessment of etiology (which we will hear more about later in this workshop), this is never achievable in practice. Pathology as a nosologic approach would also be ideal, but this would require biopsy or autopsy in all patients. Using clinical anatomic location as a basis for classification is useful, however, many syndromes involve a variety of locations. Most clinicians use a clinical syndrome approach, and this has been adopted for the new revised WHO case management algorithm. A radiographic classification can also be useful, but radiology is often not available and the lack of an accepted classification has been discussed above. Finally, illnesses can be classified by severity, witness the old WHO algorithm that used mild, moderate and severe ARI; or by therapeutic implication (8,9).

Most clinicians use a syndrome approach in practice. Unfortunately, each syndrome can be caused by a wide variety of etiologic agents and moreover each etiologic agent may cause a variety of syndromes. Although etiology is difficult to predict by syndrome classification, a standard classification of respiratory illnesses is still an essential first step for all clinical studies of ARI. Table 4 illustrates a definitions of clinical syndromes that my colleagues and I are using for a multi-center study with the Rockefeller INCLEN program (10). It was necessary to develop this list of definitions because we discovered that there were wide variations in the meaning of the terms bronchitis and bronchiolitis among Anglophone pediatricians.

There has been a recent publication that will serve as an example of the variations in syndrome classification. A recent report of the variations in hospitalization rates of children in 3 northeastern US cities noted that while the rates for meningitis were similar among the cities, they varied by a factor of 2 to 6 times for acute respiratory illnesses

categories (11). Among the determinants of this variation are varying criteria for syndrome diagnosis, and for hospitalization once the diagnosis is made.

There is a need for a system for describing the severity of pulmonary disease. A number of respiratory failure and asthma clinical severity scores based on signs and symptoms have been published (12,13), but they have been shown not to be useful when evaluated critically for their ability to predict outcome or p_aO_2 (14,15).

We propose that one measure of severity of LRI could be oxygen saturation of hemoglobin, as measured by pulse oximetry. Because pulse oximetry provides objective information of pulmonary function, is both an outcome measure and an indicator. The technical basis of pulse oximetry has been reviewed elsewhere (16) and I will summarize by saying it is a painless, non invasive, rapid technique that provides a digital readout of the oxygen saturation of hemoglobin in vivo. A variety of studies have shown that oximetry readings are highly correlated with the independent measurement of arterial oxygen saturation when the latter is in the range of 70% to 100% (17). There are known inaccuracies associated with diminished arterial perfusion, patient movement, abnormal hemoglobins, and ambient light; though bilirubin, fetal hemoglobin or skin pigmentation do not appear to affect accuracy (18). Definitions of desaturation by pulse oximetry have been proposed for neonates, (19) but for older children most clinicians accept that values below 90-95% are abnormal (20). In our own experience we have rarely found a healthy, well child to have pulse oximetry saturation below 95%. We have been evaluating pulse oximetry in a hospital in India recently, and table 5 presents some data from a convenience sample of patients. Note that over 30% of the children admitted with pneumonia (and 21% of all studied children) were desaturated in this preliminary sample. An assessment in the Johns Hopkins Hospital pediatric emergency department has shown us that 1% of children who had a chest radiograph were similarly desaturated. While these preliminary experiences are not directly comparable, they confirm the common perception that children presenting with acute respiratory disease in developing countries are more likely to be severely ill.

The lower partial pressure of oxygen at high altitude obviously requires modified interpretation of oximetry values. A colleague from our department has evaluated oximetry in 24 normal healthy infants 2 to 12 months old in the Peruvian Andes at 3,700 meters (12,000 feet) and noted a range of saturations of 83 to 93% with a mean $\pm$ S.D. of 87 $\pm$ 2.5%. (Six (25%) of these healthy infants had respiratory rates > 50 min.). We feel the use of pulse oximetry will provide one objective standard for severity of pulmonary disease. Pulse oximetry instruments are reliable, and our experience with a battery-powered portable device in India and Peru indicates they have a high utility in developing country settings.

In summary, I encourage the wider teaching and use of standard methods of describing

signs and symptoms. We need to work further on defining clinical syndromes as clearly as possible as a prerequisite for studies of therapies and prevention. We look forward to the development by WHO of a standard for radiologic description and interpretations. We suggest that pulse oximetry should become a more widely used technique to describe one important physiologic aspect of severity.

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Table 1

Classification of Common Lung Sounds

Acoustic Characteristics*	American Thoracic Society Nomenclature	Common Synonyms	Laennec's Original Terms
Discontinuous, interrupted explosive sounds Loud, low in pitch	Coarse crackle	Coarse rale	Rale muquex ou gargouillement
Discontinuous, interrupted explosive sounds Less loud than above, shorter duration; higher in pitch than coarse	Fine crackle	Fine rale crepitation	Rale humide ou crepitation
Continuous sounds high pitched; a hissing sound	Wheeze	Sibilant rhonchus	Rale sibilant sec ou sifflement
Continuous sounds low pitched; a snoring sound	Rhonchus	Sonorous rhonchus	Rale sec sonore ou ronflement

Modified from Loudon and Murphy (1)

Table 2

Inter-observer Variation in Perception of Physical Findings

finding	kappa value	author
crackles (rales)	0.41	Spiteri
	0.44-0.30	Mulrow
	0.36±15	Gjorup
	0.25	Margolis*
wheezing	0.51	Spiteri
	0.70-0.54	Mulrow
	0.59	Margolis*

*studies in infants and children; personal communication, Margolis, Univ. North Carolina

Table 3

Nosologic Approaches to Respiratory Infections

Criterion or basis	Example
microbial etiology	H. influenzae pneumonia, R.S.V. bronchiolitis
pathologic process	bronchitis
anatomic location	laryngotracheobronchitis
clinical syndrome	bronchiolitis, URI
radiographic appearance	interstitial pneumonia
severity	"moderate ARI"
therapeutic implication	bacterial vs. viral

Table 4

Clinical Classification of ARI Syndromes
JHU-INCLEN Oximetry Study

Cold (URI):	Excessive nasal discharge, nasal obstruction, sneezing, often associated with pharyngitis and cough.
Pharyngitis:	Sore throat, painful swallowing, pharyngeal erythema ± exudate, enlarged cervical nodes.
Croup:	(laryngotracheobronchitis)Barking cough, hoarseness, inspiratory stridor.
Tracheobronchitis/ bronchitis:	Cough and rhonchi, no laryngeal obstruction or wheezing, often associated with fever, URI and pharyngitis.
Bronchiolitis:	First episode of expiratory wheezing in infants with cough, URI, fever, and tachypnea.
Pneumonia:	Cough with crackles (crepitations or rales) or evidence of alveolar consolidation on radiograph. 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.

Adapted from: F.W. Denny, J Pediatr 1986;108:635-646;S.D.M. Court, Post Grad Med J 1973;49:771-776.

Table 5

Clinical Diagnosis and Oxygen Desaturation
106 Children in CMC Hospital Vellore, India

Clinical diagnosis	No. of children	No. (%) with desaturation
URI	26	0 (0)
LTB	1	1 (100)
Bronchitis	6	0 (0)
Bronchiolitis	18	2 (11)
Pneumonia	55	18 (33)

SpO2 < 90% = desaturation; LTB = laryngotracheobronchitis

BOSTID Study on Acute Respiratory Tract Infections in Children in Developing Countries

Patricia Charache, M.D.
The Johns Hopkins University

Introduction

In 1983, the Board on Science and Technology for International Development (BOSTID) Program of the National Academy of Sciences, elected acute respiratory tract infection in children as one of five programs designed to provide scientific information and resources in developing countries. The program was developed coordinated and monitored by Dr. Judith R. Bale, Senior Program Officer and Dr. Michael P. Greene, Associate Director of BOSTID. The purpose of the study was: 1) to define the etiology and risk factors associated with pneumonia in developing countries, and 2) to advance the scientific and technical capacities of each study center. The studies were to be performed under controlled conditions which would permit comparison of results between countries and with those reported in the literature from the United States and elsewhere.

The BOSTID program differed from previous studies of cause of respiratory tract infection in developing countries in: 1) study design; 2) definition of terms; 3) networking between study centers; and 4) provision of an integrated, consultative program. This paper reviews the nature of the study and its features which permit improved data quality and permit accurate comparison of data from studies of respiratory tract infection in developing countries.

Overall Study:

The BOSTID Program in ARI was initiated at an organizational workshop meeting held at the University of North Carolina in May 1983. The study design emphasized etiology and risk factors, considering at each location both bacterial and viral pathogens, and both culture and non-culture techniques. The study was to be designed by the host country but coordinated through BOSTID in order to ensure that the data collected could be compared between countries. The study country locations and principal investigators are

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summarized on Table 1.

Studies were community based, in different centers, in hospital based, or both community and hospital. Argentina, Bangladesh, and Pakistan had hospital based studies, Colombia, Papua New Guinea, and Kenya had community studies, while Brazil, Guatemala, the Philippines, Thailand, Nigeria, and Uruguay studied both hospital and community populations. Hospital and community programs were performed concurrently in some centers, sequentially in others. In the community based studies, primary questions were directed towards incidence of infection, attack rates per child/month, colonization patterns and risk factors for mild, moderate or severe disease. Hospital based studies were concerned primarily with the etiology of severe pneumonia that required hospitalization, as well as clinical presentation. In both groups, risk factors were assessed. Risk factors analyzed included the child's demographics, number of siblings, number of individuals sharing the child's bedroom, exposure to cigarette, cooking or heating smoke, parental education and income, and seasonal factors such as time of year, or rain fall. Specific questions addressed varied.

In Uruguay, for example, the question addressed was that of the prevalence of respiratory viruses in the low socioeconomic community. Children were monitored at 10 day intervals with viral cultures obtained at each visit. This permitted analysis of colonization patterns, as well as monitoring of etiologic agents in children who developed upper or lower respiratory tract symptoms. In this community study, however, few children had lower respiratory infection during the study period and risk factors associated with severe disease could be assessed only in subsequent study of hospitalized children.

In the community study in Colombia, children were entered into the study at time of birth, and followed at weekly intervals for early colonization with Hemophilus influenzae and Streptococcus pneumoniae, as well as for development of upper and/or lower respiratory tract infections. Specimens for viral antigen detection and culture were obtained from symptomatic children.

In some hospital based studies (Argentina, Bangladesh, and Pakistan), only children admitted for inpatient care were analyzed, while in other centers outpatients were assessed in addition to hospitalized children. Thus, the specific study design and questions emphasized varied by study site according to the study design proposed by the grantee. All were concerned with the questions of etiology of respiratory tract infection in infants and young children, and with risk factors associated with incidence and/or severity of disease.

Definition of Terms:

Key definitions that required concordance included the detailed definition of acute

respiratory tract infection, as well as definition of upper versus lower respiratory tract disease, and mild, moderate and severe pneumonia. New episodes of infection and duration of episodes also required sharp clarification. Control subjects were defined by age only. The family unit for most studies was defined as those eating from the same cooking pot. Because the above parameters would have modified the analysis of incidence of infection, clinical presentation and outcome, and/or risk factors associated with infection, the study could compare results only when such parameters were agreed upon and followed.

Program Networking:

A key feature of the BOSTID Program was the networking that permitted the results from the different countries to be assisted and compared. Aspects of the international study for which networking was achieved included: 1) definitions and general procedures; 2) microbiology; 3) data handling; 4) trouble shooting; and 5) study control and supervision.

Five mechanisms were employed to achieve this networking. These may be summarized as follows:

1. Meetings of Principal Investigators:
   Regular meetings of principal investigators were held at approximately six month intervals. These meetings achieved several important goals. First, they permitted presentation of data, and frequently served as an opportunity for the investigators to examine their data in the context of the experiences of their colleagues. Secondly, since all study sites shared problems, it provided an opportunity to explore those problems and derive consensus solutions. It permitted the BOSTID leadership team to determine areas in which education and/or monitoring programs were required, and provided the personal contact, the key to maintenance of an integrated program capable of providing reliable data in a timely manner.

2. Procedure Manuals:
   Procedure manuals were developed for bacteriology, virology, and data management. Bacteriology and virology manuals were drafted and parts tested by study participants at workshops designed for each discipline. Based upon review of these manuals, and the consensus information developed during the workshops, manuals were revised and expanded. The goal of the procedure manuals were to ensure that the methods to be used were in written form which could be followed not only by those who attended the workshops, but by non-attendees on location in the study sites. Manuals were supplemented as required with experience. Included, were consensus procedures for specimen transport and storage, detailed directions for media preparation, sterility control, and quality control, and detailed descriptions of the specific procedures to be followed for individual patient sample management.

3. **Workshops:**

Workshops were developed to meet two goals. The first was that of coordinating the technology to be employed. It was essential that detection of etiologic agents be optimized. Further, it was important that recovery or failure to recover an infectious agent have the same significance in each country. A second goal was that of ensuring that the methods selected were appropriate for all study sites.

The workshop in virology was held in March, 1985 at the University of Michigan coordinated by Dr. John MaSaab. Technologies reviewed included tissue culture technology, including media selection, appearance, maintenance and support of various cell lines, procurement of clinical specimens and viral identification techniques. Antigen detection technologies reviewed included ELISA technology and fluorescence microscopy. Decisions made included choice of cell lines to be employed at all sites, clinical specimen preparation for tissue culture and for antigen detection testing, length of processing of tissue culture cell lines inoculated with clinical samples, speciation methods for hemadsorptioningand non-hemadsorptioningviruses, and selection of fluorescence microscopy as the method to be used for direct antigen screening of pellets of clinical samples, and for most viral speciation. Each decision was reviewed with the virologists from each center to ensure their ability to process samples according to agreed upon methods.

The workshop in bacteriology took place at the Johns Hopkins University Schools of Medicine and Public Health and Hygiene in June, 1985, coordinated by Dr. Patricia Charache. The bacteriologists from each center participated. As in the virology workshop, methods were reviewed and tested, and consensus was achieved. Material reviewed included the specimen types to be collected and processed, media selection, method, organisms to be identified, methods of detection and speciation, extent of processing. Antigen detection approaches reviewed included ELISA technology, particle agglutination, fluorescence microscopy and counter-immunoelectrophoresis,the latter being chosen for screening of urine samples.

Workshops in epidemiology and computer support workshops were held in Bangkok, Thailand in January, 1986, and in College Park, Maryland in June, 1986. These involved those responsible for data analysis as well as Principal Investigators. These workshops, led by Dr. Harris Pastides of the University of Massachusetts and Dr. Beatrice Selwin of the University of Texas were designed to clarify definitions and sharpen study protocols, as well as to assist the Principal Investigators and/or the study data coordinators computer in the use of statistical and analytical software packages selected for the BOSTID Program.

4. **Site-Visits:**
A limited number of consultants were involved in multiple site visits during the study period. Each consultant sent to a given study site was familiar with the study design of the BOSTID program, the details of decisions made, and in most cases, worked with the principal investigators at the principal investigator meetings. All were also experienced in research in developing countries. The consultative site visit program permitted swift review of problems being encountered in executing the study procedures, and resulted in sharp improvement in the information obtained. The specific type of consultation provided was determined in part by specific requests by the principal investigators for assistance in a given area, as well by the BOSTID leadership upon review of results being provided in discussions with principal investigators, and in the semi-annual reports. Consultation in virology and bacteriology proved important, especially early in the course of most programs, while on site consultation in epidemiologic analysis, important throughout the study, was of key value during the data analysis and preparation of results for presentation.

5. **Reference of Laboratory Review:**
In order to optimize information in return, and avoid presentation of erroneous data, reference laboratory resources were established for fluorescence microscopy, bacteriology, and virology. Dr. Monica Grandien, National Bacteriology Laboratory, Sweden, received a subset of slides on which the diagnosis of respiratory viruses was made by fluorescence microscopy, and for which identification of viruses and tissue culture employed that technique. In addition, Dr. Grandien sent unknown slides to each center which permitted an assessment of the ability of that center to correctly diagnose the presence or absence of specific respiratory viruses. Similarly, Dr. Daniel Granoff, Washington University, submitted quality control specimens of Hemophilus influenzae for serotyping, and for use in counter immunoelectrophoresisanalysis. Bacterial isolates from blood cultures of Streptococcus pneumoniae and Hemophilus influenza were shipped to Dr. Granoff for confirmation, typing and added analyses. Submitted were all cultures from sterile body sites, as well as a subset of those from respiratory sites. Viral isolates identified as respiratory syncytial virus or parainfluenza virus were sent to Dr. Kenneth MacIntosh, Children's Hospital, Boston, Massachusetts, while those identified as influenza virus A or B were sent to Dr. Alan Kendall at the Centers for Disease Control. The availability of the reference laboratory resources permitted validation of the accuracy of the information being returned. In addition, it provided strains for further collaborative studies as desired by the principal investigator and the reference laboratory director.

Study Monitoring:

An additional aspect of the BOSTID study was the control and supervision of the program as a whole, under the direction of Dr. Judith R. Bale, Senior Program Officer and Dr. Michael P. Greene, Associate Director of BOSTID. This involved the monitoring of the progress being made through the meetings of the principal investigators, annual reports of the study status and results, as well as monitoring consultant visits. In addition, the program structure permitted close monitoring of the individual budgets. Funds were authorized for purchase of quality reagents, consultant visits or travel to principal investigator meetings, etc., could not be redirected without review.

Key reagents and supplies were purchased and distributed through the BOSTID office. This was a particularly important feature of the microbiologic program for both bacteriology and virology. Thus, all reagents used for fluorescence microscopy were pretested by Dr. Grandien to ensure that the lots distributed were of high quality. Centers that did not have access to high quality reagents such as fetal calf serum, appropriate media, etc, were also supplied directly from the BOSTID office. This level of control and monitoring ensured that the results from the various study centers could be of high quality, and that if any data were problematic, they could be denfined and offered opportunity for improvement.

Bacterial Pathogens:

The cultures obtained at the time of entry into the study were blood cultures where possible, and throat cultures. When available, specimens such as pleural fluid or lung tissue were also processed. In some centers urine cultures were obtained as a means of ensuring the quality of the urine samples used for counter immunoelectrophoresis. The bacteria sought were Hemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, and heavy or pure growth of other potential pathogens. The media employed was sheep blood and chocolate blood agar for throat cultures, trypticase soy or heart infusion broth for blood cultures. The antigen detection test that was primarily used in this study was counter immunoelectrophoresis of concentrated urine. This method was recognized to be less sensitive than latex agglutination tests, but was chosen because it gave fewer false-positive results, and because slides could be stained and retained for further review.

The throat cultures served three purposes. First, as part of the study design, they were designed to assess the question of whether the semi-quantitative procedure employed to detect moderate or heavy growth of Streptococcus pneumoniae or Hemophilus influenzae, could differentiate between a healthy control population and an infected population, providing information on the role of those pathogens as a cause of respiratory tract infection on an epidemiologic, population based assessment. In addition, the throat cultures provided the ability to detect problems with the bacteriology culture techniques. Many study sites initially had problems with recovery of Hemophilus influenzae, and/or

Streptococcus pneumoniae, problems which were detected on site visiting by review of throat culture. In addition, the study detected otherwise unsuspected antibiotic usage in some study populations. As a result of evaluation of the throat culture studies, key repetitive problems were identified. Included in many centers were timing problems with the procurement of the sample. Many patients had received antibiotics prior to obtaining the sample. Repetitive problems with bacterial cultures included problems associated with water quality, glassware quality, and glassware washing, media source and manufacturer, source, quality and quantity of blood used for making the blood agar or chocolate agar plates, problems with autoclaving, plate pouring, recognition of positive cultures, and identification of specific bacterial species. A key problem in the bacteriology was the problem of the preparation of the solid media containing blood. Sheep had to be purchased for the study, and in many laboratory centers, problems were encountered in blood collection and processing. A recurrent problem was the addition of anticoagulants toxic to Hemophilus influenzae, Streptococcus pneumoniae, or both. Five centers had inadequate numbers of blood cells due to sheep that had been bled excessively. The above problems resulted in false-negative blood cultures, due to subculture on problem media. These were the problems detected through statistical and on-site observation of throat culture results. Antigen detection test issues included the quality of the urine specimens available, many being heavily contaminated with cross-reacting bacteria.

Virology Pathogens:

Virology specimens used nasopharyngeal aspirates for the specimen source. The viruses emphasized were respiratory syncytial virus, influenza viruses A&B, parainfluenza viruses 1,2,3, and adenovirus. Two centers also cultured for cytomegalovirus. The cell lines employed were MRC5, Hep2, LLC-MK2, and MDCK cells. The use of primary kidney cell lines was limited by problems of obtaining the cells in some centers, and of possible simian viral contamination in others. The processing procedure used rapid transportation to the laboratory on wet ice, centrifugation of the specimen, with the supernatant used to inoculate the cell lines. Inoculated tissue culture cells were examined for cytopathologic effect over a period. Tests for hemadsorbing virus were performed twice during this period. The cell pellet was used for fluorescent microscopy. Slides were read for adequacy of sample as well as presence of positives. Key problems observed in Virology during the study included problems of specimen procurement, tissue culture cell maintenance, and antigen detection issues. The most common problem noted with specimen procurement was that of inserting the aspiration tubing into the pharynx resulting in sampling of the tonsillar area rather than the nasopharynx. Timing of sample collection, requiring correction during the study period, included early loss of tissue culture monolayers well in advance of the requirements for viral detection, usually due to wash and final rinse procedures and toxic glassware or stoppers. Media problems included inadequate amounts of appropriate fetal calf serum and toxic glassware or stoppers. Training in the recognition of typical cytopathologic effect (CPE) in laboratories unaccustomed to looking for respiratory viruses was required early in the program. For

the antigen detection tests, relatively little difficulty was experienced in learning to read positive patient specimens for RSV. In some centers, initial problems were encountered with specimen preparation, and use of appropriate counter stains.

Summary of Research Results:

The results of the BOSTID study which utilized this networking and at close supervision, included the following generic information:

1. Results from different study centers can be directly compared with each other. All study sites have produced helpful scientific data on or more aspects of the ARI study, e.g. epidemiology of ARI bacterial etiology, viral etiology, prevalence of ARI, and of pathogens associated with community or hospital mild, moderate or severe disease, and risk factors.

2. Data which would have been otherwise misleading was identified, corrected, and/or removed from presentation.

3. Data established from this study include the facts that the number of episodes of ARI per child per year was high (average of 4-10 episodes)

4. Risk factors varied somewhat by location and social environment, but in all studies included parental smoking, family size, crowding, existence of concurrent diarrheal disease, malnutrition, maternal education.

5. Increased mortality was seen with malnutrition and/or stunting, diarrhea disease, measles, parental health awareness and education.

6. Bacterial causes of pneumonia were difficult to assess due to widespread antibiotic use. Hemophilus influenzae, often non-typeable and Streptococcus pneumoniae are primary etiologic agents in developing countries as in the United States. Gram negative pneumonia was a prominent finding in fatal cases.

7. Documented RSV was the overwhelmingly most important viral agent identified, Parainfluenza 3 being the second most common agent. The distribution of other viruses varied by study site.

8. Fatal pneumonia resulted from cases appearing to be truly purely viral disease, purely bacterial disease, and mixed viral and bacterial infection. RSV was associated with bacterial superinfection in these studies.

Summary:

The BOSTID studies present a currently unique opportunity to assess risk factors and etiology of pneumonia in children in developing countries. Information from different countries could be validated and compared because of the study design which emphasized networking, scientific assistance and result validation, close study monitoring and interactive education, and control. The many papers currently in press or preparation by the study Principal Investigators will detail diverse, important facets of ARI determined through the BOSTID studies. The data also highlights the importance of both bacterial and viral pathogens as causative agents and defines risk factors for ARI. The results emphasized the importance of the study design employed, and help define profitable directions for further work in the field.

TABLE 1

ACUTE RESPIRATORY INFECTIONS IN CHILDREN
BOSTID PROGRAM

COUNTRY	PRINCIPAL INVESTIGATOR
Argentina	M. Weissenbacher
Bangladesh	D. Sack M. Rahman
Brazil	F. Sutmoller
Colombia	I. Borrero
Guatemala	J. Cruz
Kenya	E.M. Wafula
Nigeria	W. Aderele C. Oxejide
Pakistan	A. Ghafoor
Papua New Guinea	M. Alpers D. Lehmann
Philippines	T. Tupasi
Thailand	S. Suwanjutha
Uruguay	M. Peluffo

Overview of Pneumonia in Early Infancy

Stephen Berman, M.D.
University of Colorado Health Sciences Center

The World Health Organization Program for Control of Acute Respiratory Infections (ARI) has identified pneumonia in the first 2 months of life as a high priority area (1). This paper reviews available background information, gaps in the existing knowledge, and potential research strategies relevant to pneumonia in early infancy. The paper first considers case definition for pneumonia, clinical characteristics that identify infiltrate and oxygen desaturation, and the frequency of clinical characteristics associated with pneumonia. Next, it reviews etiologic studies of bacterial and viral agents; finally, it summarizes data on incidence and mortality. When possible, data from both developing and developed countries is presented according to the population studied: community, neighborhood health center, hospital clinic/emergency room and inpatient ward. However significant variations in case definitions, study designs, age of population, laboratory methods and technical quality limit the comparability of the data.

Case Definition and Clinical Characteristics of Pneumonia

Background

Unfortunately, there is no consensus on the case definition for pneumonia during early infancy or later in life. The most objective case definitions are the presence of infiltrate on chest x-ray and oxygen desaturation with pulse oximetry. Mok, et al., have studied oxygen saturation values in normal 6 week and 3 month old infants while asleep and during feeding (2). In 34 infants 6 weeks of age, the mean minimum and maximum oxygen saturations while asleep were 95 and 99% and while feeding 88.5 and 99%. For 37 infants 3 months of age, the mean minimum and maximum oxygen saturation values were 91.5 and 100% while asleep and 92.5 and 99% while feeding. These data support the use of 88-90% as a cut-off to indicate oxygen desaturation in this age group. Clinical case definitions of pneumonia are frequently used in ARI studies. Clinical case definitions are less reliable than chest x-rays or pulse oximetry because of concerns about intraobserver reliability. Concern has been raised that the clinical characteristics of pneumonia in early infancy differ from those observed in older patients, especially with respect to respiratory rate (RR) and retractions. The normal mean respiratory rate (50/min in an active wake

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infant) and its variability are highest in the first week of life, declining over the following 3 months to 45/min (3). In addition, the respiratory rate during the first 3 months is markedly affected by the infant's state: active awake, feeding, active sleep, or quiet sleep. The mean respiratory rate in active sleep drops from 50/min at one week to 35/min at 3 months with considerably less variability than that observed in the awake infant. WHO has chosen 60/min as the cut-off for a normal respiratory rate under 2 months of age. The observation of an elevated respiratory rate (>60) in a sleeping infant is a more reliable indicator of lower respiratory infection (LRI) than in an awake infant. Young infants are also more likely to have retractions or chest indrawing (usually mild) without pneumonia than older patients. These retractions may be related to upper airway obstruction in obligate nose breathers with mild colds or to mild tracheomalacia. In neonates, the compliant rib cage may also result in mild intercostal retractions without respiratory tract infection.

How often does pneumonia present in the first 3 months without cough and/or signs of respiratory distress? Heulett retrospectively reviewed the chest x-rays of 192 infants less than 3 months admitted to the hospital with fever (4). The prevalence of x-ray pneumonia in the population was 6%. Chest x-ray pneumonia was present in 7 of 19 patients with signs of respiratory distress and 5 of 173 without signs. It is unclear whether any of the five patients without signs of respiratory distress had cough. Signs of distress included RR>60, retractions, flaring, rales, grunting, apnea and/or cyanosis. Almost half of the pneumonia cases in this population would have been missed by these respiratory signs. If the prevalence of pneumonia is considerably higher than the 6% in this population, it would be important to use non-respiratory signs to identify pneumonia and/or other serious infections such as sepsis and meningitis. Krober reported 10 cases or x-ray pneumonia among 182 febrile infants less than 3 months, none of whom had clinical signs or symptoms of respiratory infections (5). Bonadio reported a series of 109 infants under 1 month of age previously well with a history of fever (6). Pneumonia was identified in 4 of 37 cases without respiratory signs who had chest x-rays.

Clinical case definitions of pneumonia and/or bronchiolitis usually include the presence of tachypnea (RR>50-60), rales, wheezing, grunting, nasal flaring or cyanosis (Table 1). I can find no published data in developing or developed countries that assess the usefulness of these signs in young infants to identify infiltrate on chest x-ray or oxygen desaturation. At the Ambulatory Pediatric Association meeting in the past year, we presented data assessing the usefulness of clinical characteristics to predict infiltrate in 66 infants with chest x-rays (7). Chest x-rays were obtained in cases with observed cough or other signs suggesting lower respiratory infection. Evidence of infiltrate was found in 80% of the cases. We did not obtain chest x-rays in all infants who presented to the clinic for ethical reasons.

However, we recognize that the failure to obtain x-rays in all patients produces a bias that overestimates the positive predictive value and underestimates the specificity of clinical

signs used as criteria to obtain in x-ray. The effect has been described by Shann (8). The usefulness of clinical characteristics to identify infiltrate in our study is reviewed in Table 1. The table displays the sensitivity, specificity, and likelihood ratio (LR) and the positive predictive value (PPV) with the 80% observed prevalence of pneumonia, and with a theoretical calculated PPV of 40%. None of the clinical characteristics had a significant correlation with the presence of infiltrate on chest x-ray. The likelihood ratio reflects the odds of infiltrate in a case with the clinical characteristics compared to a case without the characteristics. The two signs with the highest likelihood ratios were retractions, LR=1.43 and rales, LR=1.73. However, retractions are more useful because this sign had a sensitivity of 66% compared to the sensitivity of 26% for rales. The presence of either retractions or respiratory rate >60 had a combined sensitivity of 79%, specificity of 46% and likelihood ratio of 1.40. The sensitivity of identifying an infiltrate on x-ray can be increased by 85% by combining retractions or rales or a respiratory rate greater than 60. With this combination, the specificity is unchanged and the likelihood ratio marginally decreased. Therefore, in young infants with signs of an acute respiratory infection, the presence of retractions or rales or respiratory rate greater than 60 will identify most infants with infiltrate on chest x-ray. The best single predictor of infiltrate on chest x-ray was pulse oximetry (oxygen saturation <90%), having a likelihood ratio of 2.7, sensitivity of 63% and specificity of 77% (P approaches 0.05).

Eric Simoes and Mark Steinhoff have recently analyzed their data from Vellore on the usefulness of clinical characteristics to identify infiltrate in 129 cases under 3 months with chest x-rays (Table 3). They have kindly given permission to present their unpublished data at this meeting. The two characteristics with the highest likelihood ratios were the appearance of drowsiness and grunting. Retractions were quite sensitive (94%), but had poor specificity (28%). Respiratory rate >60 had fair sensitivity (61%) and specificity (55%). It must be remembered that all patients did not have x-rays, so that these results have a bias that underestimates specificity as described above.

An alternative to the use of infiltrate on chest x-ray as the standard for pneumonia is to correlate the clinical characteristics with oxygen desaturation. Respiratory rate has been considered the best predictors of oxygen desaturation in young infants. Hall studied oxygen desaturation in 32 infants hospitalized with RSV bronchiolitis and pneumonia (9). Respiratory rate correlated with oxygen saturation (R=0.49), but retractions and wheezing did not correlate with oxygen saturation. In our study of infant pneumonia (done in Denver, Colorado), pulse oximetry was done in 30 cases, 16 of which had a oxygen saturation less than 90% (7). We found that there is no linear relationship between a respiratory rate and oxygen saturation as the correlation coefficient was only 0.22. Twelve of 16 cases with an oxygen saturation less than 90% had retractions, but only 4 of the cases with an oxygen saturation 90% or higher had retractions. In addition, 5 of the 7 infants with a respiratory rate greater than 70 had oxygen desaturation. The predictive value for retractions or respiratory rate greater than 70 for oxygen desaturation was 14/20

(70%) with a sensitivity of 14/16 (88%) and specificity of 8/14 or 57%. Retractions was the only clinical sign significantly correlated with oxygen saturation (at the P<.05 level) with a sensitivity of 75%, specificity of 71% and predictive value of 75%. Wheezing approached significance at the P<.07 level. On physical examination, cough, respiratory rate, respiratory rate greater than 70, retractions, and rales did not have significant correlations with oxygen desaturation.

The relative contributions of retractions, wheezing, and a respiratory rate greater than 70 to oxygen desaturation were determined by multiple regression analysis. The p value associated with retractions was 0.05, respiratory rate greater than 70 was 0.19, and wheeze was 0.55. Therefore, wheezing and respiratory rate >70 in the presence of retractions did not contribute significantly to the relationship of retractions to oxygen saturation.

Etiology of Lower Respiratory Infection (LRI) in Early Infancy

Background

Early infancy can be divided into the neonatal period during the first 28 days and the extended postnatal period during the following 1-2 months. Infection in the neonatal period may be acquired congenitally in utero, at delivery, in the nursery, or at home. Limited information is available on the bacterial etiology of acute respiratory infections in early infancy from developing countries (Table 4). Community studies in the BOSTID program (Colombia, Uruguay and Guatemala), reported few cases with positive blood cultures. There were 7 LRIs associated bacteremic cases among the 340 newborns followed during their first 5 months of life in Cali, Colombia: 4 Staphylococcus aureus, 2 gram negative enterics, and 1 Salmonella (10). The rate of bacteremic LRI is higher in studies carried out in hospital emergency rooms and inpatient units. The BOSTID study carried out in Islamabad, Pakistan was remarkable for the very high isolation rates from blood cultures (11). There were three positive isolations in 21 hospitalized cases of LRI in infants under 1 month of age: 1 Streptococcus pneumoniae, 1 Haemophilus influenzae, and 1 gram negative enterics. Bacteremia was present in 66 of 224 infants 1 through 5 months of age hospitalized with LRI: 24 gram negative enterics, 21 H. influenzae, 15 S. pneumonia, and 6 Salmonella. Most infants under 6 months of age seen in the outpatient clinic were bacteremic with S. pneumoniae and H. influenzae. A retrospective review of hospitalized young infants in Cali, Colombia identified 17 cases under 1 month of age and 4 cases from 1 to 3 months (12). The number and percentage of isolation were as follows: 8 (38%) S. aureus, 8 (38%) gram negative enterics, 2 (10%) group B Strep, 1 (5%) H. influenzae, 1 (5%) group D strep, and 1 (5%) enterococcus.

Studies of bacteremia (5,6) in infants under 3 months of age carried out in the United States have identified group B streptococcus and gram negative enteric organisms as the

most common pathogens in the first month of life and S. pneumoniae and H. influenzae during the next two months. Additional bacteria isolated less frequently from young infants include S. aureus, Salmonella, group A streptococcus, enterococcus, Neisseria meningitis, L. monocytogenes, and Shigella.

Studies of the bacterial etiology of pneumonia in young infants in developed countries (13-16) have identified chlamydia as the most common etiologic bacterial agent. The next most common identified bacterial agent is pertussis. Two studies have investigated maternal transmission of chlamydia. In San Francisco, infants born to 262 culture positive women for chlamydia (4.7% of all pregnant women cultured) were followed prospectively (17). Chlamydial pneumonia was diagnosed in 21 (16%) of exposed infants. In Arizona, 25% of mothers cultured antenatally were positive for chlamydia and the relative risk of chlamydial pneumonia in the first 6 months of life in exposed infants was twice that of unexposed infants (18). In our outpatient study of 90 infants under 3 months, 18% had chlamydial infection (7). This compares to a frequency of chlamydial pneumonia in hospitalized patients of 16% in Denver (14) and 31% in Birmingham (13). The Birmingham study also identified frequent infections with ureaplasma and pneumocystis. I know of no other studies that have confirmed these findings.

There are remarkable similarities in developing and developed countries in the frequency of viral infections when similar culture and rapid diagnostic techniques have been employed (Table 4). Respiratory syncytial virus (RSV) is the most common viral agent identified and its frequency tends to be higher in hospitalized cases than in community cases. This is supported by our finding that 67% of RSV infections in the first 3 months of life required hospitalization (7). RSV infection has also been shown to cause infection in neonates and produce non-specific signs and symptoms (19).

Gaps in Knowledge and Research Strategies

Etiologic data on LRI in young infants from developing countries is still needed. It is very important to clarify the relative frequency of infection in this age group with agents such as group B streptococcus, chlamydia, pertussis, S. aureus and gram negative enteric organisms. It is also necessary to determine if differences exist between the etiology of pneumonia in patients under two weeks, from two to four weeks, and older than four weeks.

Research Strategy

Etiologic studies similar to the BOSTID studies should be carried out in hospital and outpatient clinic settings in infants under 3 months of age, using appropriate technology (chlamydia diagnostic test, pertussis diagnostic test, and blood cultures.)

Incidence and Mortality of Lower Respiratory Infection in Young Infants

Background

It is unclear exactly why early infancy is a high risk factor. Several possibilities include poorly developed immune systems, immaturity of the central nervous system respiratory drive center, anatomic features of the upper airway that predispose to collapse and obstruction, a compliant rib cage and poorly developed respiratory muscles, small lower respiratory airways prone to collapse and obstruction, and limited available energy stores to compensate the infant during decreased feeding.

Several studies have reported incidence data on acute respiratory infections in young infants (Table 5) (20-23). It is difficult to compare incidence data between studies because of variations in case definitions and methods of monitoring. The inclusion or exclusion of runny nose or coryza is especially important as it has a large impact on overall ARI incidence rates because of its chronicity. When runny nose is included, most studies in developing countries found an incidence of 4 to 6 total ARI episodes per child year during the first 6 months of life. In Cali, Colombia, runny nose was excluded and an overall ARI incidence of 2.83 episodes per child year was observed. There are few studies that have reported LRI incidence data during early infancy. The Cali, Colombia data found an incidence of 1.51 LRI episodes per child year during the first 6 months of life (10). The incidence of neonatal pneumonia in Beijing, China was reported as 0.77 to .106 episodes per child year (20). Mortality data from ARI in the first 6 months of life from developing countries is also limited. Datta reported a rate of 5.6 ARI deaths per 1000 child years for infants in the first 6 months of life living in Delhi, India (23).

Table 6 displays the proportiate ARI mortality by age from WHO sponsored intervention studies in Kediri Indonesia and the Kathmandu Valley, Nepal. (The WHO intervention data is unpublished, but is based on a report by Breiman from CDC.) In the Kathmandu Valley of Nepal, 40% of the childhood ARI mortality occurred in infants under 3 months during the control surveillance year; 75% of these deaths under 3 months occurred in the neonatal period. In Kediri, 19% of the childhood ARI mortality occurred during the first 3 months during the surveillance year and 10% of the deaths under 3 months were in the neonatal period.

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Table 1

Clinical Characteristics of Young Infants With Suspected ALRI

Study Site	Date	Age (mos)	No. Cases	Cough (HX)	Cough (Obs)	RR>50	RR>60	Retrac.	Rales	Wheeze	Cyanosis	RR>50 or Retrac or Cyanosis	RR>50 or Retrac or Wheeze
Developing Countries:													
Community													
Cali, Colombia	1987-88	0-5	2.4	-	-	60%	-	71%	14%	21%	0	93%	96%
Clinic Hospital													
Islamabad,	1987-88	0-1	9	-	-	56%	-	89%	56%	33%	44%	-	-
Pakistan		2-5	89	-	-	92%	-	81%	44%	64%	8%	-	-
Vellore,	1985-87	0-2	59	-	-	-	58%	95%	-	-	-	-	-
India		0-3	87	-	-	-	62%	95%	-	-	-	-	-
Inpatient Hospital													
Islamabad,		0-1	21	-	-	95%	-	81%	76%	47%	28%	91%	95%
Pakistan		2-5	217	-	-	87%	-	70%	74%	63%	15%	92%	94%
Developed Countries:													
Clinic Hospital													
Denver, USA	1985-87	0-3	90	94%	42%	67%	57%	37%	19%	24%	-		
Inpatient Hospital													
Birmingham, USA	1976-84	0-3	205	-	56%	-	-	-	75%	34%	-		

Table 2

ASSESSMENT OF THE USEFULNESS OF CLINICAL CHARACTERISTICS TO IDENTIFY INFILTRATE ON CHEST X-RAYS IN 66 CASES

SIGN (Cali)	SENSITIVITY	SPECIFICITY	LIKELIHOOD RATIO	Prev 80% PPV	Prev 40% PPV
Resp. rate >50	73%	23%	0.95	80%	39%
Retractions	66%	54%	1.43	85%	50%
Resp. rate >60	40%	61%	1.02	7x%	40%
Wheezing	30%	69%	0.97	80%	40%
Rales	26%	85%	1.73	88%	53%
Either resp. rate >60 or Retractions or rales	85%	46%	1.57	87%	51%
Either retractions or resp. rate >60	79%	46%	1.4	86%	49%
Either retractions or rales	72%	54%	1.56	86%	51%
Pulse Oximetry*	63%	77%	2.7	91%**	64%

* available in 30 patients, frequent pneumonia 59%
** Calculated for Prev 80% and 40%

Table 3

ASSESSMENT OF USEFULNESS OF CLINICAL CHARACTERISTICS TO IDENTIFY INFILTRATE IN CHEST XRAYS IN 129 CASES UNDER 3 MONTHS IN VELLORE INDIA

	Sensitivity	Specificity	Predicitive Value*	Likelihood Ratio
Resp Rate>60	19/31(61%)	55/99(55%)	19/63(30%)	1.35
Retractions	29/31(94%)	27/98(28%)	29/100(29%)	1.32
Drowsiness	12/23(52%)	67/81(83%)	12/26(46%)	3.05
Unable to feed	20/31(65%)	46/99(46%)	20/73(27%)	1.20
Grunting	11/23(48%)	76/98(78%)	11/33(33%)	2.18

* Prevelance of infiltrate 24%

Table 4

Etiology of ALRI Cases in Young Infants

Study Site	Date	Age (Mos)	No. Cases or Weeks At Risk	No.(%) of Viral Infections: RSV	PI	Inf	Ad	Rhino	CMV	No.(%) With Bacterial Infections (Blood Cultures) No. Cases	Chlamydia	Pertussis	S. aureus	S. Pneu	H.Inf.	Sal.	GNE
Developing Countries:																	
Community																	
Cali, Colombia	1987 -88	0-5	340 pts 7332 wks	27 (.19)*	12 (.09)*	1 (.01)*	1 (.01)	-	-	-	-	-	4 (.03)	0	0	1 (.01)	2 (.014)
Clinic																	
Islamabad Pakistan	1987 -88	0-1	9	1(11)	0	0	2(22)	0	0	6	-	-	1	1	-	-	-
		2-5	97	41(42)	1(1)	2(2)	2(2)	0	0	94	-	-	15	8	-	-	-
Inpatient																	
Islamabad Pakistan	1987 -88	0-1	22	8(36)	0	0	0	0	0	21	-	-	0	1	1	0	1
		2-5	224	113(50)	1	1	2	0	0	224	-	-	-	15	21	6	24
Developed Countries:																	
Inpatient																	
Denver	1978-79	0-1	24 (19 viral infections, 5 bacterial infections)							24	1(4)	-	-	-	-	-	-
		1-2	15 (11 viral infections, 3 bacterial infections)							15	6(25)	-	-	-	-	-	-
		2-3	18 (12 viral infections, 3 bacterial infections)							18	2(8)	-	-	-	-	-	-
Chicago	1967-68	0-1	82	12(15)	11(13)	1(1)	3(4)	2(2)	-								
Birmingham	1976-84	0-2	205	47(23)	10(5)	1(<10)	10(5)	-	41(20)	205	63(31%)	-	-	-	-	-	-
Chicago	1975-77	0-6	56	12(2.1)	4(7)	4(7)	10(19)	1(2)		56	41(73%)	-	-	-	-	-	-
Clinic:																	
Denver	1985-87	0-2	90	25(28)	6(7)	-	-	-	-	90	16(18)	2(2)	-	-	-	-	-

* Incidence in episodes per child year

Table 5

Incidence and Mortality of ARI, ALRI in Young Infants

Study Site	Date	Age Mos	Number Children	Time Wks Obs	Time At Risk	Prevel ARI (per 100)	Incidence (per child yr) ARI	Incidence (per child yr) LRI	Hosp Rate LRI	Mortality (per 1000 child mos) LRI
1. Matlab Bangladesh	1978-79	2-5	28	1652(d)	899(d)	54.4	-	-	-	-
2. Delhi India	1962-67	0-6	1964	6064(mos)	-	-	5.5	-	-	5.6
3. Vellore India	1965-67	0-5	110 fam.	-	-	-	5.9	-	-	-
4. Nigeria	1963-65	0-5	350	-	-	-	4.1	-	-	-
5. Ethiopia	1968	0-5	202	-	-	-	2.6	-	-	-
6. Bejing		0-1	10634	-	-	-	-	.106		
China	1982	0-1	8937	-	-	-	-	.077		
7. Cali Colombia	1987-88	0-5	340	-	6724(ARI) 7332(LRI)		2.83	1.51	-	-

1 case definition includes runny nose, visits every other day
2 no case definition
3 case definition includes runny nose, visits first month weekly than twice a month
4 no case definition
5 no case definition
6 case definition cough, tachypnea, foaming mouth, cyanosis, fever, course BS, rales, very increased markings, infiltrates (my 2)
7 case definition excludes runny nose, weekly home visits

Table 6

Proportionate ARI Mortality by Age

Site	No. Deaths <1 mos	No. Deaths <3 mos	No(%) Deaths <3 mos/<12 mos	No(%) Deaths <3 mos/<5 yrs
Katmandu Valley, Nepal				
Surveillence	6	8	8/12 (67%)	8/20 (40%)
Intervention I	1	2	2/4 (50%)	2/8 (25%)
Intervention II	1	1	1/1 (100%)	1/6 (17%)
Kederi Indonesia				
Surveillence	2	21	21/67 (31%)	21/111 (19%)
Intervention	1	4	4/28 (14%)	4/38 (11%)

Hierarchy of Risk Factors: Feasibility and Status of Primary Prevention

Robert Breiman, M.D.
Centers for Disease Control

Introduction

In addition to better rates of immunization and improvements in diagnosis and timely management, an effective long-term response to the challenge of morbidity and mortality from acute lower respiratory infections (ALRI) in children in developing countries must take into consideration factors that increase the probability of developing ALRI. Efforts to definitively identify individual risk factors for ALRI have often been frustrated because these factors tend to be interrelated. In this review, the evidence available linking certain factors to ALRI will be presented. In addition, I will discuss the weaknesses of some of the associations and how they might be remedied in future studies. Since these factors are frequently associated with socio-economic status, cultural belief systems, and level of education, modification of behavior patterns linked to disease may pose an even greater challenge for those concerned with public health intervention in developing countries.

The factors felt to have the greatest bearing on the incidence of ALRI are nutrition, indoor air pollution, low birth weight, and overcrowding. Cultural beliefs and level of education of the parents which influence the likelihood of acceptance of immunization policies and the tendency to seek medical care may also be important factors for morbidity and mortality due to ALRI.

Malnutrition

In the developing world in 1983, 42% (about 145 million) of children <5 years of age in the world were estimated to be malnourished (1). Malnutrition is a major determinant of risk for serious, often fatal infections in young children (2). Infection compounds malnutrition by creating a catabolic state, leading to a vicious cycle (3). The association of malnutrition with infection is confounded by other factors related to decreased socio-economic status, such as household crowding, and non-compliance with immunization

schedules. These factors are difficult to control for during field studies (4).

Nutritional status appears to specifically affect ALRI incidence and mortality. Moderately to severely malnourished children <15 years of age were 3 times more likely than well-nourished children to develop ALRI in a two year study conducted in an urban center in Colombia (5). In a study conducted in Costa Rica, nutritional status did not affect incidence of acute respiratory tract infections; however, malnourished children experienced a mean longer duration of infections as well as a much greater incidence of lower respiratory tract infections (1).

Of nutrient deficiencies that may contribute to risk of infections in childhood, hypovitaminosis A is the most studied. It is unclear if deficiencies of other nutrients, such as vitamins B, C and E, and minerals including iron and zinc, are important risk factors for ALRI.

Vitamin A Deficiency

In addition to its role in the visual process, growth, bone development and reproduction, vitamin A is important for normal immune responses and in epithelial cell differentiation and maintenance of normal barrier function of surface epithelium (6). In laboratory animals, vitamin A deficiency interferes with normal B- and T-cell function (7, 8). Vitamin A deficient rats have a markedly reduced specific antibody response when immunized with a capsular polysaccharide of Streptococcus pneumoniae (9). The antibody response normalizes when these animals receive vitamin A supplementation.

Vitamin A deficiency may be an independent risk factor for development of ALRI in children, as well as for diarrheal diseases (10) and for morbidity and mortality attributed to measles (11, 12). In one study, Indonesian children < 5 years of age, with pre-existing vitamin A deficiency, as estimated by the presence of xerophthalmia (nightblindness and Bitot's spots), were twice as likely to develop acute respiratory infection (ALRI) (defined as clinically significant cough, rhonchi or rales) during a 3 month observation period than children without xerophthalmia (10). This difference was independent of nutritional status. On the other hand, children whose xerophthalmia resolved by the end of the 3 months period were not at increased risk for developing ALRI when compared with children who did not have xerophthalmia at any point. A follow-up study in Indonesia, demonstrated a reduction in mortality in children receiving vitamin A supplementation (6).

These data suggest that vitamin A supplementation may significantly reduce the risk for ALRI. Vitamin A should be given when children are reasonably healthy since absorption from the gastrointestinal tract is markedly reduced during respiratory and parasitic infections (13, 14). It is unknown if children with moderate or severe malnutrition are

able to adequately absorb and utilize vitamin A if their nutritional status remains otherwise unchanged.

Method of Infant-feeding

Infants who are breastfed appear to be less likely than those that are formula-fed to develop gastro-intestinal infections. However, an association of the method of infant-feeding to development of ALRI is not as defined. Breast milk is rich in secretory antibodies (15), phagocytes (16), and non-specific resistance factors including lactoferrin, lysozyme and interferon (17, 18), but it is unknown whether ingestion of these factors and cells protects against respiratory infections. Another consideration is that infant formula may become colonized with respiratory pathogens; thus, a protective effect of breastfeeding would be expected because of avoidance of potentially contaminated infant-formula.

Some studies indicate that breastfeeding is protective against severe respiratory infections when compared with formula-feeding(19, 20, 21), and that early weaning may predispose to increased mortality from ALRI (19). In a study in England, children who were breast-fed had a significantly reduced risk of infections due to respiratory syncytial virus when some potentially confounding variables were considered in multivariate analysis, but the effect was not significant if quality of maternal care, the mother's smoking habits, and sharing sleeping quarters with another child were controlled for (22). Other studies do not demonstrate a significant protective effect (23, 24).

Interpretation of these studies is hampered by methodological problems, such as an inability to control for potentially confounding variables of socio-economic status, over-crowding in the home, and smoke exposure (19,20) as well as failure to use an adequate case definition for ALRI (21,22) in the studies showing a protective effect and by inadequate sample sizes in studies not showing this effect (23,24).

Although most studies suggest that breastfeeding is protective against ALRI, the conclusion will remain tentative until future investigations resolve these methodological problems. The issue is particularly important in urban settings in developing countries since the use of infant-formula can give mothers freedom of employment and the potential of raising the economic status of the household.

Indoor Air Pollution

Acute and chronic inhalation of smoke can damage respiratory epithelium and decrease mucociliary clearance and secretory functions (25). It appears that such damage increases the risk of ALRI in children. Numerous studies have demonstrated that exposure to cigarette smoke in the home increases the incidence of respiratory infections in children (26, 27, 28, 29).

In developing countries, about half of households use combustible organic matter (biomass or biofuels), including wood, or domestic animal manure, for cooking and/or heating (1). In most cases the biofuels are burned indoors, often without adequate ventilation, producing levels of respirable particulates >20 times those from environmental tobacco smoke in developed countries (30).

In a study in Nepal, the risk for infants or children <2 years of age developing severe ALRI increased in proportion to time spent near a cooking stove (31). However, potentially confounding variables were not considered. In the Gambia, biofuels are burned primarily in cooking huts to which young children are restricted from entering unless carried on their mothers' backs. Carriage on the mother's back and number of cigarettes smoked by the father were each associated with a significant risk of developing an episode of difficulty breathing during a three month period (32). A study to better evaluate the preventive effect of limiting exposure to smoke from biofuel combustion would require: a sample size large enough to measure a relatively small effect and to control for confounding variables; a more direct way of determining exposure, such as households that cook inside or outside the home; and the use of an objective outcome variable (such as pneumonia). Such a study would be difficult to perform because determinants of exposure to biofuel combustion are multi-faceted and difficult to control for (32).

The strong epidemiologic evidence linking passive cigarette smoke to ALRI suggests that smoke from biofuel combustion is also a likely risk factor. Future studies should evaluate the effect of introducing practical means to limit production of indoor air pollution, such as the use of smokeless stoves or improvement in ventilation, on incidence of ALRI.

Low Birth Weight

In developing countries, fetal growth retardation may occur in between 20-40% of pregnancies and is the major cause of low birth weight (<2500 grams), which is the most important factor in child survival and healthy development (1). Premature delivery is the other major cause. The occurrence of fetal growth retardation is associated with maternal malnutrition, physical labor, illnesses during pregnancy, young maternal age, high parity and close birth spacing. In a study in England, low birth weight children were 5 times more likely to die during the neonatal period and 4 times more likely to die in the first year of life than children weighing >2500 grams at birth (33). ALRI is the most frequent cause of death due to infection in low birth weight children (1).

Socioeconomic Factors

As discussed above, socioeconomic factors are intertwined with all risk factors for ALRI. Overcrowded households and sleeping quarters may increase the risk of transmission of ALRI (34).

Education and Cultural Beliefs and Practices

Parents unaware of dangerous signs and symptoms of ALRI may not bring their sick child to health care providers for treatment early enough to prevent morbidity and mortality. Public health education should define the services available as well as educate parents about the potential complications of ALRI, the importance of timely therapy, and recognition of simple signs and symptoms of ALRI. These efforts should be carried out by individuals well known and trusted in the community, such as schoolteachers, village traditional mid-wives or primary health workers (35). Such efforts should take into consideration local cultural beliefs that may give a higher value to health care by traditional or ritualistic healers than by modern medical practitioners who distribute antibiotics. In a study in Tanzania, >50% of children who died from ALRI were treated only by traditional healers (36). The importance of traditional medicine in some cultural belief systems should be considered when planning ALRI interventions. Efforts should be made to educate traditional healers about recognition of signs and symptoms of ALRI and the value of referral of children with ALRI to hospitals or health care clinics.

Age

Children <6 months of age have a disproportionately high mortality rate from ALRI. In a Bangladesh study, 50% of fatal ALRI cases among children <5 years old occurred in infants <6 months of age (37). Similar findings were observed in Tanzania where children <6 months of age accounted for 38% of all ALRI deaths in children <5 years old (36).

Prevention of ALRI in children <6 months old is especially challenging since most vaccines are not effective in this age group. Studies determining etiologies of ALRI specific to this age group will help to determine whether strategies such as immunization of women of childbearing age with capsular polysaccharide vaccines against S. pneumoniae and Hemophilus influenzae might be of value. The effectiveness of such an approach depends at least partially on whether the vaccine used increases levels of IgG-1 antibody that crosses the placental barrier (37). The specific type of IgG response to bacterial polysaccharide antigens is unclear (38, 39). Although conjugated protein-polysaccharide vaccines for S. pneumoniae and H. influenzae may be useful in younger children, they are unlikely to provide much protection in children <6 months.

Conclusion

Of the risk factors for ALRI in children presented here, only a few are easily addressed by intervention strategies. Vitamin A supplementation once-a-month is a practical and potentially beneficial intervention that could be studied on a nationwide scale in a developing country. Better studies are needed to determine whether breastfeeding is effective in reducing the incidence of ALRI. Educational efforts integrated into local

cultural beliefs should be feasible in most settings. Efforts to reduce the presence of smoke in the home are unlikely to be immediately practical since they involve educational to discourage smoking (which has been largely ineffective in developed countries), changes in ventilation, and new cooking devices.

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Available and Potential Vaccines for Control of Lower Respiratory Tract Infections in Developing Countries

Neal Halsey, M.D.
The Johns Hopkins University

Several vaccines routinely used in all countries of the world are effective in preventing respiratory tract infections in children. In developed countries, additional vaccines for prevention of respiratory infections have been introduced for routine use or for high risk groups. At this time these additional vaccines are expensive and provide inadequate protection for young infants to justify use in all countries. The minimum immunization schedule recommended by the Expanded Programme on Immunization of the World Health Organization and a comparable schedule recommended for the United States differ in several respects (Table 1).

Table 1

Recommended Routine Immunization Schedule for Developing Countries and the United States

WHO

AGE	
Birth	BCG, TOPV
6 Weeks	DTP, TOPV
10 Weeks	DTP, TOPV
14 Weeks	DTP, TOPV
6 Mos.	Measles (Edmonston-Zagreb*)
9 Mos.	(Measles **)

(Additional booster doses of DTP and TOPV are offered in many countries).

UNITED STATES

AGE	
Birth	---
2 mos.	DTP, TOPV
4 mos.	DTP, TOPV
6 mos.	DTP, TOPV
15 mos.	Measles
18 mos.	DTP, TOPV, Haemophilus influenza (Conj.)
4-6 yrs.	DTP, TOPV, Measles #2 (USPHS)
12 yrs.	Td, Measles #2 (AAP)

* High titer (10^5 TC1D50)
** Standard titer (10^4 TC1D50) all strains

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Bacilli Calmette - Guerin

BCG vaccine is recommended by WHO for use at birth in all countries where tuberculosis continues to be an important public health problem. Pulmonary tuberculosis is obviously an important cause of respiratory disease and mortality in developing countries. Although the results from efficacy trials have been variable, the majority of studies have demonstrated that BCG vaccine administered in the first month of life has effectively prevented severe forms of tuberculosis in children. Protective efficacy has been evaluated with both perspective, randomized, controlled trials, and retrospective case-control studies. The variability in the estimates of protective efficacy are believed to be due to differences in study methodology, different strains of BCG used in the production of the vaccine, differences in production techniques, and perhaps differences in the host response to vaccines in different geographic areas. Most investigators believe that BCG vaccine has little or no efficacy when administered later in life.

Diphtheria

Corynebacterium diphtheriae is an important pathogen that causes severe respiratory tract disease. The organism is transmitted from person-to-person with inoculation onto the respiratory epithelium or in breaks in the integrity of skin. Most severe disease is noted in nasopharyngeal and tracheopharyngeal disease. The organism releases a toxin that results in local tissue destruction and severe edema. In severe cases, an artificial airway (tracheostomy) is necessary in order to maintain life. The toxin also causes severe cardiac and neurologic complications.

Unfortunately, few data are available on the incidence of diphtheria in developing countries although the disease is recognized throughout the world. In most series of severe respiratory disease, diphtheria is either not included or the incidence rates are relatively low.

Diphtheria toxoid is prepared by inactivation of the toxin with formaldehyde. Diphtheria toxoid is combined with tetanus toxoid and pertussis vaccine to make DTP. Three doses are recommended in the first year of life. In many countries, booster doses are given in the second and fourth to sixth year of life in order to maintain immunity. Diphtheria toxoid is highly effective with an estimated protective efficacy of 85% to 95% following three doses.

Bordetella pertussis

Bordetella pertussis is an important cause of severe respiratory tract disease in developing countries and in many industrialized countries of the world. Although studies in developing countries are limited, the available evidence indicates that pertussis is an important and

common cause of severe lower respiratory tract disease with high case fatality rates in most developing countries. Unfortunately, the recently completed Bostid studies did not include diagnostic techniques for detecting pertussis. However, other studies in Africa and South and Central America indicate that pertussis is a common cause of pneumonia. In many languages, pertussis is known as "the 100 day cough". The persistent nature of the illness is associated with decreased food intake and significant malnutrition in affected infants. The disease is most severe in children under 9 months of age. The true incidence of this disease is probably underestimated since many infants under 9 months of age do not have the characteristic whoop or paroxysmal coughing episodes and because laboratory diagnostic methods are not usually available.

Three doses of DTP induces 70% to 90% protection against clinical disease in protective efficacy studies conducted in the United States and Europe. I am not aware of any published studies of pertussis vaccine efficacy trials in developing countries. In some industrialized countries, pertussis vaccines have been controversial because of high rates of local and systemic side effects. Efforts to produce subcomponent or acellular pertussis vaccines have been underway for over ten years. The Japanese have lead the research in this area and now acellular vaccines are routinely used in Japan. Six different acellular preparations are produced that appear to induce protection against clinical disease comparable to the rates of protection observed with whole cell vaccine in earlier trials.

Unfortunately, there have been no direct comparisons between acellular and whole cell vaccines in large scale clinical trials. The recently completed field trial of acellular pertussis vaccines in Sweden resulted in lower rates of protection (59% to 80%) than anticipated by the investigators. The Swedish officials who conducted the trial were also concerned about four deaths that occurred among the 3,000 children who participated. Although the cause of death in these children and the time following vaccination did not indicate a causal relationship, concern persists in Sweden and the acellular vaccines have not yet been licensed.

Additional data are needed on the incidence of pertussis in different countries, the protective efficacy of the current whole cell vaccines, and field trials comparing whole cell with the acellular vaccines. Efforts to control this disease would be aided by the development of simplified techniques for confirming the diagnosis in the field.

Measles

Measles is the most important preventable cause of respiratory disease in developing countries. Although effective vaccines have been available for more than 25 years, measles causes between 1.5 and 2 million deaths a year and respiratory complications are responsible for the majority of deaths. Almost all children with measles develop a severe cough. When chest x-rays have been taken, 85% of infected individuals had radiographic changes.

In most instances, these changes consistent of increased interstitial markings, but diffuse pneumonia and secondary lobar pneumonia are common. Pneumonia was diagnosed in 10% of children under 5 years of age with measles in studies conducted in the inner city of Chicago. In developing countries, the acute mortality rate from measles has been estimated to be three to five percent. In some countries, the case fatality rate has been 15% to 30% in selected outbreaks. There have been no carefully conducted clinical studies of community acquired measles to document the incidence of respiratory complications in most developing countries. The pneumonia that occurs is primarily caused by direct effects of the measles virus on the respiratory tract. Secondary viral infections with adenovirus and herpes simplex virus have been documented. However, secondary bacterial pneumonia caused by Streptococcus pneumoniae, Haemophilus influenzae, staphylococcus and gram negative enteric organisms commonly occur.

Measles vaccines are highly effective. In studies where children have been vaccinated after the disappearance of maternal antibodies, 90% or more of the children are protected by a single dose of vaccine. Unfortunately, measles occurs at a very early age in developing countries, where 15% to 30% of children contract measles by the time they are 12 months of age. Therefore, vaccination is necessary at an earlier age. The World Health Organization recommended 9 months of age as the best possible compromise age for administration of standard measles vaccines. The recommended age for administration of measles vaccines is older than for other EPI recommended immunizations. Since mothers are less likely to seek preventive services for children as they get older, measles vaccine coverage rates are usually lower than for other EPI antigens. WHO currently estimates that 55% of children receive measles vaccine by the time they are 12 to 23 months of age.

Several years ago, concern was raised that measles vaccination might not effectively prevent mortality in developing countries. This speculation arose out of one study in Africa where the investigators thought the replacement mortality had occurred. However, a reanalysis of those data has revealed that significant protection against mortality did occur. More recently, studies in Bangladesh, Haiti, and Guinea Bissau have demonstrated significant reductions in mortality for children who received measles vaccine as compared with unvaccinated children. Clemens and coworkers observed a protective efficacy for measles vaccine of 59% for prevention of diarrhea related deaths and 22% for respiratory related deaths in Bangladesh. Our studies in Haiti have also demonstrated a preventive effect of measles vaccine on mortality. We conducted a case-control study of children residing in an urban slum population in Port-au-Prince, Haiti. The study was conducted two and one half years after measles vaccine was first introduced. Having received measles vaccine was strongly associated with survival these children. Several other factors, including socioeconomic status, maternal literacy, maternal knowledge of oral rehydration, and birth interval were also associated with protection against mortality. The impact of measles vaccination on prevention of mortality was noted most strikingly in children born to illiterate mothers of a lower socioeconomic status.

The cumulative data from these studies are convincing that measles vaccine is an effective means of preventing mortality and severe morbidity in children.

A major improvement in our ability to vaccinate children under 9 months of age has recently been adopted by the World Health Organization. By increasing the titer 10 to 100-fold and using the Edmonston-Zagreb strain of vaccine, 80% to 90% of children can be effectively vaccinated at 6 months of age. We found that the high titer Edmonston-Zagreb vaccine induced protective immunity in 83%-100% of Haitian children vaccinated at 6 months of age. Similar studies conducted in Mexico and Africa have revealed that over 90% of children responded at this age. These data indicate that we can now achieve seroconversion rates at 6 months of age comparable to the rates achieved at 9 months of age with standard vaccines. The Global Advisory Group of the EPI endorsed the use of these high titer (10^5 TC1D50) vaccines in countries where measles is a significant problem in children under 9 months of age. In other areas, the global advisory group has recommended that the titer of all measles vaccines used at 9 months of age be increased to at least (10^4 TC1D50). This increase in titer should improve the seroconversion rates for children vaccinated at 9 months of age. The use of higher titer vaccines has not been associated with any change in the incidence of adverse events. We believe that the recent changes in the immunization schedule will result in a marked improvement in our ability to control measles in urban areas and help to achieve increased immunization coverage rates.

Other Vaccines

Several additional vaccines have been licensed for prevention of respiratory pathogens (Table 2). The most commonly used vaccine for prevention of respiratory viral infections is influenza vaccines. The inactivated (or killed) vaccines currently recommended for high risk populations in the United States are not likely to be incorporated into developing country EPI programs. Although individual vaccines are effective against the identical viruses used to make vaccines, rapid antigenic changes develop in the wild type virus and limit the effectiveness and duration of protection offered by these vaccines. In the United States, the inactivated vaccines are recommended for use in populations at high risk of severe complications from influenza, including persons with underlying cardiorespiratory disease, immunodeficiency states diabetes and other metabolic disorders. The high cost and limited efficacy will prohibit the use of this vaccine in EPI programs. Live viral influenza vaccines are under development and may provide a reasonable alternative if means are found to induce protection against a wide variety of strains with a single immunization.

Table 2

Available Vaccines and Toxoids for Prevention of Respiratory Disease

Routine Use

BCG
Diphtheria Toxoid
Pertussis Vaccine
Measles Vaccine
Haemophilus influenza type b

Recommended for high risk groups in developed countries

Influenza vaccines (inactivated)
Adenovirus types 4, 7 and 11
Streptococcus penumoniae - 23 types - polysaccharide

Similar live vaccines are under development for prevention of parainfluenza infections. Parainfluenza viruses are the most important etiologic agent of laryngotracheobronchitis (croup) and these viruses also cause pneumonia. No projected timetable for the availability of these vaccines has been made, but the preliminary studies in animals and the first human subjects have been encouraging.

Respiratory syncytial virus (RSV) has been shown to be the most important cause of severe lower respiratory tract illness in infants throughout the world. A formalin inactivated RSV resulted in an altered immune response in vaccinated children, so that they suffered hypersensitivity disease after exposure to the wild type virus. Therefore, this vaccine was never licensed for routine use. More recently, the pathogenic mechanisms for inducing the hypersensitivity phenomenon have been identified, so that this problem should not occur with new vaccines currently under development. Encouraging work with both live and subcomponent vaccines is underway. There are no vaccines available for large scale field trials in developing countries, but these vaccines may become available within the next 3 to 10 years.

Vaccines for prevention of adenovirus infections are available. Military trainees in the United States have suffered high rates of adenovirus infections associated with upper and lower respiratory tract disease that interfered with training. Live vaccines administered orally have been shown to be effective against adenovirus types 4, 7 and 11 and are currently administered to all military trainees. Over 10 million doses have been administered, and the vaccine appears to be safe and highly effective. The vaccine is currently administered in a tablet or capsule form which would be difficult to administer to young infants. Also, the types of adenovirus that cause most severe lower respiratory tract illness in childhood are types 1, 2, and 5. Although vaccines have been made and tested for prevention of adenovirus infections, these vaccines have not been tested in large

populations. Serious consideration should be given to the possible use of adenovirus vaccines in children since studies have demonstrated that these viruses contribute to the respiratory disease burden in children.

Orally administered vaccines or the live vaccines administered intranasally might be very attractive for use in widespread immunization programs in developing countries. The great success of the poliomyelitis eradication program in the Americas is largely due to the ability to conduct large scale immunization programs with vaccines administered by lay personnel.

Bacterial Vaccines

Streptococcus pneumoniae, and Haemophilus influenzae type B are the most important bacterial causes of lower respiratory tract disease in children after the first month of life. Plain polysaccharide vaccines are available for prevention of these infections. Unfortunately, the immune response to plain polysaccharides is suboptimal in children under 18-to-24 months of age. Since that is the age with the highest incidence of infections due to these organisms and the target age for immunization programs, it is unlikely that the plain polysaccharide vaccines will ever be routinely used in developing countries.

Conjugating the polysaccharides to proteins has resulted in marked enhancement of the immune response in children at a young age. Two Haemophilus influenzae type B conjugate vaccine preparations have been approved for routine use at 18 months of age in the United States. The polysaccharide vaccine conjugated to an altered diphtheria toxin molecule has been shown to induce 83% protection against invasive Haemophilus influenzae type B vaccine in young infants in Finland. However, these encouraging results were not duplicated in a population of native Americans in Alaska with characteristics similar to those of many developing countries. The reasons for these discrepant results are not known. Several other conjugate vaccines that appear to be more immunogenic are currently undergoing evaluation in large scale efficacy trials. The results of these trials should become available by mid 1990 and may provide the basis for widespread use of these vaccines in both industrialized and developing countries.

The efforts to develop effective conjugate Streptococcus pneumoniae vaccines have not progressed as far as they have with Haemophilus influenzae vaccines. Preliminary data in animals and in small numbers of humans indicate that conjugation of the Streptococcus pneumoniae polysaccharides with a variety of proteins is also effective at inducing high rates of immunity.

Pneumonia in neonates has not been discussed as an important target for prevention of lower respiratory tract illness. Group B streptococcus is an important pathogen in this age group. Studies conducted by Baker and colleagues have demonstrated that vaccination of

mothers during pregnancy effectively increased the amount of passive antibody transferred from most mothers to their offspring. Efforts are being made conjugate the group B streptococcal polysaccharide with proteins to enhance the immunogenicity and duration of immunity with these vaccines.

Several other organisms are potential targets for vaccine development to prevent lower respiratory tract illness in children (Table 3). With the recent rapid advancements in the technology for production of vaccines, it might be possible to develop effective vaccines against these organisms within the near future.

Table 3

Experimental Vaccines for Prevention of Respiratory Diseases

Viral

Influenza - live, cold adapted
Parainfluenza - live
Respiratory Syncytial Virus (RSV) - live and polypeptide
Adenovirus Types 1,2,5 - live

Bacterial

Haemophilus influenzae conjugate vaccines for use in infancy
Streptococcus pneumoniae conjugate vaccines for use in infancy
Group B Streptococcus conjugate vaccines for immunization of women of childbearing age.

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The BOSTID Research Program: Future Research Needs

Floyd W. Denny, Jr., M.D.
University of North Carolina

Judith R. Bale, Ph.D.
National Research Council

A summary of the components of the BOSTID research program in acute respiratory infection (ARI) has been presented earlier in this workshop by Dr. Patricia Charache. As the twelve developing country research teams worked to complete projects on the etiology and epidemiology of ARI, a National Research Council Committee on ARI in Third World children was appointed (Floyd Denny, chairman, Stephen Berman, Patricia Charache, W. Paul Glezen, Kenneth McIntosh, Harris Pastides, Beatrice Selwyn and Judith Bale, staff director). The purpose of this committee is to guide continuing research, to identify future research directions in light of findings from the BOSTID and other ARI projects, and to determine the policy implications of the BOSTID research. The committee identified future research directions in three general areas: prevention of ARI by reduction of risk factors, case management, and pathogenesis. This paper outlines the various components of each of these areas; an attempt is made to indicate their priority as regards the perceived importance of the research.

Prevention of ARI by Reduction of Risk Factors

I. Further analysis of BOSTID data. Several papers from the twelve individual BOSTID projects are currently being submitted for publication in a journal supplement. Because of the standardization of data collection and laboratory technology used in these studies, it will be possible to compare results from several populations. This, in turn, will add considerable weight to the collective observations. Completion of the analysis of collected data was assigned the highest priority.

II. Risk factor reduction. Children in developing countries are at greatly increased risk for severe morbidity or mortality due to ARI. Although it is clear that such factors

Previous Page Blank

as age (the very young and the elderly) and malnutrition place individuals at increased risk, the precise mechanisms of these factors are not known. Specific areas needing more attention were identified as follows:

A. Follow-up epidemiological studies to allow more accurate interpretation of the association of specific agents with clinical syndromes, the age and health status of the child and the impact of crowding and smoke pollution, all of which were found important in the completed studies.

B. Specific areas for emphasis.

1. Malnutrition. Malnutrition is associated with increased risk. Since the mechanism for this association has not been established, this area was assigned a high priority. Specific emphasis was placed on two aspects of nutrition research:

   a. Immunity. It is well known that severe malnutrition affects immunity adversely, but the specific effect on acute lower respiratory infections (ALRI) has not been studied.

   b. Vitamin A. Preliminary studies in Indonesia suggest that vitamin A deficiency may be an important risk factor; a high priority was placed on an intervention study to determine the effect of vitamin A on ALRI in young children.

2. Crowding. BOSTID studies revealed crowding to be a risk at all study sites. These findings deserve follow-up with more detailed studies.

3. Physiological risks. The following changes in the anatomical or physiological integrity of the lung were suggested as fruitful avenues for research:

   a. Chronic lung disease
   b. Low birth weight
   c. Oxygen deprivation

4. Inhaled pollutants. It is known that a variety of inhaled pollutants including ozone, nitrous oxide and cigarette and wood smoke can damage the respiratory tract and increase the incidence and severity of respiratory infections in developed countries. The effect in developing countries is largely unknown.

C. ALRI in young children. Studies suggest that the etiology and severity of ALRI in children during the first few months of life are different than in older children, and

that significant mortality in this age group in developing countries may be due to these infections.

D. Vaccines. A high priority was placed on the development and use of vaccines, as follows:

1. Haemophilus influenzae type b. Because of the difficulty in diagnosing H. influenzae pneumonia and the possibility that pneumonia is caused by haemophilus organisms, not type b, a limited priority was placed on use of the presently available vaccines.

2. Streptococcus pneumoniae. At this time, no pneumococcus vaccine is available which is suitable for use in young children. When such a vaccine is available, its use should be pursued vigorously.

3. Maternal immunity. Because of the high mortality rate of ALRI among very young children and the possible benefit of passive antibody from the mother, enthusiasm was expressed for research to determine the efficacy of vaccinating mothers late in pregnancy.

4. Measles and pertussis vaccines. Although effective vaccines for measles and pertussis are available, these diseases continue to cause excess morbidity and mortality in developing countries. Widespread use of both vaccines is encouraged. In addition, it would be highly desirable to develop a measles vaccine that is temperature-stable,and a pertussis vaccine that is less toxic than those presently available.

5. Development of greater diagnostic capability. Research in the use of respira-tory vaccines is hampered by the lack of effective, simple, and inexpensive methods for establishing etiological diagnoses. Pursuit of this problem should receive high priority.

Case Management

In spite of difficulty in making etiological diagnoses and a lack of understanding of the pathogenesis of severe and fatal ALRI in developed countries, presently available diagnostic and treatment tools for case management are successful in most cases. It would be highly desirable to pursue the use of these tools in developing countries. The areas that seem worthy of pursuit are as follows:

I. Operational research

A. Oxygen delivery systems. Oxygen is clearly indicated in the care of children with severe ALRI; its use is hampered frequently by its unavailability. Efforts to rectify this are clearly indicated.

B. Use of bronchodilators. Bronchodilators might be useful in certain types of ALRI and, if found to be useful, could be important adjuncts to therapy.

C. Fluid and electrolyte maintenance. Fluid and electrolyte maintenance may be important in the survival of children with ALRI in developing countries. It is poorly understood and needs to be studied.

II. Antibiotics. The proper and improper use of antibiotics remains one of the largest problems in developing countries. The following areas should receive high priority:

A. Appropriate drugs, schedules, and doses. Emphasis should be placed on lower drug cost and ease of administration, in addition to effectiveness.

B. Compliance. Compliance is always a problem wherever antibiotics are used, and especially in developing countries.

C. Adverse reactions.

D. Bacterial resistance. Efforts should be made to monitor the development of resistance to currently used antibiotics. This has already proved to be a problem with H. influenzae and S. pneumoniae.

III. Treatment of very young children. Because the etiology of neonatal ALRI and its clinical aspects and treatment are frequently different from those of ALRI in older children, this problem requires special attention.

IV. Early detection and treatment. One of the big problems in ALRI in the developing countries results from late detection of infected children and resulting late treatment. The various reasons for this are unclear and should be determined.

V. Assessment of knowledge, attitudes, and practices of mothers. It is possible that these problems are the basis for much of the serious outcome of ALRI in developing countries. Comprehensive studies of these problems and the formulation of strategies for their resolution are badly needed.

Pathogenesis

In spite of the tremendous advances that have been made in our knowledge of the etiology, epidemiology, and treatment of ALRI in developed and developing countries, the pathogenesis of most ARI is unknown. As a result, there are real problems in addressing adequately the problems outlined above under prevention of ARI by Reduction of Risk Factors and Case Management. In all probability, progress will need to be made in unraveling some of the problems in pathogenesis before satisfactory answers can be found in the other areas. The following areas were mentioned by the committee as important:

I. Autopsies or equivalent. In some BOSTID studies, autopsy results for children with ALRI have shown changes consistent with profound immunodeficiency and/or vitamin A deficiency. These suggestive findings need to be confirmed by more such studies. It is suggested that limited or equivalent examinations be attempted if full autopsies cannot be done.

II. Methods for assessing diagnosis.

A. At the present time, there are limited techniques for establishing the role of various microorganisms in infections involving the larynx, trachea, bronchus, or alveolus. Better methods are clearly needed for establishing diagnoses for both viral and bacterial infections.

B. Physiological. The physiological changes that take place in the lung, especially those leading to hypoxia or hypercapnia, have been inadequately studied, especially as they may be related to the need for hospitalization and eventual outcome.

C. Relationship between microbes and physiological reactions. As the etiological roles of various microorganisms become better defined, their relationship to physiological reactions should become clear; this could aid immensely in the management of children with ALRI.

III. Role of anatomical factors/functions. The role of damage to the respiratory mucosa caused by viral infections and the superimposition of bacterial infections is unknown, but these could be important as risk factors in severe ALRI. The role of other diseases, such as bronchopulmonary dysplasia, is likewise unknown in developing countries and should be investigated.

IV. Interaction between viruses and bacteria. At present, the only well-accepted situation in which viral lower respiratory infections predispose the host to bacterial superimposition is with influenza virus and Staphylococcus aureus, Streptococcus

pneumoniae, or Haemophilus influenzae. However, since it is commonly believed that this predisposition occurs frequently with other respiratory viruses, antibiotics are almost routinely given to children with ALRI. This is a very important problem, and high priority is therefore placed on gaining a more complete understanding of the interaction between viruses and bacteria.

V. Role of carriage of H. influenzae and S. pneumoniae. These two bacteria are carried in the nasopharynx of a high proportion of children in developed countries, and some studies have shown that the proportion of carriers is much higher among children in developing countries. The role this plays in primary bacterial ALRI and possibly secondary bacterial infection of the lung warrants investigation.

VI. Role of risk factors. The need to reduce certain probable risk factors was mentioned above in the section on prevention of ARI by reduction of risk factors. In addition, it is desirable to learn more about how certain risk factors contribute to increased severity in some children. Important factors for study are as follows:

A. Environmental. Environmental factors, especially inhaled pollutants, have an adverse effect on the respiratory tract, but the mechanism of this effect is not clear. Damage to the mucosa leading to ciliary dysfunction, disturbances in mucous secretion, and impaired immunity have been implicated and need further study.

B. Host defenses. Impairment of host defenses seems the most likely contributing factor in the production of severe ALRI due to viruses or bacteria, or to the interaction between the two. The host defense mechanisms deserving further study are as follows:

1. Immunological. B cell and T cell functions are involved in all respiratory infections, playing an important role in pathogenesis and recovery, and are therefore important in ALRI among Third World children. Dysfunction could be caused by a wide range of factors that are presently unknown.

2. Mucosal barriers. The role of damage to respiratory mucosa by various factors has been mentioned above and is added here for emphasis.

3. Alteration of white blood cells. It has been demonstrated that the white blood cell is profoundly altered in influenza virus infections. This could contribute to the severity of complications, especially superimposed bacterial infections. This type of research needs to be

expanded to include other infections and to determine the importance for ALRI in developing countries.

C. Infections due to other microorganisms. It has been demonstrated that a variety of microorganisms, including CMV, EBV, herpes simplex virus, hepatitis B virus, HIV, several parasites, and the influenza virus, all suppress the immune system. Because the prevalence of infections due to these agents is so great among developing world children, these agents could be playing a large role in severe ALRI, a role that should be investigated.

Epidemiology of ALRI: State of the Art

Discussion Summary

Importance of standardization in epidemiologic research: The variation in ARI nosology was discussed. When past studies of ARI are compared, there appears to be great variability in the data reported on ARI. In these studies of ARI, the ascertainment procedures were quite different, which can result in a significant difference in the incidence and prevalence rates that are reported. The lack of rigidity or standardization in such studies can lead to erroneous conclusions about the relative importance of certain risk factors, clinical signs and symptoms, clinical syndromes and etiologies. The other major issue that has plagued the study of ARI is determining the beginning and ending of ARI episodes, which is much more complicated than determining the end of a diarrheal episode. The definition of the various exposure factors, for example domestic smoke exposure as mentioned above, can vary, leading to results that are difficult to compare. The BOSTID studies did, however attempt to standardize case definitions, ascertainment, viral and bacterial laboratory procedures, and therefore should be helpful in constructing an overview of global ARI incidence, risk factors and etiology.

Ascertainment techniques: Where case assessment is done, and who does it will result in different incidence rates. For example, the incidence of ALRI will vary depending not only on case definition but also on whether cases are ascertained in the home, in health centers, or in the hospital. Mothers, trained field workers, and physicians each apply different levels of expertise as well as definitions to case ascertainment.

Importance of institutional capacity in determining viral etiology: Prior to the BOSTID studies, none of the 12 BOSTID study centers were capable of recovering respiratory viruses and diagnosing them accurately. Now at least 9 of them have the resources required to pull together epidemiology, clinical presenta-tion, risk factors assessment, and etiology. Prior to the development of laboratory capability in virology, RSV was assumed to be a minor cause of pneumonia. This incorrect assumption arose from the inability to make a correct diagnosis from an etiologic standpoint.

Role of prior antibiotic use in determining bacterial etiology: The use of antibiotics in the treatment of ARI before seeking advice of a health practitioner is widespread in many developing countries. Prior antibiotic treatment may limit the isolation of bacteria from children sampled in etiology studies, resulting in an underestimation of the ARI disease burden due to bacterial infection. Therefore, prior antibiotic use may limit the generalizability of etiologic data.

Importance of the seasonality of transmission of ALRI: As experience with other programs such as EPI has shown, the seasonality of ARI should be considered in the design of strategies to control disease. The BOSTID studies clearly demonstrate seasonality during which ARI incidence is increased in colder seasons and in rainy seasons, in those countries that have rainy seasons.

Rapidity of death: This is an epidemiological variable that is extremely important in program planning. It pertains to the speed at

Previous Page Blank

which the disease progresses, especially in the youngest children. From community studies, it is becoming apparent that a high proportion of deaths are occurring between three and five days, or less than three days[1]. From a programmatic perspective, there is a relatively small window of opportunity to reach these children. It is not known how rapid death children may be identified earlier, nor are the risk factors, besides age, clearly delineated for this group.

Malnutrition: Prior studies have suggested an increased risk of ALRI mortality in malnourished children. Similarly, vitamin A deficiency has been identified as a risk factor. However, if the definitions of ARI are examined in these studies, the same problems of varying case definition and case ascertainment are evident. These design issues, as well as the association of malnutrition with other socioeconomic factors that place the child at risk for ALRI mortality, prevent firm recommendations for the use of vitamin A specifically for the prevention or treatment of ALRI.

Radiologic classification: The WHO is developing a classification system because they have had many requests for standards and clinical sign studies. At this point, what is evolving is actually a working group of radiologists, accepting the fact that there will always be the problem of interobserver variability. This panel of radiologists are working towards reducing their own interobserver variability sufficiently to improve the yield of standardized readings. The description of radiologic criteria for classification and supplying sample chest-xray films will never limit interobserver variability enough, but may yield more reproducible outcomes for clinical science studies than have been produced in the past.

Role of anemia: In developing countries, anemia, primarily due to iron deficiency, is very prevalent in very young children. Many of these children with ALRI or pneumonia probably have low hemoglobin levels so the total delivery of oxygen to the tissues would be decreased in children who are anemic. So anemia is probably a risk factor for severity (e.g., death) once pneumonia occurs. Like malnutrition and vitamin A deficiency, anemia may also be strongly associated with other socioeconomic variables that place a child at an increased risk of ALRI morbidity and mortality.

Effect of altitude on pulse oximetry studies: Oxygen saturation is going to be different for those children living at 12,000 feet than for children living at sea level. Dr. Steinhoff shared preliminary data from colleagues working in 3,700 meters in Peru, which is a little more than 12,000 feet. Pulse oximetry was obtained on 26 well children ages two months to 12 months. The range of saturation was SpO2 of 83 to 93%, with a mean of 87. The interesting finding among these 26 children over two months, but under 12 months was that nine out of the 26 at rest were breathing faster than 50 per minute.

Epidemiologic research and implementation needs: A distinction should be made between what is needed for treatment and the management of illness and what is needed to do the research, as these may be somewhat different. Research requires standardization in order to draw conclusions across various studies, cultures and ecologies as opposed to what health workers must do when they manage sick people. There is a wide overlap in these areas. Where there are no stethoscopes, Western doctors or x-rays, how are treatment decisions best made? These are the recommendations sought for those simple places. For a field worker who has a primary level of three or four years of education and probably three or four weeks of training, he or she has to be able to make the first

decision. This decision will probably be based on clinical signs or symptoms, or algorithm entry criteria, which have the most reliability in terms of field worker training and the best clinical yield in terms of sensitivity and specificity to detect pneumonia.

1 Editor's note: For example, see description of the Jumla, Nepal ARI program in Daulaire N, "Practical issues of ARI program implementation," p. 99, this volume.

Review of ALRI Intervention Studies: Effect on Mortality

Robert E. Black, M.D., M.P.H.
The Johns Hopkins University

The ALRI case management (CM) strategy is based on the premise that childhood pneumonia is largely due to bacterial organisms and that appropriate antibiotics can be successfully used in a community-based health program to treat the illness and prevent death. Evidence that pneumonia in young children was predominantly due to Haemophilus influenzae and Streptococcus pneumoniae was derived from a number of studies using lung puncture cultures, for example in Papua New Guinea. The first demonstration that a pneumonia case management strategy utilizing community health workers was feasible was in the Narangwal Study in India in the 1970's.

To further investigate the efficacy of a community- and clinic-based ARI case management strategy, a series of studies have been undertaken since 1982. Six of these studies were begun with WHO support and a more recent one in Jumla, Nepal with AID support. I will review the results to date from these six WHO funded studies using data provided by the investigators at a WHO meeting last year (1). These studies have in common the following 1) they attempted to recognize signs of pneumonia in children and 2) they provided a systematic program of antibiotic manage-ment for pneumonia, often combined with improved immunization coverage, especially against measles. The studies also had a number of differences among them that are summarized in Table 1.

Table 1
Differences in ARI Intervention Study Design

Setting:	IMR (49 - <200), malnutrition, other services, literacy
Design:	Concurrent control, before/after
Case Detection:	Active, passive (± health education) both
Pneumonia Treatment:	CHW or clinic ± referral
Antibiotic:	Penicillin (oral), cotrimoxazole, ampicillin
Outcome:	Total IMR, ALRI-specific IMR
	Total <5 MR, ALRI-specific <5 MR
Cause of Death Assessment:	Verbal Autopsy

Previous Page Blank

The study in Abbottabad, Pakistan targeted children <5 y/o; 31 villages served as intervention areas/ nine as control. After two years, the intervention was also introduced in the control area. Active case finding by every-two-week household visits was implemented by CHW who identified pneumonia and treated it with cotrimoxazole. Treatment failures were referred. Immunization, ORT and nutrition program were also implemented in both intervention and control area.

- There was a reduction in total and ALRI-specific mortality, and a 50% reduction in ALRI-specific IMR. There was also a similar reduction for <5 year olds. The mortality fell somewhat between year 1 and year 2 in the control area, but dropped significantly when the ARI intervention was introduced.

- This study is one of the most impressive in that it showed an effect of ALRI CM in addition to the effect of EPI and other programs.

Studies in Bayamoyo, Tanzania also utilized both a concurrent control and before/after design. ARI education and passive case finding was done and treatment employed was with cotrimoxazole. Immunizations were also implemented, and coverage was higher in intervention (I) vs control (C).

- There was a significant reduction in ALRI and total <5 mortality comparing control with intervention in YI and subsequent years.

- The conclusion is that the study had an impact on mortality, but one cannot distinguish effect of immunizations and CM.

A study in Bohol, the Philippines, involved <5 year old children in area with relatively low IMR (50), and used both concurrent control and before/after design. The study intended to implement community education on ARI but did not and relied on passive case finding. Cotrimoxazole R_x was given at clinics.

- The IMR fell by 20% in I, with no change in C (NS). ALRI-specific mortality in <5y/o exclusive of measles fell by 28% in I and 10% in C.

- The conclusion is uncertain since the intervention seems inadequate, but nevertheless there was a possible effect.

A study in Haryana, India is interesting and unique in involving only low birth weight (LBW) infants. There were 21 villages in the intervention and 16 in the control. The study used active case finding by weekly visits and CHW treated with oral penicillin. The intervention area also had increased immunization coverage.

- The ALRI-specific mortality was about 60% lower in the intervention area than in the control area, total IMR was somewhat lower in the intervention area.

- The conclusion is that ARI CM probably had an impact on this high risk group of LBW infants.

A previous study in the Kathmandu Valley of Nepal was a before/after comparison of an intervention involving active case finding and ampicillin treatment by CHW.

- ALRI-specific IMR and <5 MR dropped by 60-70% and total IMR and <5 MR also fell significantly.

- The conclusion from this study is that case finding and treatment had a substantial impact.

A study in Kediri, Indonesia, involved a before/after comparison of active ALRI case finding and cotrimoxazole treatment. Immunization coverage also increased substantially in the intervention area.

- ALRI-specific mortality dropped by about 75%, total <5 mortality fell from 43 to 25. Since a large measles outbreak occurred in the pre-intervention year and measles vaccine coverage increased to very high levels, the role of measles-associated pneumonia needs close examination.

- In 6 month periods, they demonstrated that measles mortality was almost eliminated but also that ALRI mortality declined.

- If one looks as age groups, there was an 80% decrease in ALRI mortality in 1-4 year/old, 71% in 6-11 month/old, and 55% in 0-5 month/old.

- The conclusion would be that the ALRI CM intervention probably had an effect beyond that of measles immunization.

- This study and the others to a lesser extent raises the general point of how commonly ALRI deaths are associated with measles. It would appear that a minority of ALRI deaths are measles-related.

In summary, these studies suggested:

1) that it is feasible to train community workers to recognize and treat pneumonia, and

2) that, taken in the aggregate, there is an effect of ALRI CM on mortality, 5 studies showed an impact, and one had a possible impact.

It must be recognized that these studies were not implemented as an ARI program would be. They largely used active case finding but the apparent rapidity of death and the relatively infrequent household visiting may have diminished the impact. A program would need to utilize community education and passive case finding. Although this may ideally have a greater impact than these studies demonstrated, the reality of implementing such a program might, in fact, diminish its effectiveness. Furthermore, the importance of local host and environmental factors, such as LBW and malnutrition or intense bacterial colonization or antibiotic resistance, that may modify the impact of CM are not yet understood.

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Clinical Signs Predictive of Pneumonia in Children

Stephen C. Redd, M.D.
Centers for Disease Control

The previous report from Dr. Black describes how case management has reduced deaths in children from respiratory infections: he has described how case management can work in a population. I will present data regarding case management of individual children; how each children with respiratory infection should be diagnosed and treated. I will concentrate on the diagnosis of pneumonia since we have the most data on this condition, and it is the most important condition to manage correctly because of its large share of the mortality burden. I will discuss the studies that have led to the current WHO recommendations for diagnosing pneumonia, the deficiencies that I think still exist in the scientific basis of case management, and the scientific and implementation issues that remain unsettled.

Microbiologic studies of pneumonia have determined that bacteria can be isolated from the majority of children who have lobar pneumonia. Early identification and treatment of children with pneumonia with antibacterial drugs is thus the cornerstone of current policy to prevent deaths from respiratory infection. The studies including lung puncture have consistently identified a high percentage of disease due to bacteria, most commonly Streptococcus pneumoniae and Hemophilus influenzae. Studies not including lung puncture have identified lower percentages of bacterial disease.

Case management is the process that occurs when a clinician, physician or community health worker, evaluates an individual patient, reaches a diagnosis, and prescribes therapy. In teaching case management the training of the clinician must be considered. Different training strategies may be needed for different cadres of health professionals as ARI control programs are implemented. The WHO guidelines and the studies these recommendations were based on represent an attempt to identify simple clinical findings that could be used by someone other than a pediatrician to provide a standard approach to diagnosis and treatment of a child who may have pneumonia.

The current WHO recommendations for the diagnosis and treatment of children 2 months

to 4 years old with cough or difficult breathing are based on 3 observations. Recommendations for younger children are based on expert clinical opinion since there have been no studies on children less than 3 months old. In evaluating 3 month to 4 year old children with cough or difficult breathing, the data the health worker must collect are: 1) Are danger signs present? These include inability to drink, convulsions, lethargy or being abnormally sleepy, stridor in a calm child, and clinically severe malnutrition; 2) Is chest indrawing present?; and, 3) Is the respiratory rate above 50 breaths per minute? These 3 findings are then used to decide how to manage the child.

In case management of a child who may have pneumonia, the clinician has 2 decisions to make: 1) Should the child receive antimicrobial drugs?, and 2) Should the child be referred to a hospital? According to the WHO recommendations children with cough or difficult breathing should receive antimicrobial drugs if any one of the 3 criteria above are met. Children with chest indrawing or with danger signs should be referred to a hospital. Other than the population studies Dr. Black described to you, there has been no true evaluation of the results of this decision.

There have been four published studies evaluating signs of children with pneumonia or lower respiratory tract infection, and I will also present preliminary results from one study that was recently completed in the Philippines with WHO support. The Levanthal study was conducted in the emergency department of the Yale/New Haven Hospital. Clinicians were asked to complete a questionnaire on clinical findings in children who had a chest x-ray ordered. A case of pneumonia was defined as a child that had changes on chest x-ray compatible with pneumonia. The purpose of the study was not to define the clinical signs of children who had pneumonia, but to identify a method to reduce the number of chest x-rays ordered. Clinical findings of patients with x-rays compatible with pneumonia were compared to findings of patients that did not have pneumonia.

The next study, one that has served as the basis for much of the current WHO policy, is the study conducted by Shann et al in outpatients presenting to Goroko Hospital in Papua New Guinea. In this study, pneumonia was defined as the presence of crepitations on physical examination; chest x-rays were not performed. A cohort of 200 children with cough, seen as outpatients, were categorized into those that had crepitations and those that did not. A second group of 100 children without cough was also examined and found to have similar clinical signs to the group of children who did not have crepitations. Findings of patients with cough and crepitations were compared to the findings of patients with cough without crepitations.

Cherian's study was conducted in Vellore, India. In this study, the findings of children admitted to the hospital with respiratory tract infection, children who mostly had pneumonia, were compared to children seen as outpatients for respiratory infections. Lower respiratory tract infection was defined as the presence of crepitation, wheeze,

bronchial breathing, or radiological abnormalities in the lungs. Radiographs were taken when clinically indicated.

Campbell studied a cohort of about 500 children under 5 years old in the eastern region of The Gambia. He defined lower respiratory tract infection as any auscultatory sign or any radiological abnormality consistent with lower respiratory tract infection. Children in the cohort who were examined for respiratory infection and judged not to have lower respiratory tract infection served as controls.

The Philippines study was conducted over a one-month period in a busy outpatient department. Lower respiratory tract infection was defined as clinical or radiological findings compatible with pneumonia as determined by a pediatrician. Findings in children who had pneumonia were compared to those who did not. In all of the above studies radiographic studies were performed to confirm a clinical suspicion of lower respiratory tract infection.

Each study used different definitions for pneumonia or lower respiratory tract infection; the studies that used clinical definitions had different clinical observers; each study had different enrollment criteria; and the durations of the study ranged from a 1 month to several years.

In Levanthal's study tachypnea, as observed by the clinician examining the patient was the best single predictor of radiographic pneumonia with a sensitivity of 81% and a specificity of 62%. Although respiratory rate was recorded, this variable was not specifically reported, but was apparently not as good a predictor as the clinicians' observation of tachypnea. In Shann's study, breathing over 50 breaths per minute had a sensitivity of 72% and specificity of 81% in predicting crepitation in children.

In Cherian's study, respiratory rate greater than 50 had a sensitivity of 75% and specificity of 96%. A major difference in the India study is that control children were selected from children attending outpatient clinic, who were less severely ill than admitted children so a higher specificity is not surprising. In Campbell's study, respiratory rate over 50 had sensitivity of 71% and specificity of 98%, This study is the only one from a community cohort, and since there were only 500 children in the cohort many of the observations in the children with upper respiratory tract infection are repeat observations in the same children. The Philippines study, using the WHO criteria of respiratory rate of more than 50, found a sensitivity of 66% and specificity of 90%.

In looking at these studies as a group and realizing the different populations studied and different definitions used, it is reassuring that the range of sensitivities is so narrow. Excluding the Levanthal study that did not use the WHO criteria, the range of sensitivities is from 66% to 75%. The wider range of specificities can be attributed to the wide range

in severity of illness of the comparison populations. What is of great concern is how insensitive this single finding is. Using respiratory rate > 50 to determine antimicrobial therapy would mean that between 25% and 34% of children meeting some definition of pneumonia or lower respiratory tract infection would not be identified and would not receive the antimicrobial therapy that we think is needed to prevent death from pneumonia.

We know that older children with lower respiratory tract infection are more likely to have respiratory rate under 50. Cherian reported that the sensitivity of respiratory rate of 50 was inadequately sensitive in identifying lower respiratory tract infection in children above 12 months old and suggested that a respiratory rate of 40 be used for these older children. In Shann's study, sensitivity for children 12 months or older was raised from 57% to 74% if the cutoff was dropped to 40. In Campbell's study sensitivity increased from 64% to 89%. Sensitivity could be improved from 58% to 89% in the Philippines study. In the Lesotho study, 75% of children 12 months and older with pneumonia would have been identified using a respiratory rate of 50 as the cutoff.

The corresponding drop in specificity that occurs when lowering the respiratory rate to 40 for older children, ranges from a difference of 33% in the Philippines' study to about 15% in the Gambia. What we really need to know is the likelihood of complete recovery without antimicrobial therapy in children who meet some definition of pneumonia or lower respiratory tract infection but have respiratory rate under 50. If these children will get worse and are at substantial risk of death, more sensitive clinical signs are needed. Making respiratory rate criteria age-specific will improve sensitivity, but will add complexity to the triage process. Other signs may be as useful and easier to implement. Potential signs that could be used include elevated temperature and intercostal chest indrawing.

The next issue I will address is that of severe pneumonia requiring referral. Unfortunately, we have no objective criterion for determining which children need to be referred. Different authors have studied this problem in different ways. Shann compared 50 children who were admitted to the hospital to children seen as outpatients and not admitted. It is not clear how the 50 hospitalized children were selected for study or whether criteria for admission included chest indrawing. Chest indrawing had a sensitivity of 100% and a specificity of 98%. In Cherian's study, admitted children were compared to those not admitted, the same design used for the entire study. Chest indrawing was seen in 88% of admitted patients and in 42% of those not admitted, for a specificity of 58%.

In Campbell's study, the chest radiograph was used to separate children into those who had lobar pneumonia and those who had segmental and subsegmental pneumonia. Chest indrawing was present 60% of children with lobar pneumonia and in 61% of those with nonlobar pneumonia. In the Philippines study, two pediatricians graded the severity of illness, and signs that were tested were those of the WHO algorithm including any of the

danger signs or lower chest wall indrawing. These criteria had a sensitivity of 70% and a specificity of 94%.

Several points deserve mention. First, what is the appropriate comparison population? In Campbell's and Cherian's studies only children who had lower respiratory tract infection were studied. In the other studies the comparison populations included children who had less severe pneumonia or no pneumonia at all. Second, the definition and reproducibility of chest indrawing seem to vary from study to study. The new WHO recommendation that chest indrawing be defined as lower chest wall indrawing may help standardize this term.

Aside from the test criterion, the bases for the definitions of severity are not standard. For example, whether to hospitalize or not depends on local conditions, such as the number of available beds, the difficulty in follow-up, and the clinical judgment of the person making the decision. What is really needed is an objective measure that would predict which children would benefit from hospitalization. Whether lobar pneumonia is in some way equivalent to severe pneumonia is open to question.

Pulse oximetry is a noninvasive method of measuring the percentage arterial oxygen hemoglobin saturation. It works through a spectrophotometric assay, essentially determining how red capillary blood is. Although the technology may be promising, in the Philippines study, only 5 of 21 children that were thought to be ill enough to require hospitalization had evidence of oxygen desaturation less than 90% by pulse oximetry.

The diagnosis of pneumonia should be the focus of ARI case management, but other respiratory diseases that may need to be addressed by an ARI program include: 1) the wheezing diseases, asthma and bronchiolitis, which require bronchodilator drugs, 2) otitis media, a leading cause of deafness, which should be treated with antimicrobial drugs, and 3) streptococcal pharyngitis, a disease that, especially in older children, can result in rheumatic fever, and its complications. Perhaps these diseases should be ignored in the initial implementation of an ARI program, and we should limit the program to control of mortality due to pneumonia.

I have not discussed details of therapy, beyond identifying children with lower respiratory tract infection. Other therapeutic modalities need to be addressed. Oxygen, in particular, can have an immediate life-saving effect for children with respiratory infection. No studies have evaluated the therapeutic efficacy of oxygen, or help us identify children who would benefit from oxygen therapy. Of particular interest is whether hypoxic children alone, a subset of children with hypoxia, or a larger group of children with respiratory illnesses would benefit from oxygen therapy. It will be very difficult to design an ethical comparative study of oxygen in hypoxic children. Regarding antimicrobial therapy, are the current recommendations that the duration of antimicrobial therapy extend for 5 days

really appropriate, and which drugs should be used?

Several questions urgently need answers so that recommendations for the diagnosis and treatment of pneumonia can be finalized. First, what clinical manifestations of respiratory disease in children 2 months old and younger should be used to decide antimicrobial treatment? How sensitive must clinical signs be to prevent deaths from pneumonia? (Another way to phrase the same question is to ask what happens to children with pneumonia who have respiratory rate less than 50 who are not treated with antimicrobial drugs?) Lastly, what is severe illness and how can it be quantitated?

Finally, implementation issues must be considered. How well will the recommendations that have been developed mostly from hospital-based studies operate in the community? We have some preliminary data from Campbell's study, but we need more community-based observations. Is the recommendation to teach age-specific respiratory rates to community health workers feasible? Will the narrow definition of chest indrawing that includes only lower chest wall indrawing, be easier to teach and evaluate than the definitions used in the current studies?

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Clinical signs of pneumonia

study design

study	case def	study pop	comparison
Levanthal	x-ray	children for x-ray	neg x-rays
Shann	crepitations	children with cough	no crepitations
Cherian	clinical	hospitalized children	outpatients
Campbell	clinical + x-ray	cohort	no findings
Philippines	clinical + x-ray	clinic attendees	no findings
Lesotho	x-ray	clinic attendees	neg x-ray

Clinical signs of pneumonia

summary of results

study	sign	sensitivity	specificity
Levanthal	tachypnea	81% (21/26)	62% (66/110)
Shann	resp rate > 50	72% (48/67)	81% (108/133)
Cherian	resp rate > 50	75% (188/250)	96% (413/432)
Campbell	resp rate > 50	71% (110/154)	98% (4104/4204)
Philippines	resp rate > 50	66% (75/113)	90% (175/194)
Lesotho	resp rate ≥ 50	68% (53/78)	67% (194/291)

Signs of severe pneumonia

Study	definition	test criterion	sensitivity	specificity
Shann	admitted	indrawing	100%	98%
Cherian	admitted	indrawing	88%	58%
Campbell	lobar infiltrate	indrawing	60%	39%
Philippines	admitted	WHO criteria	70%	94%
Lesotho	admitted	indrawing	35%	83%
Lesotho	lobar infiltrate	indrawing	28%	82%

Effect of age on sensitivity of Resp Rate predicting pneumonia

study	RR>50		RR>40
	<12 mo	≥12 mo.	≥12 mo.
Shann	80%	57%	74%
Cherian	89%	57%	71%
Campbell	85%	64%	87%
Philippines	86%	58%	89%
Lesotho	74%	64%	75%

Practical Issues of ARI Program Implementation

Nils M.P. Daulaire, M.D., M.P.H.
JSI/INTERCEPT[1]

Over the past few years ARI has been increasingly recognized as a major killer of children in the developing countries. A number of studies carried out in Nepal in the early 1980s found ARI to be a leading contributor to that country's high infant and child mortality as well. As part of AID's initiative in Child Survival in Nepal, support was provided to several Nepali organizations with technical assistance from John Snow, Inc. in order to determine what elements would be needed to implement an effective large scale ARI control program in an underserved population.

Planning for this effort was started in late 1985. Early on we determined that the ideal site in which to develop and test ARI implementation strategies and to determine impact would be one in which there were few if any confounding health services, in which childhood mortality was high and in which ARI was clearly a major factor. In order to assure reproduceability on a large scale and to allow adequate testing of significance of any mortality impact, a population of at least 10,000 children under five were needed.

Jumla District in the mountainous region of western Nepal met these criteria, and field implementation of the Jumla ARI Intervention Trial began in early 1986; it has continued through the present. The program is based on the use of specially trained villagers who visit each household in their communities every two weeks actively seeking out cases of childhood pneumonia ("active case detection"), who respond to calls from parents to see sick children ("passive case detection"), and who carry out treatment of confirmed cases of pneumonia in the household with oral antibiotics according to protocol. To date the program has treated nearly 30,000 cases of childhood pneumonia. Through it we have learned a great deal about the practical needs of program implementation and about the epidemiology of childhood pneumonia.

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[1] The International Center for the Prevention and Treatment of Major Childhood Diseases, P.O. Box 168, Hanover, New Hampshire 03755.

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At the very start we learned that community workers could not be reasonably expected to deal with the broad range of illnesses that comprise Acute Respiratory Infections, and that trying to do so would distract them from the major issue at hand, pneumonia. In Nepal and, we believe, globally, it is more appropriate to focus on pneumonia control rather than ARI as the basis for program development, and programs should be named to reflect that emphasis in order to reduce the inclination of many training programs to try to teach too much about too many things. This maintains the focus on the form of ARI which has the greatest health consequences.

The main thrust of our program has been on the in-home treatment of pneumonia cases; therefore it is important to recognize what can and what cannot be done in the home. The current scientific consensus is that although clinical case management of pneumonia with antibiotics can effectively be carried out in the home, there is no regimen of home care which can keep a cold (also known as mild ARI) from developing into pneumonia: nose clearing and other mechanical remedies have no impact on the progression of disease and it would be highly expensive and very counterproductive to treat every cold with antibiotics. There is also no effective home remedy for pneumonia. Therefore, if antibiotics and trained personnel cannot be provided, there is no point in initiating any sort of pneumonia or ARI control program. Further, field workers should not be distracted and burdened with instructions to educate mothers in ineffective home care.

Even though the elements which need to be taught to community health workers regarding pneumonia recognition and treatment are fairly simple and straightforward, we have found that actually conveying and maintaining the necessary skills and practices require considerable training time and continuous ongoing supervision. The training course which we have developed takes fully nine days of lectures, demonstrations and field work devoted almost exclusively to pneumonia detection and treatment.

The workers are taught to distinguish pneumonia based on a respiratory rate of greater than 50 breaths per minute or the presence of chest retractions ("indrawing"). A critical element of the training is the experience of actually practicing respiratory rate determination, measuring out the appropriate dosage of antibiotics, and counselling mothers regarding care and follow-up; each trainee carries out these activities in local households under the observation of a program trainer.

Even the well-trained rapidly lose their skills if they are not regularly reinforced through on-site supervision. Our supervisory program calls for each new worker to be visited by a supervisor at least once every two weeks initially, and at least every month once their skills are determined to be well integrated. The supervisor accompanies the worker on his household rounds and reinforces or corrects practices. He also assures that the worker is adhering to the program's protocol and reporting accurately on his activities.

Without this intensive level of supervision there is considerable risk that diagnostic skills and precision would be eroded to the point where the decision to treat would be made on the basis of subjective rather than objective criteria. This is a major concern in the development of community-based pneumonia control programs, since the end result might be profligate antibiotic distribution, at considerable cost and with little if any impact aside from the development of widespread resistance to the antibiotic used.

As a support to the objective determination of respiratory rate, we have found that a timepiece is essential, and that the field worker cannot adequately assess respiratory rate without it. Since most of the villagers of Jumla do not have a watch, it was necessary for us to develop our own timing device, which is a simple hand held electronic beeper which sounds 30 seconds after being pressed. This prototype device has been found to be highly effective, and is in the process of being adopted by WHO and UNICEF for use by field workers involved in pneumonia control around the world.

The antibiotic used in our program is oral co-trimoxazole (sulfamethoxazole) syrup. This was chosen for reasons of efficacy, simplicity and cost. Co-trimoxazole is generally effective against most varieties of pneumococcus and Haemophilus influenzae, the predominant organisms in severe childhood pneumonia in the developing countries; we have no indication of resistance to this antibiotic in western Nepal. Co-trimoxazole has the added advantage of requiring only twice-daily dosages, for a total course of five days, reducing the likelihood of confusion or missed doses compared to other antibiotic regimens which may require four daily doses. Syrup was chosen because of the simplicity and acceptability of administration to young children (co-trimoxazole tablets are intensely bitter and are often rejected after the first taste); however there are considerable consequences in terms of cost (syrup is more expensive per dose than tablets) and transport of bulky bottles which have not yet been fully resolved.

The use of an oral antibiotic as opposed to an injectable has considerable advantage since it obviates the need for training lay workers in sterile injection technique and providing the materials necessary to carry this out on a routine basis. However, we have found that the sickest children have a very hard time taking anything orally, so early treatment becomes all the more important; there are times in which oral treatment is simply impossible.

Based on more than three years of program experience to date, with detailed and repeated field evaluations, it is clear that with the necessary training, supervision and support programs in place, community workers can in fact carry out appropriate diagnosis and treatment of childhood pneumonia cases according to technically accepted protocols. The managerial requirements of such a program are high, but there should no longer be any doubt about its operational feasibility from the standpoint of health services delivery.

However, the benefits of an operationally successful program should be carefully assessed before it is widely expanded or replicated. We have devoted considerable attention to the question of mortality impact, as well as to reviewing the underlying assumptions on which our program protocols were based. In the process we have learned a great deal about the natural history of childhood pneumonia and factors which influence treatment programs.

We have found the infant mortality rate in our population to be 180, with 27% of mortality attributable to pneumonia, second only to diarrhea as a leading cause of death. Pneumonia is particularly important as a cause of mortality in the very youngest: more than half of all pneumonia deaths occurred before the age of three months, and nearly two thirds before the age of six months. Rather than targeting all under-fives, as we had done initially, we have now revised our program to target children under the age of two years, since they account for 91% of all pneumonia deaths, and with particular emphasis on children under six months. Evidence is now accruing from other areas of the world that seems to support this emphasis on the very young.

Although the program has from early on collected data on the mortality impact of this intervention, the data analysis which will be used to determine whether there has been a significant reduction in overall and cause specific mortality will not be carried out until late in 1989. To date the data which has been used for modifying the program has come from our ongoing management information system and our detailed verbal autopsies.

To our surprise and concern, we found after analyzing the first year of our data that, in spite of extremely high coverage rates as measured by the nearly 100% of households visited every two weeks, and high overall treatment rates of approximately 0.9 antibiotic treatments per child per year, only 25% of the children who died of pneumonia had received treatment. This led to concern that our coverage was not as good as we had believed it to be, or that it was misdirected. However in program reviews we found that adherence to our protocols was extremely high; the explanation for low coverage of fatal episodes related to the disease pattern itself.

Among those children who died of pneumonia, information collected from mothers indicated that the average duration of major symptoms prior to death was on the order of only three and a half to four days, leaving only a small window of opportunity to initiate treatment in time; yet among children who recovered from pneumonia, the average duration of symptoms was nearly eight days. Obviously, a two-weekly home visiting schedule relying entirely on active case detection would miss most of the serious cases; considerably more frequent home visiting is hardly feasible.

Over the past two years we have been working on strategies to increase our coverage of severe pneumonia cases; currently, approximately 80% of all childhood pneumonia cases in the district are being treated, and yet even in this past year only 35% of fatal cases

received treatment prior to death. Statistical analysis has indicated that there is evidence of clinical efficacy in children who have received antibiotics, and so our operational question has become how to reach children with severe pneumonia more quickly.

This has necessitated a shift in our program emphasis from one of pushing effective service delivery, in which we have been largely successful, to generating effective and appropriate demand for these services in a timely fashion. The obvious key to effective demand is the mother, and we have developed conceptual model highlighting a number of key issues which we believe underlie the generation of true effective demand.

Active case detection, as discussed earlier, is inadequate to deal with this problem because, although the health worker is active in seeking out cases, the mother continues to be a passive recipient of these services. Although this is preferable to a system in which both the provider and client are passive (the usual situation in traditional passive case detection) and in which very few services are delivered at all, the need is to develop an ethic of what I would term active case presentation among the community of mothers. Active case presentation requires the fulfillment of a number of conditions, which we now believe to be the key to an effective program.

The first condition which needs to be met is to help the mother to develop a sense of empowerment, to help her to realize that she can in fact do something that will have an effect on the survival of her child. Given the strong role of fatalism in Jumla and in much of the least developed areas of the world, this is an extremely difficult task, and will require the assistance of behavioral scientists, as well as ongoing proof from their own experience.

The second condition is one of maternal recognition. This has become a major emphasis in our program, and we have made considerable advances in teaching mothers to recognize the signs and symptoms of pneumonia. Community education tools and one-on-one discussions are essential to get this message across, and we are seeing progress.

The third condition is effectively conveying to mothers the importance of and the need for action on her part in seeking care when they recognize pneumonia in their children. We have found in many of our pneumonia deaths that mothers recognized the symptoms in their children, were aware that their children had a serious disease, but nevertheless they did nothing about it for a variety of causes, some reflecting back on their basic sense of fatalism. Clearly a program will not be effective until mothers take action. We are assessing this in Jumla by a continuous analysis of what proportion of our pneumonia cases are coming to the attention of health workers due to self-referral by the mother.

The fourth necessary condition is trust in the health worker. This is often lacking in developing countries, and generally for good reason from the standpoint of the mother.

Because we have recruited local people and trained them intensively in their responsibilities in service to their communities, our program has been able to instill this sense of trust, but in places where health workers treat their clients poorly and where there are no services or medicines, even mothers who are prepared to take action will not call on the health system. This is not an issue of traditional medicine versus Western medicine. Mothers are very practical; they will use what they think works. It is our job to make sure that the service providers are in fact trustworthy.

The fifth necessary condition is access to the health worker. The closer they are, the more likely they are to be called on. In Jumla we have dealt with this by increasing the number of workers so that the considerable majority of the population is within one hour of a worker. Alternatives could include the use of community "gatekeepers" who would be trained in diagnosis and who would call on a health worker in confirmed cases of pneumonia. In better served areas, the answer is likely to lie in assuring that services are actually available on a full-time basis in nearby existing facilities.

As part of the condition of accessibility, there are also cultural needs that need to be addressed connected with the cultural acceptability of self-referral. In many societies, including Jumla, it is difficult or impossible for a woman to seek services from a male provider, and yet female providers may not be feasible; somehow programs must address the issue of reassuring the husband or other household authority figure in order to gain his approval for seeking this outside care. And of course, access also means that somehow there must be means either to fetch the health worker or to go to his point of service delivery. This can be a major impediment if the population is widely scattered.

Once these five necessary conditions are met, the sixth condition for an effective program is appropriate response from the health care provider. In a sense, we began our program in Jumla with this step, and have had to go back to deal with the issues of generating effective demand. As noted earlier, we believe we have proven that even in the most remote and difficult of circumstances, a delivery program can be developed which will assure appropriate response. As mothers' awareness, willingness and ability to take action continue to improve, that response is increasingly being called forth based on mothers' requests, as documented by our continuing trend of increasing self-referral. We believe that the necessary conditions for a successful and effective program are now in place.

The Jumla ARI Intervention Trial has shown conclusively that clinical case management of childhood pneumonia can be appropriately carried out at the community level. It has also taught us that simply delivering appropriate services is a necessary but not a sufficient condition for promoting the survival of children. This program has been a valuable source of experience and information that can help with the development of effective pneumonia control programs in developing countries.

The Therapeutic Significance of the Presence of Wheezing in Acute Lower Respiratory Infection

Robert C. Welliver, M.D.
State University of New York at Buffalo and Children's Hospital

Introduction

Viral infections are common causes of wheezing-associated respiratory illness in infancy and early childhood. It has often been observed that asthmatic individuals who have bacterial infections of the respiratory tract do not wheeze and, from this, it has been assumed that bacterial infections do not play a major role in precipitating asthmatic attacks. This communication will review the evidence for a role for bacterial infection in causation of wheezing or complication of wheezing-associated respiratory illness.

Wheezing-associated Respiratory Illness in Developed Countries

While there is some variation with age, viral agents and Mycoplasma pneumonia are the most common causes of bronchiolitis and infectious asthma in developed countries (1). Respiratory syncytial virus (RSV) and the para-influenza viruses are predominant in pre-school age children, while rhino-viruses and mycoplasma become predominant in older children and adolescents. However, even in adolescents, respiratory syncytial virus (RSV) and the parainfluenza viruses account for approximately 20% of all episodes of wheezing-associated respiratory illness. This latter finding suggests a similarity in pathogenesis of wheezing at all age groups in childhood.

In contrast, virtually no evidence exists to support a role for bacterial infection in childhood asthma in developed countries. In one study (2), bacterial pathogens such as Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes and Staphylococcus aureus were recovered from throat cultures of children with respiratory illness with equal frequency whether or not wheezing was present. In the same children, viral agents were recovered with far greater frequency in individuals with wheezing than from individuals with upper respiratory illness not associated with wheezing. A similar role

for viruses, but not bacteria, in precipitating asthma in adult asthmatic patients has been demonstrated (3). Respiratory viruses were recovered from 11% of adult asthmatic individuals when wheezing was present and from only 3% of individuals with a respiratory illness in the absence of wheezing. Bacterial infection was defined as the presence of bacterial pathogens in sputum samples containing alveolar macrophages, suggesting infection of the lower respiratory tract. Bacteria were found in 9% of such samples whether or not wheezing was present in adults.

Wheezing-associated Respiratory Illness in Developing Countries

The etiologic agents that precipitate wheezing-associated respiratory illness in developing countries have only recently begun to be identified. Data from several areas indicate that the overall incidence of acute lower respiratory illness is not increased in developing countries when compared to that incidence in developed countries. The incidence of ALRI in children less than 5 years of age in the United States and the United Kingdom has been estimated to be between 4.5 and 8.0 episodes per year. In contrast, episodes of acute gastroenteritis are from two to ten times more common in small children in developing countries in comparison to similar children in the United States and the United Kingdom. Similarly, while pneumonia occurs with a high frequency in all age groups from birth through 12 years of age in developing countries, bronchiolitis is seen predominantly in infants in these countries much as in developed countries. As in the United States, these finding are limited by the tendency to refer to wheezing in infancy as bronchiolitis, and to wheezing in older children as asthma. However, the above epidemiologic data suggests that the frequency and age distribution of respiratory illnesses in developing countries is not greatly different from that in developed countries, but only that the severity of illness may be greater in developing countries. Information obtained at multiple sites in developing countries indicates that viruses are the agents recovered most frequently from cases of bronchiolitis. Recovery rates vary depending on whether tissue culture isolation alone is used to identify infectious agents, or whether rapid diagnostic techniques are used to identify infecting agents. As in the United States, RSV appears to be the most common cause of bronchiolitis in developing countries when more sensitive measures for identifying infectious agents are used (4).

Secondary Bacterial Infection in RSV Disease

In developed countries, the risk of secondary bacterial infection complicating RSV disease appears to be very small. In one study of 352 infants hospitalized with RSV infection, only 2 (0.6%) developed any secondary bacterial infection (5). In both these cases, the infection was classified as pneumonia. None of these infants received antibiotic therapy prior to the development of bacterial infection. No bacterial infections occurred in 103 individuals who received oral antibiotic therapy at the time of RSV infection. One-hundred ten individuals with RSV infection received parenteral antibiotics and five (4.5%)

developed secondary bacterial infections. Of these five infections, three were pneumonia. It is interesting to note that secondary infections occurred only after parenteral antibiotics had been administered for four days or more. This study suggests that the incidence of secondary bacterial infection in RSV disease in developed countries is very low, but there is a suggestion that this rate may be enhanced by prolonged administration of parenteral antibiotics. In two other studies, antibiotics were administered to infants and young children with wheezing-associated respiratory illness, including both bronchiolitis and infectious asthma cases (6,7). In neither of these studies were beneficial clinical effects observed which could be attributed to antibiotic therapy. In one study (7), the rate at which bacterial pathogens were cleared from sputum samples was investigated. Bacterial pathogens were recovered from 14% of sputum samples before antibiotic therapy was instituted. When second sputum samples were analyzed, bacteria were recovered from 5% of individuals who had received antibiotic therapy and from 7% of those who had not received antibiotic therapy. These studies suggest that, in developed countries, bacterial superinfection is very uncommon in RSV disease, and that antibiotic therapy would not be expected to be beneficial unless strong evidence of bacterial secondary infection is present.

Considerable caution must be taken currently before applying these data to infants and children with wheezing in developing countries. There is no information that has been submitted to peer review and critical analysis to indicate whether secondary bacterial infections occur in the context of RSV-related illness. It may be that only certain viral infections predispose to secondary bacterial infection, or it may be that RSV infections presenting as bronchiolitis do not predispose to secondary bacterial infection, while RSV pneumonia may permit bacterial infection. Some of these distinctions may be of only academic interest in developing countries, where the decision to institute antibiotic therapy is made by an individual who is not able to distinguish wheezing-associated respiratory illness from respiratory illness without wheezing, or is unaware of the local epidemiologic patterns of RSV disease. However, it is almost certainly true that infants with mild to moderate degrees of wheezing in developing countries probably have uncomplicated viral infections. Infants with wheezing of this nature, with or without retractions, and with respiratory rates near the normal range for age can probably be managed without antibiotic therapy. In contrast, infants with wheezing with severe chest retractions and very high respiratory rates may have secondary bacterial infection, or it may be beyond the abilities of primary care providers to exclude bacterial infection clinically in those patients. It would seem wise, therefore, to refer these latter patients and institute antibiotic therapy according to the same clinical criteria that would be used if wheezing were not present.

Bronchodilator Therapy

Numerous studies of the effect of aerosolized bronchodilator agents in bronchiolitis and wheezy bronchitis have been carried out (8-10). While no harmful effects have been

observed in these studies, the majority of patients with what appears to be wheezing-associated respiratory illness do not seem to respond to aerosolized bronchodilator therapy, at least in infancy and early childhood. While it has been stated frequently that a small percentage of children do respond to bronchodilator therapy, and while the experience of this author is in agreement with these comments, there are no reliable ways to identify clinically which infants will respond before therapy is instituted. Such therapy seems to be quite safe, since many infants and children hospitalized with bronchiolitis are maintained on aerosolized bronchodilator therapy, even if they did not have an initial beneficial response, without evidence of later toxicity. In a brief review of our own experience in the past two years (unpublished data), over 50% of infants hospitalized with RSV bronchiolitis were maintained on aerosolized albuterol throughout hospitalization without adverse effect. In summary, bronchodilator therapy can be administered without expectation of adverse outcome, but will benefit only a small number of infants of young children with wheezing-associated ALRI. Severely ill infants should probably only receive bronchodilators if supplemental oxygen is administered.

Again, it is difficult to determine how this information should be applied to pediatric practice in developing countries. Currently, there is no reason to believe that infants in such situations will be more or less likely to respond to bronchodilator therapy. Infants with mild illness associated with wheezing can be managed safely without aerosolized bronchodilators. If feasible in a given clinical setting, individuals with moderate degrees of dyspnea in association with wheezing (mild retractions and respiratory rates between 40 and 60) might be given an initial trial of aerosolized bronchodilators, but attempts to continue these medications should only be made if there is a good initial response. Beneficial responses are unlikely to occur with prolongation of therapy. More seriously ill infants will presumably be referred for more sophisticated medical care, at which time the response to bronchodilators and the need for continued therapy can at least be made by people with greater medical experience, and supplemental oxygen can be administered.

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Usage of Antimicrobial Agents and Development of Resistance to Them

Thomas F. O'Brien, M.D.
Harvard Medical School

Emergence and Spread of Resistance Genes:

When antimicrobial agents were first used to kill infecting bacteria a half century ago, few bacteria were resistant to them (1). The exceptions belonged to species of bacteria with species-specific obstacles that kept intact molecules of certain agents from reaching their target sites of action, as for example, a chromosomal beta lactamase that makes all Klebsiella pneumoniae resistant to penicillin and ampicillin (2).

After each new antimicrobial agent became widely used, however, genes encoding resistance to it eventually emerged and spread through the world's bacterial populations. Resistance genes emerged either by being mobilized from obscure strains or by evolving from obscure ancestral genes. Once emerged, resistance genes spread largely by becoming inserted in plasmids that could transfer from one bacterial cell to another of the same or of a different species (3).

About a hundred resistance genes have been recognized to date. Each encodes a protein that either inactivates one or more antimicrobial agents or otherwise keeps it from blocking its target function or provides a new function to substitute for the function blocked by the agent (4).

A gene encoding resistance to an antimicrobial emerges and spreads through a sequence of events: mutation to enhanced resistance, transposition to a plasmid, recombination with other plasmids, linkage with other resistance genes, transfer of the plasmid to new strains and migration of resistant strains from one host to colonize or infect others. Continuing use of the agent amplifies the population carrying the resistance gene at each stage in this sequence and so increases the chance of occurrence of the event that will start the next stage. Since each succeeding stage tends to distribute the resistance gene in progressively

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larger populations of bacteria and of bacterial hosts, the process tends over time and with continuing antimicrobial usage to cascade and become progressively harder to reverse (5).

Regional Differences in Prevalence of Resistance

The spread of antimicrobial resistance genes in bacterial populations appear to have progressed irregularly in different parts of the world. As a consequence, bacteria colonizing or infecting people in some regions of the world are more often resistant than are comparable isolates in other areas (6). Different rates of resistance to various antimicrobials in different regions have been shown not only for clinical isolates from hospitalized patients, but now also for bacteria colonizing healthy people living in communities of the regions compared (7).

The chances that a particular antimicrobial will fail to cure an infection because the particular infecting strain is resistant to it may be ten times greater in some places than in others (8).

The limited data available also suggest that resistance to antimicrobial agents is more frequent in bacterial isolates from people in developing than from people in developed countries. This has been true for isolates of enteric pathogens, for gonococci, for nosocomial isolates of hospitalized patients and for Escherichia coli colonizing healthy people (9,10).

It would be difficult to establish all the factors making resistance more common in one region than in another, but some suggest themselves. In developed countries, for example, ubiquitous laboratories test the susceptibility of significant isolates and trained physicians, backed up by consultants where needed, select from an extensive formulary of available antimicrobial agents one to which the infecting strain is not resistant. Infection control teams in the hospital and public health officials in the community work to prevent person to person spread of resistant strains, which is already minimized by high levels of personal and institutional hygiene. These factors would tend to minimize both selection of resistant strains in patients and their spread between patients.

In developing countries, on the other hand, blind antimicrobial therapy selected without susceptibility testing from a limited list of available agents often by an untrained person may not only fail to arrest the infection if it is resistant to the agent chosen, but may actually select for overgrowth of the resistant strain and so increase its chances of spreading to other people. Such spread would be further facilitated if the hospital could not afford optimal isolation practices or the community could not afford clean food and water supply.

The bacteria that live in or on people outnumber the people's own cells, but only a tiny

fraction of the bacteria in these enormous complex ecosystems ever infect their hosts. Yet usage of antimicrobial agents may select for overgrowth of resistant strains and spread of resistance genes in this entire flora. Resistance in the rare bacteria that actually happen to infect people at any given time is thus the proximate cause of treatment failure, but the reservoir of resistance genes and plasmids in the vast colonizing flora of both patients and currently healthy people in the community can be seen as a predictor of future treatment failure (7).

Cost of Resistance

Excess resistance in a region can incur costs at several levels. Resistance causes treatment of infection to fail so that patients remain infected or die. Resistance blocks the effectiveness of antimicrobial prophylaxis so that needed surgical procedures carry an unacceptably high rate of infection. Resistance makes inexpensive available antimicrobials obsolete and thus diverts needed health funds to the purchase of expensive newer agents. Overuse of the newer agents, in turn, in regions where resistance genes and plasmids are prevalent has provided the setting for emergence and spread of new genes encoding resistance to the newer agents, some of which may ultimately be exported to other regions (11).

Surveillance and control of resistance

Evidence has thus accumulated from clinical practice, from epidemiology, and now from molecular biology that the problem of antimicrobial resistance is multifactorial, communal, and global. Multiple local factors of antimicrobial usage and hygiene may increase the prevalence of resistance genes and the probability of antimicrobial treatment failure for everyone in a community and may ultimately contribute to the prevalence of resistance elsewhere in the world.

Control of resistance can be aimed at delaying or preventing further increases in or actually reducing prevalence of existing resistance genes to some or to all agents in some or all bacterial species in some or all regions or to preventing or delaying the emergence of or containing the spread of new resistance genes when they first emerge. Any of these goals can be seen to be ambitious and to require improved practices for usage of antimicrobials and for diminishing exchange of bacteria between people.

Surveillance of antimicrobial resistance seems essential for its control. Without information on prevalence of resistance to different agents in different regions of the world it will be difficult to chose antimicrobial agents for individual patients, to devise general strategies for usage of these agents, or to determine the effectiveness of such strategies.

Such surveillance is, in fact, nearly in place in the world, but not quite. Tens of thousands

of laboratories throughout the world test each day the susceptibility to antimicrobials of clinical isolates of bacteria and make the results for each patient's isolate available to the health care professional caring for that patient. This constitutes a potential global or near-global network of laboratories doing now about 95% of what is needed for detailed surveillance of the global distribution of antimicrobial resistance genes. The remaining 51% effort, however, the filing of the results or some of the results in a common data base, which would generate an ongoing detailed and critically important overview of the problem, is scarcely being done at all (12).

The World Health Organization has repeatedly reviewed the problem of antimicrobial resistance, emphasized its importance and targeted its surveillance as an essential step for its control. It has supported the development of a technician-friendly personal computer program, WHONET, which allows any laboratory to enter its susceptibility test results, analyze them at any time for management of its own local problems of resistance or infection control, and exchange and pool the results globally by virtue of a universal file format. Pilot WHONET projects are underway in several cities, but it needs to be promoted if it is to achieve effective scale (11).

An important feature of WHONET is that it provides for entry of susceptibility test results of bacteria surveyed randomly from normal flora of healthy untreated individuals in the community of each surveillance laboratory in order to provide surveillance of the reservoir of resistance genes in normal flora, as discussed above, in addition to surveillance of the resistance of clinical isolates. This opens the possibility making a low carriage of resistance genes in normal flora a targetable health goal, as low serum cholesterol or normal blood pressure have become.

Significance for Acute Lower Respiratory Infection (ALRI)

The preceding considerations frame the problem of antimicrobial resistance for an ALRI program. Unlike diarrheal diseases, where education about and supplies for rehydration were paramount rather than intervention with medication, ALRI is presumed to need prompt intervention by trained workers with antimicrobials. Among the many questions to be answered, however, is the question "which antimicrobials". This question is preceded by several others. How much ALRI is caused by bacteria in different parts of the world? Which bacteria are causing it? How often are they resistant to candidate antimicrobials. There are not definitive answers at present, but working expectations seem to be that bacteria will be a substantial cause and *Streptococcus pneumoniae* one of the more likely pathogens.

Information on the prevalence of resistance to candidate antimicrobials of isolates of *S. pneumoniae* in different parts of the world is sparse for the reasons discussed above and

for others as well. Where surveillance data has been collected it has often lacked values for isolates of S. pneumoniae out of the long held belief that these isolates need not be susceptibility tested since all were susceptible to penicillin. This practice persisted even after penicillin-resistant S. pneumoniae caused an outbreak in South Africa 15 years ago, because they were still believed to be rare in other parts of the world. When isolates of S. pneumoniae were susceptibility tested it was often only to penicillin since that seemed to be the issue, rarely to an agent such as trimethoprim sulfamethoxazole, which is now a prominent candidate agent. Surveillance thus needs to be systematic and comprehensive because the questions it will be called upon to answer are often not anticipated.

Scattered reports illustrate the problem for S. pneumoniae. In a review of the literature, Applebaum found isolates with intermediate resistance to penicillin were as high as 34% of all pneumococci isolated in some areas while there were none in collections elsewhere. In several places strains were resistant to penicillin and all other beta lactam antibiotics as well as to sulfonamides, tetracycline, erythromycin, lincomycin, clindamycin, chloramphenicol, aminoglycosides and rifampicin (13). Similarly, a report from Spain found all 84 penicillin resistant isolates of pneumococci to be resistant also to trimethoprim sulfamethoxazole (cotrimoxazole, bactrim) (14). Henderson found in a day care center in North Carolina that the percentage of pneumococci resistant to trimethoprim sulfamethoxazole, had risen from 5% before 1981 to 35% between 1981 and 1985 (15). At the same time most isolates of Haemophilus influenzae in the U.S. remained susceptible to this agent (16).

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Community-based ALRI Treatment

Discussion Summary

Where to begin: in the community or in the health facilities?: The ARI case management approach, particularly one that utilizes active case finding by CHW's on the village level, emphasizes improved access and timely treatment as a strategy for decreasing pneumonia mortality. Although the main thrust of the program is targeted at the community level, the health facility level must be prepared prior to the institution of health communication efforts designed to increase passive case finding or self referral. Or else CHWs will refer to facilities that are not prepared for standard case management. The role of the CHW as gatekeeper for the triage of ARI cases must be reinforced by support, adequate supervision and feedback from the referral health facilities. Capacities for community based ALRI treatment should not be developed in isolation; rather, the upgrading of supporting health facilities should take place in parallel or in advance of instituting community based ARI case management.

Entry criteria: The entry criteria are those clinical signs and symptoms which allow the classification of the ARI illness by the health worker and help guide treatment. At the community level, criteria which emphasize sensitivity are needed in order to effectively screen the caretaker's initial concerns. At referral levels of the health care system, criteria of greater specificity can be employed by better trained health workers to refine the illness classification and treat accordingly.

Determinants of health service utilization: Where there is a health infrastructure, health services may not be utilized because in fact the services were not very useful. One reason may be because, especially in Africa, there are no medicines. This fact is quickly perceived by the community. Much has been written about the role of distance from the health center as a determinant for health center utilization. However, women travel long distances for water, to markets, etc., so other reasons must be sought for non-utilization. The acceptability of services plays a large role. In EPI, there have been good studies demonstrating the importance of cultural beliefs in the use of health services. For example, some diseases are attributed to supernatural causes that, viewed within the cultural context, cannot be addressed by the health services. Additionally, the referral facility, or hospital is looked upon by the community as a place where one goes to die. Also, if people are treated poorly or with disrespect, this filters into the community level and negatively affects utilization of health services.

There is a large body of literature on how curative services are very important, necessary to prime and sustain the preventative services. Failure of curative services, such as ARI case management program, can have repercussions on other programs as well.

Supply of antibiotics: The case management approach depends not only on the rational use of medicines, but also on the availability and reliable supply of these medicines. The sudden availability of antibiotics in the health center may lead to an incredible response or an incredible demand. It will be difficult to quantify and plan for this, in terms of how much antibiotic has to be provided into the

system in order to meet ALRI needs. Additionally, assuring not only an initial supply but a continuing supply is a key element of effective implementation. In Jumla, an average of .85 antibiotic treatments per child under five per year were given, which is a large supply of antibiotic. However, the disease burden in a place like Jumla is probably higher than in most places, so this figure may not be applicable to other settings.

Rationalizing the use of medicines: There is so much antibiotic flowing into most of the communities in certain developing country settings already. One of the major objectives of an ARI program could be to stop the antibiotic use for inappropriate uses and to get it channeled in the right direction. Given current levels of antibiotic misuse overuse, a program manager may have to inflate his/her estimate of antibiotic doses needed by 50% or more to cover the wastage. Given the many other potential uses for these antibiotics in the community, it is a challenge to get these drugs used for what they ought to be used for. Because once they get out, especially in the hand of the community health worker, it is easy to imagine the pressure from the community to use these drugs for many other conditions. Special packaging of antibiotics for use in the ARI was raised as a possible means for presenting these drugs so that they are used for pneumonia. Programs should be carefully evaluated as to how drugs are used.

Controversy over turning caretakers away without prescribing some sort of medicine: Another issue raised was how people are turned away empty-handed when it is determined that their child does not require an antibiotic. The experience of traveling a long distance, waiting in a long cue, being told "no, your child doesn't need antibiotics" and being turned away without concrete rewards may constitute a reason for being reluctant to return to the health worker next time the child is ill. There was no agreement on how this should be handled, so the various viewpoints are presented in the following paragraphs a, b, and c. There was more consensus on the need for the CHW to act as a "gatekeeper" at the village level who is trained to say "you really should take your child and go get care". This would help maintain the credibility of the system provided that the CHW has enough training to know when a child requires next level of care.

a. **Pro-Providing safe cough/cough mixture:** Children who do not have pneumonia ought to be given something anyway. There are those who feel that a mother who travels 1 km or 10 km ought not to go home empty handed. With diarrhea, this issue was more straightforward, in that a mother could be given an ORS packet (and hopefully instructions). However, with ARI, policy makers have to struggle with determining what kind of safe mixtures could be given to mothers whose children do not have pneumonia. The approach of providing something in the form of a medicine yields to what mother's want, what they recognize as important now given the ARI their child has, and would make them feel they have gotten something for their effort. Reported experience with ORT suggests that good educational training for instance in ORT preparation, making home mixtures has been invariably found to be not satisfactory in terms of what the mothers came to seek care for, i.e., stopping the diarrhea. The analogy here may be stopping the cough, the runny nose, etc. Perhaps after 5 or 10 years of changing attitudes, education would suffice. But this point of view espouses the position that in terms of the point of contact credibility of the program, education will not do it in the real world.

b. **Pro-education and positive interaction with mothers:** Often in medical settings, it is thought that if there are no drugs, then there is no medicine. That's not quite true with regard to education. In the USA, there are many people that come the health services and are sent home with nothing but education, and they continue to come back. In developing countries, people will go long distances to visit traditional healers. Traditional healers do not always give medicine per se, but they do usually give a ritual which brings a person into a successful therapy. These examples illustrate that going home with nothing is not necessarily a bad thing. Education is something, particularly if it is a positive interaction with the mother. The mother goes away feeling that someone has recognized their concerns, and she has been drawn into successful human interaction. Educational input would appear to be a broader longer-term oriented response than prescribing a drug for that sick child today. Education of both mothers and health workers would appear to be essential if the program aims for a long-term impact on drug use on a community level.

c. **Pro-immunization:** Going home immunized is better than going home empty-handed. One of the most appropriate things to be given the child that does not require antibiotics is age appropriate immunizations. From multitude of EPI studies that have been done in every country, children dying from vaccine preventable diseases have been seen multiple times for other illnesses. The biggest problem is inappropriate contra-indications to immunizations. Mild and moderate ARI illnesses are clearly not contra-indications. Immunization and ARI ought to be integrated and work together on a community level.

Deaths at home vs deaths in health facility: ALRI deaths that are occurring in children who are coming to health facilities and getting bad treatment imply a different course of action than ALRI deaths in children that are coming late in the course of their disease. The former requires an upgrading of the standard of care in peripheral and referral level health centers. Here the case management algorithm may be helpful in standardizing the treatment of ALRI.

In the latter situation where deaths are occurring on account of late presentation to health services, or health care is not sought at all, community health worker will be necessary to promote timely and appropriate health seeking. Training of these health workers in the recognition of key signs and symptoms will be critical to their performance. These personnel must be supported by a communication strategy to reach the mothers who are not utilizing the system. Behavioral studies will be necessary in constructing the messages caretakers should hear that will encourage timely and appropriate health seeking behavior.

Support for the community health worker: The community-based health worker can ideally function as some kind of a gatekeeper and a link between mothers and medical facilities. As yet, very little is known on how exactly to train community health workers. What will maintain their behavior once they have been trained? What kinds of interventions will be necessary to keep them active in the community, to keep their information and their practices accurate over the years? As unpaid volunteers working for things like status, their level of expertise can often fall off rather quickly even after completing a careful training program.

Importance of pediatricians: Experience with many program in many countries has underscored the importance of garnering the support of pediatricians for any ARI program. They need to be informed of the program, and provide technical advice. They rightfully

are concerned about how antibiotics are going to be used by other health workers, and worried that such a program will allow for "sanctified abuse" of antibiotics and other medicines.

Importance of the private sector: As one goes into areas of drugs, a chapter from diarrheal disease experience should be drawn. ARI planners should realize the importance of involving medical associations, and pharmacies, as well as revising medical and nursing curricula.

Adverse drug reaction monitoring: As children tend to be more susceptible than adults to drug overdoses, an ARI program should monitor drug effects and collect the data on drug use. Of 35,000 antibiotic treatments in Jumla, there have been a half dozen or so minor reactions.

Development of antimicrobial resistance: Success of an ARI program from the implementor's point of view depends on getting the right drug to the right child at the right time. Whether or not the antibiotic chosen for the program is the right drug will depend on local patterns and levels of antibiotic resistance. It is important that the antibiotic resistance be monitored in the community. What remains uncertain is: at what level of antibiotic resistance in what strains of bacteria should antibiotic policy be changed? More information will be required on this issue.

Role of co-morbidities or mis-classification: In consideration of the management of pneumonia, there are severe illnesses that can look like pneumonia or have similar clinical findings, e.g., sepsis in neonates, malaria in older children. There needs to be consideration of how to integrate various primary health care activities.

Efficacy vs effectiveness studies: The case management intervention studies reviewed by WHO were more on the order of efficacy studies. These were attempts by the investigators, in some ways at least, to optimize the delivery of case management, and measure an effect on mortality. It is true that these studies were not perfect in design, or implementation, and that the effect of other interventions such as immunization may make it difficult to discern the effect that can be attributed to case management alone. One conclusion from the review of these studies would be that there is inadequate information on efficacy of this approach and that more detailed and more intensive efficacy studies are needed. On the other hand, the conclusion could be that there is enough information on efficacy, and what is needed is information on effectiveness. The gap in knowledge seems to be "can we deliver a feasible strategy through a public health system and still have an effect on mortality?." There is likely to be relatively few places where one can measure the effect of case management on biological outcomes like mortality, and case fatality rate. However, one can do the effectiveness studies with regard to service indicators, and that should be documented as some of the national ARI programs get underway. In these evaluations or effectiveness studies, indicators or criteria both from the service delivery standpoint and the biological standpoint need to be clearly defined.

Implementing ALRI Programs: An Operations Research Framework

James R. Heiby, M.D., M.P.H.
Agency for International Development

A number of recent field studies have focused on measuring the mortality impact of clinical algorithms for diagnosing and treating bacterial pneumonia in small children, with encouraging results. While further refinements in the current algorithm are likely, ALRI case management remains relatively complex, compared to other child survival services. Others will discuss how clinical, epidemiological, and social science research can contribute to improving the design of an ALRI intervention. But the large scale implementation of any such intervention presents the program manager with a range of practical issues that are not fully addressed by KAP studies or mortality data. This discussion will outline how operations research can support the incorporation of pneumonia case management into existing LDC delivery systems. A better understanding of program implementation may, in turn, suggest areas where the algorithm should be modified. The general approach I will describe has been applied to a variety of child survival services, including ALRI case management, under the PRICOR II project.

A. Process Measures: A growing body of research deals with the overall effects of ALRI programs, such as changes in mortality from pneumonia. To a large degree, however, these studies treat the program delivery system as a "black box", a poorly-understood entity that somehow produces the results that are so carefully studied. In principle, the implementation of ALRI services can be described in terms of concrete activities carried out by the program staff. Further, the details of how program personnel do their jobs appears to be highly amenable to action by the manager. Nevertheless, studies of 13 child survival delivery systems under the PRICOR II project have consistently shown that managers lack systematic information on the quality of care provided by their staff, the effectiveness of educational activities, and the nature of outreach efforts. Further, these managers also lacked widely-accepted methodologies for collecting such process information routinely. Neither could they point to a body of knowledge from other programs to guide their interventions in these areas.

Perceptive managers do, of course, have insights into service delivery problems

based on intuition or casual observation. Expert evaluation teams may also contribute astute observations. But these are examples of art, not science. There is a need for objective, well-defined methodologies to describe the process of delivering ALRI services and to systematically identify problems in the implementation of these demanding services. Techniques to measure the overall performance of an ALRI program, such as impact surveys and verbal autopsies, are obviously important. But these approaches must be complemented by similarly well-tested techniques for measuring the performance of the distinct activities that together produce the program's impact.

Managers have an interest in monitoring details such as how well clinicians counsel the mother of a child with pneumonia, or the effectiveness of referrals. Preliminary experience under the PRICOR II project suggests that indeed, managers generally welcome such data and institute corrective measures where needed. Many would argue that a major implicit assumption of impact surveillance is the ability of managers to take the indicated corrective steps where impact is suboptimal. It is difficult to see how the overall impact of such a complex service can be improved exclusively throughout non-specific measures. Someone in the program must have a detailed understanding of how individual service delivery activities are being carried out. A manager who is poorly informed about details such as how field supervisors monitor patient followup, is severely handicapped in dealing with the larger issue of preventible mortality from bacterial pneumonia.

B. The Nature of the Measurement Problem: Figure 1 (pg. 126) illustrates how the major areas of service delivery can be organized into distinct systems. Each of these systems can be broken down into a number of discrete, concrete activities of the involved program staff. The current WHO algorithm suggests how a complex abstraction like quality of care can be reduced to its component activities. For example, the performance of service providers in counting respirations in children presenting with respiratory symptoms is a relevant component of quality of care. An activity as specific as this appears highly approachable as a study variable, even for field observers with limited training. Taken individually, it appears feasible to provide managers with a description of such variables.

In order to serve as the basis for management interventions, process variables should allow the objective measurement of change in a given activity. Thus, activities should be described in terms that are sufficiently quantitative or scaled to determine if the health worker's performance has gotten better, worse, or stayed the same since the last time it was measured. We want to be able to say, for example, how the counselling of mothers regarding signs of deterioration was affected by a given supervisory action.
The WHO algorithm also illustrates the need to define these service delivery

variables before making field observations. The measurement process should not rely on the subjective impression of experts, but on detailed methodologies suitable for use by a wide range of program personnel. Our ability to define performance in operational terms depends on available knowledge and such variables are necessarily provisional in most cases. If, for example, further research results in modified recommendations for the followup of cases, the operational definition of this activity is subject to change. Indeed, for many variables, such as those related to supervisory problem solving, operational definitions are little more than educated guesses. The relationship of these process variables to measures of program impact requires empirical examination. Some activities currently prescribed by expert opinion may prove to be relatively unimportant or seriously flawed, and new standards, such as those related to the management of very young infants, may be developed.

From this perspective, we can assemble a list of operationally-defined activities of the program staff; this list defines the universe of variables of interest. Implicitly, we think that effective performance of these activities produces the impact of the program. Such a list is subject to continual reassessment and refinement, but it is a useful starting point. As illustrated in Figure 2, the process of taking the clinical history of an ARI patient could be viewed as 14 distinct activities (often designated "subactivities" or "tasks" at this level of specificity). Extending this analysis to the range of quality of care activities outlined in the WHO algorithm results in approximately 160 distinct activities. Since each of these activities has been recommended for implementation in ARI programs, all appear to be worthy of study.

C. Dealing with a Large Number of Process Variables: For service provider activities that can be observed directly, the cost of including a large number of different variables is minimal: For all practical purposes, only the size of the observer's instrument (such as a checklist) changes. Observing history-taking, for example, would still take only a few minutes. For indirect observation, such as role play simulations or exit interviews of the mother, the feasibility of different data collection approaches is an important consideration. We need a better understanding of the trade-offs involved in selecting different techniques, particularly where rapid and cheap techniques like interviews may be of uncertain reliability and validity.

For most purposes, small sample sizes are probably adequate, as illustrated by lot quality assurance sampling (LQAS). Frequently, the major issue is whether or not the level of performance of a given activity is low enough to trigger some kind of action. Where the chief issue is identifying performance that is grossly inadequate, LQAS requires sample sizes on the order of 6-12. Further, in contrast to studies of

health impact, process studies deal with events that are relatively common and accessible.

The number of variables to be studied in a given program can also be reduced as needed by selecting a sample of activities. A study limited to 10 selected activities in case management, for example, or one limited to patient counselling could still be revealing. It is not necessary for a given study to be comprehensive in order to be useful. Whatever the resource limitations of the program, however, it would be appropriate to examine every ALRI service delivery activity over time. Experience may show that some activities require assessment only very infrequently. But any element of service delivery that managers never examine is of doubtful relevance.

D. Program Determinants of Service Provider Performance: When shortcomings in the performance of service providers are identified, increased training is a common response. As program staff, trainers have an indirect but important influence on how effectively each of the 160 service delivery activities are carried out. Among the observations relevant to estimating the performance of trainers are: (1) The degree to which trained health workers are competent in the various service delivery activities after training, and (2) the extent to which these competencies were documented at the time of training.

But there are other program influences on service provider performance, most prominently the interventions of field supervisors. In principle, a critical role of supervisory staff is to monitor the performance of each of the service provider activities, identify problems in their performance, and then take steps to correct these problems. If a health worker misclassifies a sizeable proportion of cases of respiratory illness, most programs have virtually no mechanism for detecting and correcting such a shortcoming other than the field supervisor. The performance of field supervisors in problem solving merits the attention of program managers.

The performance of service providers in the 160 service delivery activities provides the basis for estimating the effectiveness of their field supervisors. If a given health worker does not perform one or more elements of the physical examination as they are defined operationally, a problem exists by definition and this can be objectively documented. A supervisor who examines that activity and does not identify the problem, or having identified it, fails to resolve the problem, is not performing effectively. These observations can be made more specific by further classifying the supervisor's efforts according to the techniques employed to identify the problem or to resolve it. There are at least 20 such methodologies that merit separate examination to assess their cost-effectiveness in dealing with different kinds of problems. We currently lack even basic observations of what is theoretically a fundamental determinant of how well pneumonia is managed.

Even less is known about how higher levels of the supervisory hierarchy monitor and support problem solving. If a field supervisor's monitoring of outreach activities is failing to pick up gross problems, most programs rely on a second level supervisor to identify the shortcoming in monitoring and then deal with it. This role of the higher level supervisor can also be studied in terms of concrete, observable activities.

For each level of the supervisory system, training and the resulting competencies related to problem solving are also amenable to study within this framework. Similarly, the content of the information system is of interest, again with regard to specific service delivery activities. In addition to conventional service statistics, the information system may or may not document measures of quality of care, counselling, outreach, problem identification, and problem solving that are relevant to effective management in these areas.

E. Absent and Debatable Activities: Some poorly-understood service delivery activities are unlikely to be clarified by simply examining current practice in a number of programs. Issues such as the content and presentation of ALRI educational messages will probably require the active testing of alternative approaches. Similarly, very few supervisory problem solving activities will be available for observation unless prospective field testing is carried out.

Such field research could be carried out in very small units, addressing only a small number of service delivery activities. By virtue of their narrow focus, these studies would generally be correspondingly small-scale, rapid, cheap, and simple in design. These properties are conducive to broader participation in operations research by regular program staff.

F. Generalizability: Will this strategy produce a body of knowledge on the implementation of ALRI programs that is broadly applicable? How useful will managers find research that focuses on a topic as narrow as, say, the use of interviewing by supervisors to monitor patient followup? Of course, we cannot be certain, but some elements of different ALRI programs are certainly comparable, even where the programs are quite different overall. These similarities should be exploited as ALRI programs expand, rather than leaving each program manager to reinvent the wheel.

FIGURE 1

ARI Program Systems Model

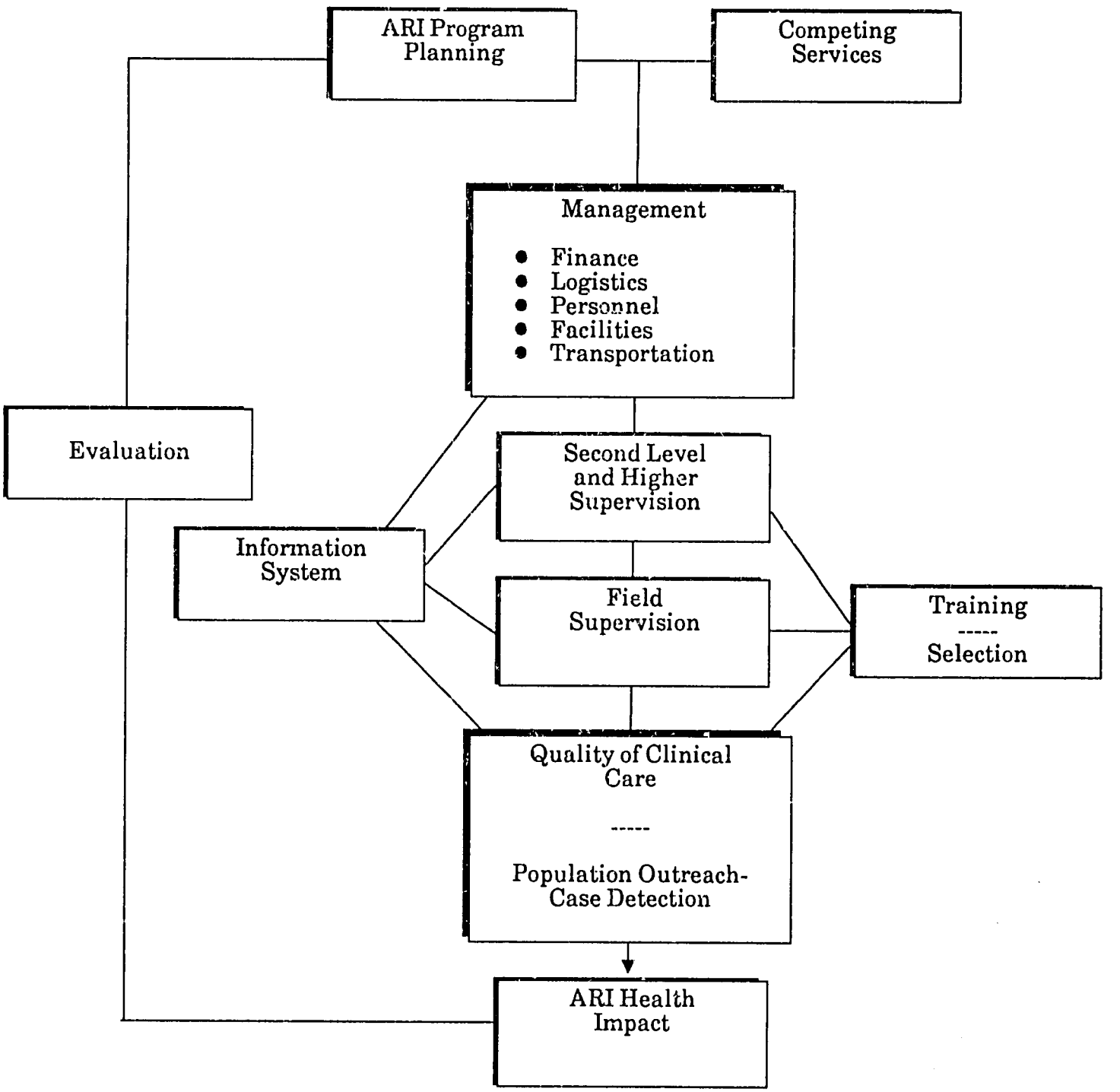

FIGURE 2

Quality of Clinical Care

A. Clinical History

1. age
2. rapid breathing noted
3. duration of rapid breathing
4. previous treatment
5. fever: duration/pattern
6. ability to drink/breastfeed
7. vomiting
8. seizures
9. asthma; previous pneumonia
10. obtundation
11. low birth weight/ nutrition status classification
12. immunization status
13. location of residence
14. record results

Systems Analysis and Operations Research in Service Delivery for ALRI

Stewart Blumenfeld, Dr.P.H.
PRICOR Project

I. Introduction

While a significant fraction of ALRI in developing countries are caused by agents for which a vaccine is available (TB, whooping cough, measles) (1), an even larger fraction are caused by organisms for which an effective vaccine is not yet on the horizon, particularly pneumococcus and H. influenzae (2). Thus, for the foreseeable future reductions in mortality due to these agents are likely to rely heavily on the ability of mothers to recognize the problem early and on the ability of first line health workers to manage cases effectively.

Both mothers and workers are important to this effort, but in a sense the latter play a double role. Not only are they expected to diagnose and treat or refer effectively, in many LDC systems they also are expected to communicate the information needed by mothers to recognize the problem and respond appropriately before the child enters the service system. Thus, their performance at the point of contact with mothers and children is critical. Critical to the service system manager, then, is the assurance that these front-line health workers are carrying out these tasks according to established norms and standards -- whether specifically stipulated by their national program or by internationally recognized standards as best we know them today.

The PRICOR staff are developing a systematic method (which we have called a system analysis) for analyzing, in operational terms, service delivery by peripheral health workers. The method is based on an assumption that these workers should perform certain tasks -- for the most part, the WHO paradigm -- in dealing competently with ARI. Our assumption is that this set of tasks is the best guide available at this time.

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II. Systems Analysis and Operations Research

Classically, systems analysis has been viewed as just one of a number of analytic and decision-assisting tools employed under the rubric operations research. The PRICOR staff, however, have found it convenient to adopt a functional distinction between what we see as two complementary technologies. The systems analysis methodology is applied primarily to identify operational problems in a service delivery system. Operations research techniques are applied to elaborate on the causes of these problems and to select from among alternative approaches to correcting them. This paper focuses on systems analysis.

Systems Analysis

Briefly, the systems analysis approach is built on the premise that the health service system can be modeled and analyzed as a classic input/output system. In such a system, processes convert inputs to outputs, and outputs lead to certain effects and, ultimately, impacts. Under this model, when outputs and/or effects do not meet expectations the assumption is that either some important inputs are missing or that the process is not being carried out correctly. Figure 1 (pg. 136) shows a model of the ARI service system. The process in this case is the set of activities carried out by the service providers.

Much has been written on techniques for measuring inputs, outputs, effects, and even impact of primary health care services. Less has been done, however, to elaborate the process, that is, the many individual activities, that PHC workers must carry out well in order to make primary health care effective in meeting its objectives and goals. Even less has been done to disaggregate those large activities into the component tasks and subtasks that comprise the operational definition of an activity. And finally, very little has been done to devise objective indicators of how well health workers perform this myriad of small tasks and subtasks. Yet, when evaluation shows that the goals and objectives of a service delivery system are not being met, it is often this level of analysis that is necessary in order for the system manager to know what exactly is going wrong. Such information is the foundation of well-reasoned corrective action.

PRICOR's approach to developing its systems analysis methodology required a tool that makes this information readily accessible. To meet this need, PRICOR has produced a thesaurus of operational definitions of primary health care services. This is essentially a compendium of service activities disaggregated into component tasks and, as appropriate, subtasks (3). In addition, the thesaurus provides quantitative indicators of task performance. Because of the level of disaggregation employed, it has been possible to select indicators of maximum objectivity, that is, requiring a minimum of subjective judgment. This high level of objectivity greatly facilitates the use of non-expert field staff in data collection, reducing costs and giving the program manager more leeway in selecting staff to carry out the task and more confidence in the data turned in. Figure 2 shows one of the

field data collection instruments developed from the thesaurus and used in a recent systems analysis in the Philippines.

The thesaurus was compiled by PRICOR staff and consultants drawing on their collective experience and relevant written materials such as WHO program guidelines. It has been (or is being) used in varying degrees in systems analyses in Thailand, Haiti, Zaire, Colombia, Costa Rica, Peru, the Philippines, Senegal, Pakistan, Togo, and Niger. Each system analysis examines service delivery and supporting systems in several areas of PHC, including immunization, ARI, ORT, growth monitoring, malaria, maternal health, and child spacing. Support areas include supervision, training, logistics, planning, information, and community organization.

Operations Research

As used by PRICOR, operations research (OR) is a set of techniques applied for the purpose of generating alternative responses to an identified problem and then selecting from among those alternatives on the basis of a clearly defined decision model. The methodology is well-described in an early publication by the project staff and will not be repeated here. Basically, it consists of specifying appropriate decision factors, incorporating them into a decision model, and evaluating alternative strategies for resolving the operational problem against the model in an effort to find the one or two "best" strategies. These may then be applied immediately if the solution is obvious, or tested if necessary to increase the decisionmaker's confidence in their soundness. PRICOR publications provide a number of useful techniques (4,5), as do other publications(6).

III. Analysis of Health Worker Performance in ARI and Related Factors

A number of issues must be considered with regard to performance of health workers in ARI.

Provider Performance

In general, the tasks required of health workers for effective case management comprise three categories: diagnosis/classification,treatment/referral,and counseling of mothers. First, the health worker must recognize the problem as ARI; the case then should be classified mild/moderate/severebased on the paradigm. Based on its category, a treatment regimen is specified and implemented. Finally, the worker should provide the mother with the information she needs (or reinforce what she already knows) to manage the case at home.

As we have seen, each of these steps can be divided into a series of discrete tasks that the

health worker should perform and an observer can determine whether these tasks actually are carried out. Such an analysis provides the service system manager with a measure of worker performance and strong clues as to why system effectiveness may not be what is expected.

Training of Health Workers

Obviously, the effectiveness of the original training of health workers, plus subsequent refresher training and provision of new information and skills, is a major determinant of their performance as service providers. Effectiveness is a combination of appropriate substantive content and presentation in a format and under circumstances that allow the worker to grasp and retain the material and skills. Competency-based training is thought to be the most effective approach to training peripheral-level health workers, and competency-based testing the most reliable way to assure that they are ready to assume their responsibilities in the field. The nature of the training and the means for assuring competence of peripheral health workers can also be analyzed as a series of discrete activities. Much of the on-job-training is performed by supervisors. It should, in fact, be the response to problems identified in the competency-assessment of workers by supervisors. Competency-assessment and OJT tasks may be used as a criterion for assessing supervisor performance.

The Role of Supervision in Health Worker Performance

Generally, even the best-trained PHC workers require steady supervision in order to function at maximum effectiveness over a sustained period. Just as health worker performance can be defined as a series of discrete tasks, so also can the act of supervision. Basically, these sets of tasks fall into the categories of knowing what tasks supervisees should be carrying out, knowing whether these tasks are being carried out, identifying gaps in performance and underlying reasons for these gaps, and then taking corrective action. However, each category is divisible into defined tasks that can be noted by an observer. If most of the tasks that constitute a particular set are carried out by the supervisor, then by definition supervision meets the standard set for it. If not, then the system manager (or the supervisor's supervisor) has an idea of where supervision is breaking down. Inherent in this system is the presumption that if supervision does not meet norms, there is a negative effect on service delivery by the supervisee.

Logistics

Materiel comprises a basic input to the service system. Absence of vital drugs and supplies vitiates the efforts of even the most diligent and well-trained health worker. Thus, a system analysis must determine if a steady supply of at least key items is available to the workers. While a focus on peripheral worker performance may allow the analyst to view

these items as an input to the system, the logistics system is usually a complicated chain with many loci where operational problems can develop. However, since the logistics system is prone to breakdown at the peripheral level as well as at higher levels, the system can be described and analyzed as a series measurable events, such as the percentage of time cold storage is not available or certain drugs are out of stock.

IV. Results of a Recent Systems Analysis in the Philippines

To illustrate the application of the systems analysis methodology, we present the results of an analysis recently conducted in the Philippines. By agreement with the Secretary of Health, the systems analysis focused on ARI, immunization, growth monitoring, and ORT. These PHC interventions were selected because special evaluations and the ongoing information system showed that outputs and effects were not meeting desired levels. It seemed reasonable to conclude, therefore, that a systems analysis could identify missing inputs and or weak processes (i.e., the tasks performed by peripheral level health workers). We will discuss only the results in the area of ARI.

Field Operations

Because the systems analysis methodology was still in the developmental stage at the time this work was carried out, it was agreed that it would be applied in just one of the country's 79 provinces. A decision model was set up using a number of criteria, including morbidity data and staffing patterns, plus cooperativeness of regional and provincial staff and accessibility in terms of geography and peace-and-order (the euphemism for the communist insurgency). Ultimately, Bulacan Province, a large province immediately adjacent to Manila but with large sections of both rural and town-oriented populations, was selected. The sampling unit within the province was the Rural Health Unit (RHU), a facility generally staffed by a Public Health Nurse (PHN) and one or two Rural Health Midwives (RHM). At the RHU, the PHN provides service to patients and also functions as supervisor to the RHMs. Most RHUs also have 2-6 satellite posts (Barangay Health Stations--BHS) staffed only by an RHM but supervised by the PHN of the RHU.

A second decision model was developed to select from among the 54 RHUs in the province. The provincial staff, using a weighted multiple criteria method, produced a decision model for ordering the RHUs from "best" to "worst". Decision factors were largely service targets achievements in child and maternal immunizations, in growth monitoring, and in use of ORT. Six RHUs (and their attendant satellite BHSs) were selected from the top of the list, 6 from the bottom, and 6 from the middle. It was felt that this bracketing approach would deliver data reasonably representative of the province and of the country. If anything, the Department of Health central staff felt, Bulacan might be a little better off than most other provinces and operational problems observed there would likely be present over much of the rest of the country.

In discussion with Bulacan, regional, and central DOH staff, observation and interview instruments were developed from the PRICOR thesaurus. Figure 3 shows the instrument used to observe service delivery in ARI. Six field staff, all recent college graduates but none a health professional, were trained to use the instruments in the field. Data were collected over a 3-month period, archived in dBaseIII+, and analyzed in SPSS.

Results

The systems analysis team was able to observe 314 cases of ARI as they were being seen by the RHMs, and 66 more seen by the PHNs. Two types of information were most striking, actual performance of the health workers (the RHMs and the PHNs) in providing this service and the perceptions of the RHMs' supervisors (the PHNs) with regard to their performance.

The graphs labeled ARSDA, ARSDB, and ARSDC (figure 3) show how well both groups did histories and physicals on these patients and how well they provide subsequent counseling. If good performance consists of carrying out the tasks specified in the WHO paradigm, then neither the RHMs or their supervisors, the PHNs, did very well. In only about half the cases, for example, did the health worker ask the mother what already had been done for the child at home. The child's breathing was observed in fewer than one-third of the cases, and respiration was counted in only about 20% of cases. It may be seen that only infrequently was adequate counseling provided to the mother during the visit to the facility. More than one-third of mothers were not reminded to maintain feeding, and almost none were told to watch for signs of worsening breathing. An antibiotic was prescribed in 147 cases and most of the time the full course for treatment was dispensed at the facility. However, in more than 90% of cases the mother was not instructed to complete the regimen. Although the systems analysis was designed to identify operational problems and not delve too deeply into their causes,

The systems analysis also revealed severe flaws in supervision of the RHM by the PHNs. In 73 cases, the PHN supervisor was actually observed to be present when an RHM was treating an ARI case. In only 23 of those cases did the PHN appear to be watching what the RHM was doing or saying. There is strong evidence, in fact, that the PHNs badly overestimate the quality of the service their supervisees provide. Graphs ARSU2B, ARSU2C, AND ARSU2D (figure 4) show again the observed results of 314 RHM-treated cases. The line in these graphs, however, shows what proportion of their supervisors (the PHNs) thought that they "almost always" or "often" perform these elements of service when dealing with a case of ARI. The systems analysis also revealed that the PHNs almost never take any deliberate action to assure themselves that their supervisees either know what elements of quality service are expected of them or that they actually do them. When asked how they assure themselves that the RHMs know what to do and do it, the

response was almost universally some variant of "But they were trained to do that!"

Implementation of Results

The results of the system analysis for the four programs (ARI, ORT, growth monitoring, and immunization) were presented to the Bulacan Provincial Medical Officer and to the staff of the Department of Health Division of Public Health Services. It is their belief that the problems identified in Bulacan are indeed representative of the country as a whole. As a result, the department is commissioning a series of operations research studies in growth monitoring and ORT, including problems of supervision in these programs. The Bulacan provincial health staff will carry out several studies of its own. And very importantly, the Department is negotiating with a major management training agency for a crosscutting operations research study to deal with supervision at the peripheral levels of the DOH system.

The ARI training program in the Philippines is still in development, and at this point it is undecided whether DOH will commission OR studies in the near future or simply use the information from the system analysis to help focus the training program design.

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Figure 1. ALRI SERVICE DELIVERY SYSTEM

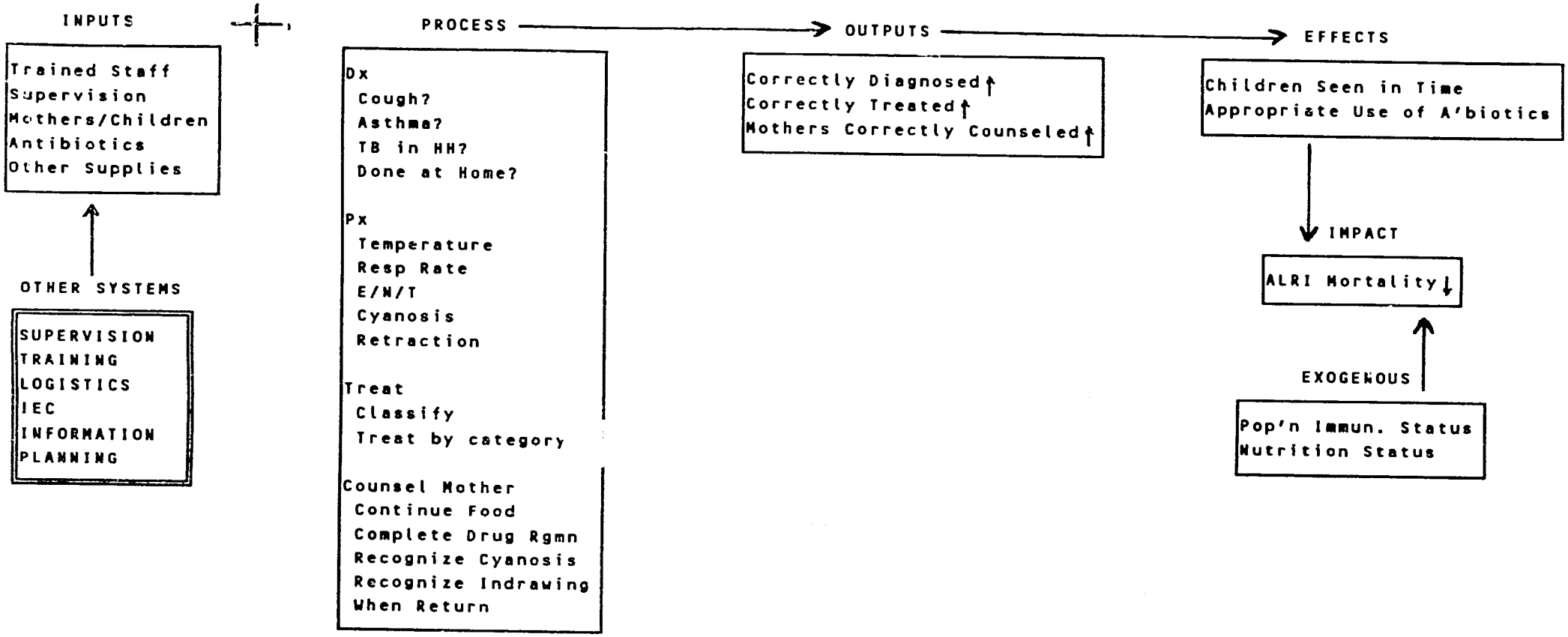


Figure 2. One of Various Instruments Used for Field Observation in Philippines Systems Analysis

DOH/PRICOR SYSTEMS ANALYSIS
ACUTE RESPIRATORY INFECTION: OBSERVATION OF SERVICE DELIVERY

ARSD1

Date(m/d)__/__ Observer(Lastname, Initial)_____

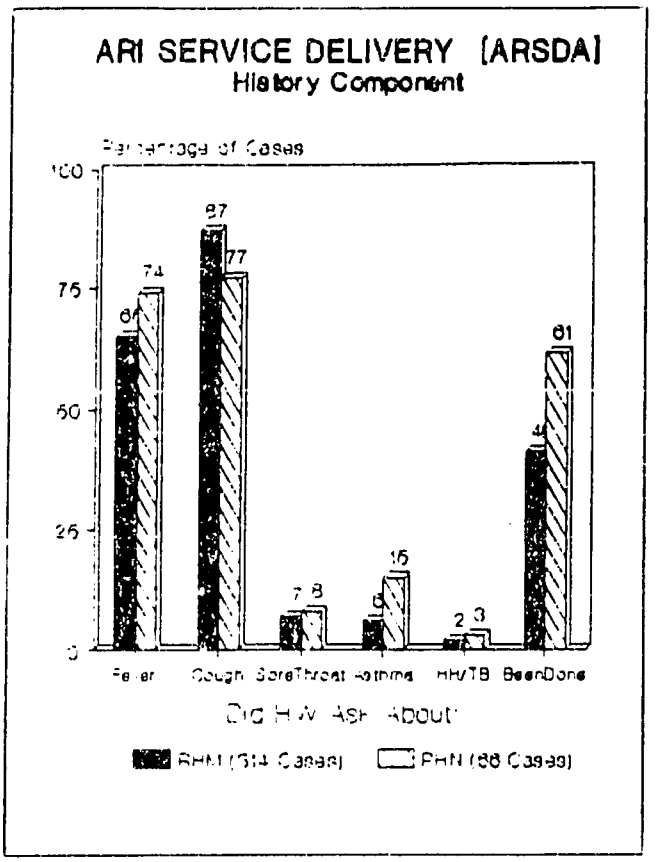
District_____ RHU_____ BHS_____

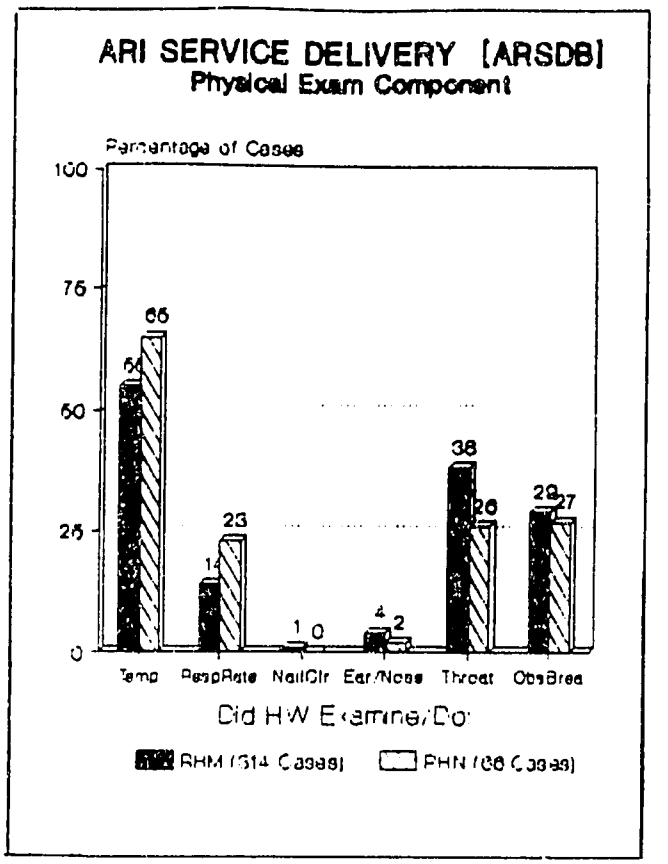
Bgy_____ HW Name_____ Position/Title_____

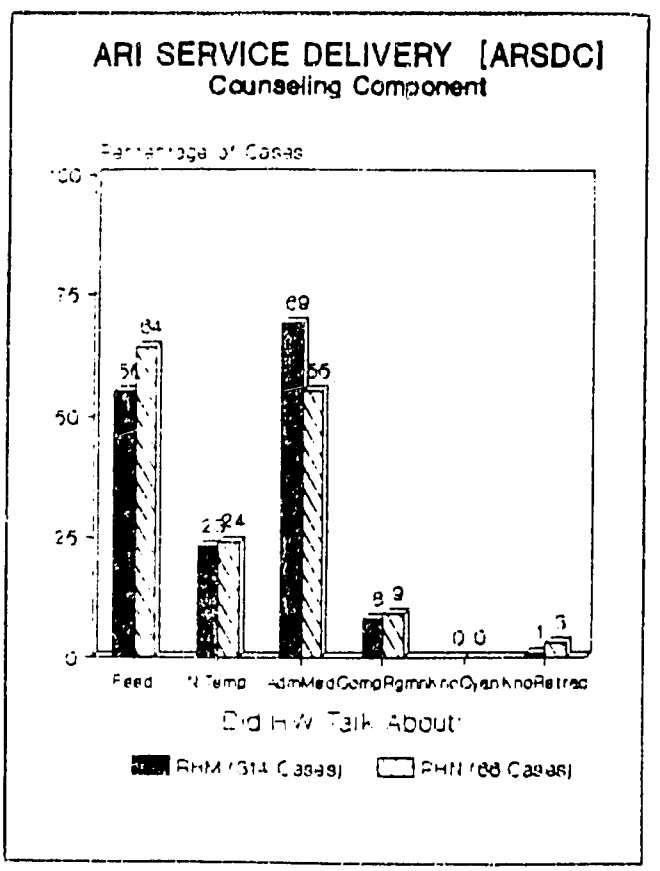
Child's Age___yrs___mos Name_____ Bgy_____

Did the HW ask:	Y	N	
If child has had fever in last week	☐	☐	
How long child has had cough	☐	☐	
If child had chest pain	☐	☐	
If child had throat pain	☐	☐	
If child has had difficulty breathing	☐	☐	☐N, but obvious
If child has ever had asthma	☐	☐	
If there is TB in the household	☐	☐	
If child has had problem drinking	☐	☐	
What has already been done	☐	☐	
Did the HW:	Y	N	
Take temperature	☐	☐	(Y,_____°)
Count respiratory rate	☐	☐	(Y,_____/min)
Note color of nails	☐	☐	☐Could not tell
Examine ears and nose for discharge	☐	☐	
Examine throat	☐	☐	
Observe for restricted breathing	☐	☐	☐Could not tell
Did the HW classify the child as to mild, moderate, severe ARI?	☐N ☐Y-Class_____ ☐Not Sure		
Did the HW prescribe an antibiotic?	☐N ☐Y-What_____		
Was this antibiotic available at this facility?	☐N ☐Y, part of amount required ☐Y, entire amount required		
Did the HW precribe/give any other medcines?	☐N ☐Y-What_____		
Did the HW refer the child to another facility?	☐N ☐Y-Where_____		
Did the HW tell the mother:	Y	N	
To continue giving fluids and food	☐	☐	
To keep child at neutral temperature	☐	☐	
How to administer prescribed medicines	☐	☐	
Importance of completing drug regimen	☐	☐	
How to watch for cyanosis	☐	☐	
How to watch for chest indrawing	☐	☐	
Did the HW test to make sure mother understood how to:	Y	N	If Y, how did the HW test the mother?
Administer the medicines	☐→	☐	_____
How to recognize cyanosis	☐→	☐	_____
How to recognize chest indrawing	☐→	☐	_____

Figure 3. Analysis of Service Delivery by Rural Health Midwives and Public Health Nurses





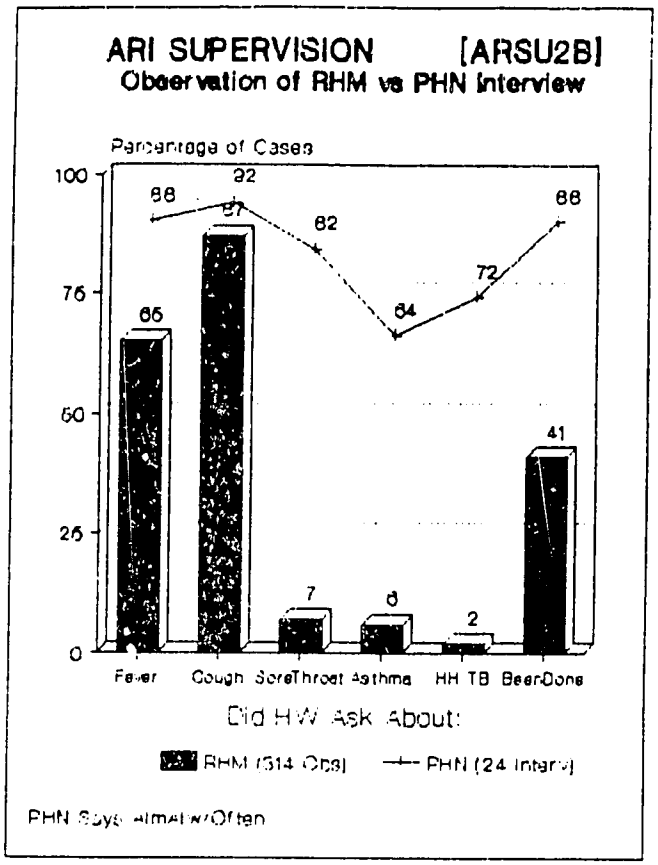


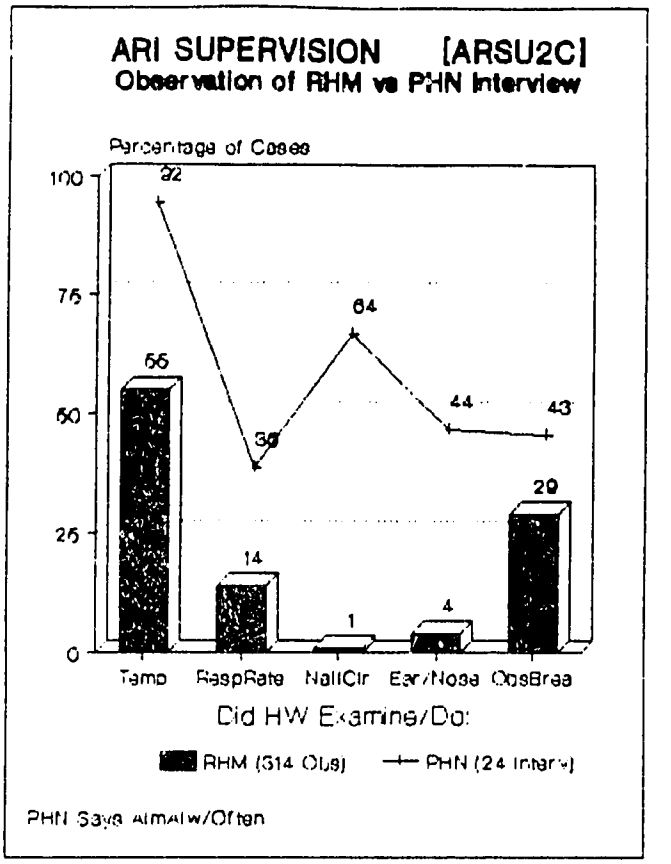
History [Did the HW ask:]
If child has had fever
If child has had cough
If child has had sore throat
If child has asthma
If there is TB in household
What's been done at home

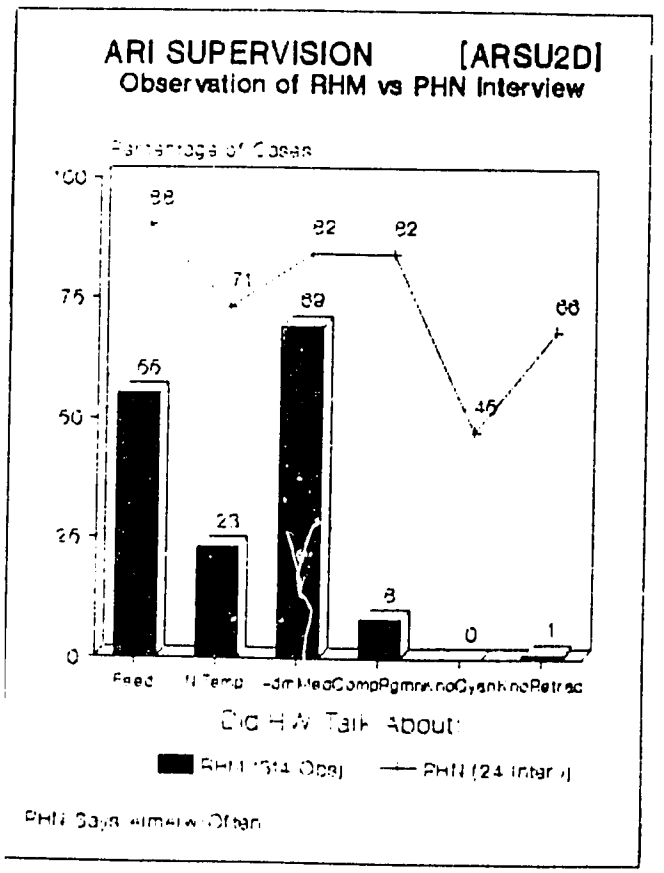
Physical [Did the HW check/do:]
Temperature
Respiratory rate
Nail color (for cyanosis)
Ear, nose, throat
Observe breathing for retraction

Counseling [Did the HW tell the mother:]
To continue feeding
To keep the child at neutral temperature
How to administer any medicines prescribed/given
To finish the entire drug regimen
How to recognize cyanosis and its significance
How to recognize retraction and its significance

Figure 4. Supervisor (Public Health Nurse) Perception of Service Delivery by Rural Health Midwives







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Nail color (for cyanosis)
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Observe breathing for retraction

Counseling [Did the HW tell the mother:]
To continue feeding
To keep the child at neutral temperature
How to administer any medicines prescribed/given
To finish the entire drug regimen
How to recognize cyanosis and its significance
How to recognize retraction and its significance

Operations Research

Discussion Summary

Streamlining record keeping and flow of information: What kind of documentation is feasible in the ARI program in terms of records, or other written kinds of documentation, that allows supervisors and other people to assess the process? At the health centers, one is struck by the enormous crowds of patients and the large volume of patients that the health worker needs to deal with in a very short period of time.

The load of time going into information systems at the present time makes program managers tend to throw up their hands. In the 1960s and 1970s, a series of functional analysis studies in several countries were done in which time motion measurements were made of what was going into a variety of functions in the health centers. In India, health centers were sending in 40 forms every month up the line and the time that it was taking overall, of the total health personnel of the health centers, was 45% of their time was going into just filling in forms. In Indonesia, similar studies demonstrated that 60% of the time of health workers was going into filling out forms. The reason for the 60% of time spent on recordkeeping was that an information consultant had devised a totally new information system that streamlined the previous one. The result of that consultation was that the healthworkers were doing both the old system and the new system, and this added up to 60% of their time. The problem of setting up revisions of systems is that often it becomes an additive revision, and not one that subtracts or reduces the amount of time and effort going into recordkeeping. The only way to inform countries of these sorts of problems is to do local studies in order to prove that record-keeping burdens can block effective program delivery.

Importance of training supervisors: Recordkeeping could be handled at the level of the supervisor who can assure himself or herself that in general the health workers are functioning effectively. When the supervisor goes out, they have to have some means for assuring that the health workers are working properly, i.e. that they're doing a good history, doing the physical exam they need to do, and they're doing the kind of counselling they need to do. One of the problems is that supervisors are not taught to be supervisors. It is assumed that since they know how to do the health workers job, that somehow they also know how to supervise. At the first level of supervision, people are not trained to be supervisors, nor are they given any kind of tools to work with. What usually happens is that supervisors appear to be just watching health workers serving patients. The interaction between the first line supervisor and the health service provider can be structured via the use of a checklist that allows for observation of important tasks. The question then becomes how do you help the supervisor become a real supervisor. The Department of Health in the Philippines is currently discussing a training program for first line supervisors for public health nurses.

Need for second line supervision or supervisor of the supervisors: The first line supervisor's records or checklists could be turned in to the second line supervisor. Effectively, the burden

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of recordkeeping and quality control is transfered up the line. This transfer of recordkeeping from the first line health workers to the supervisors, could reduce the work load at the CHW level.

Lessons learned from Jumla study: Experience reported from the Jumla, Nepal, ARI project supports the importance of supervision, and lends pragmatic insight into the management of an ARI program. Recordkeeping at the service delivery and at the community health worker levels was kept at the absolute minimum for two reasons. First, such record keeping becomes too burdensome to the CHW, and second, on a larger scale, ministries of health have so many records filling up their offices that no use is made of available information. So at the level of the service provider, the bare minimum of information required was a case record of a child seen with pneumonia, antibiotic given and the age of the child. This information allows supervisors to do one essential thing which was to monitor antibiotic usage on a monthly basis at the district center. If there is no record of number of children seen and who got antibiotics, there's no way to ensure that indiscriminant use of antibiotics is not occurring. That alone is not enough to indicate whether the assessment is correct or not, or whether the program is working well. But it does allow the first level of management to use this information to detect unusual treatment patterns. For example, health workers who start going into business on their own would be detected because their antibiotic usage increases out of proportion to past treatment rates and in comparison to their colleagues.

The supervisory aspect of the Jumla project developed over two years minimized the number of things that supervisors were asked to look for. For example, do the CHW's know how to count respirations? Are they doing it right? Direct observation of case detection, direct observation of the amount of antibiotics prescribed, direct observation of the counseling were emphasized. Immediate feedback was stressed. Supervisors were told that the primary objective was not to get information back to the district center. Rather they were told observe and then take action. They also have a second level of activities which is to go to visit households without the health worker and to assess whether, in fact, they have been operating according to standards. Households that are supposed to be visited regularly, were asked did the health worker come? What did he do? Households in which there has been treatment in the last few weeks, were asked what the CHW did, as well as what the mother remembers as having been said.

Second level of supervision was comprised of staff from the district center going out and making sure that the supervisors themselves are carrying out these tasks. This however is an intensive project with a minimum of once a month contact between each supervisor and his various health workers on a one-to-one basis at their point of work. When less frequent visits were attempted, CHW performance started dropping significantly. Once a month appeared to be a reasonable minimum for this most peripheral level of health workers.

Lessons learned from PRICOR studies in the Philippines: During interviews with supervisors from the Philippines, the question asked was "how do you assure that your health workers are doing these tasks properly?" Verbatim answers in dBASE were recorded, and a majority of supervisors responded that "they were trained". The health workers may have been trained properly but that training might have been several years ago and the circumstances are very different. The health workers may know what they're supposed to do but they may not

have time so they begin to make these decisions about what's really important. Sometimes they do this in a sketchy or impressionistic way, sometimes it's done because it's convenient to do only a couple of things and not do all the rest. Other times there are political pressures to do one thing and not another.

The filling out of records is a good example. Why do you often see supervisors focusing on records? Why do you see health workers filling out the records so desperately? The reason is that their supervisors are demanding that they fill out these records. Because the supervisor of the supervisors is demanding that data be sent upstream. That's what the definition of supervision is according to most first line supervisors. It's a pressure that they're getting that comes all the way down from the top to the region, to the province, to the district, to the rural health unit. If that's what the pressure is that is what's going to get done. So there is a need to change the definition of supervision because in the above scenario, it is equivalent to simply filling out records.

Role of donors and international agencies in streamlining information flow: Donors and international agencies are at the top of the supervision chain and sometimes the information chain. To aid in the streamlining of information flow, these agencies could work toward agreeing on some indicators that are required of the system could produce on a intermittent basis. Example from AID in diarrheal disease was the adoption of the ORT use and access indicators. It was recognized that these are not comprehensive nor perfect indicators, yet it was acknowledged that it was important to simplify and to not expect national programs to track many, many variables in order to be responsive to various donors and agencies. Coming up with something comparable for ALRI to use as effective indicators for program would help in simplifying the demands for information made by the donors community.

Refining the list of operations research variables: OR starts out with an analysis of the problem which is an extension of the systems analysis. In other words, the systems analysis is designed to find out what problems there are in this system. The operations research then begins to find out what the causes of the problems are, what the potential solutions are, then establish some sort of a decision framework. One has to determine what variables count in deciding from among competing strategies, select a strategy and then implement it, usually on a pilot basis, sometimes as a quasi-experiment. Sometimes some of the problems have such easy, obvious solutions that there is no need for further testing. But most of the time the problem requires some study of an intervention to address the problem, with evaluation to see whether there is improvement after implementation. That is how, for example, the key elements in a supervisory checklist could be refined down to manageable number.

OR could address the question of how often does good process lead to good outcome? What elements are correlated with good outcomes? Operations research activities could begin to address these issues as a way of refining criteria and creating more feasible and parsimonist lists of criteria to provide the supervisor with what s/he really needs to know.

Otherwise, the list of operational variables describing ARI management might suggest a massive data reporting form. When program managers look at a series of 160 activities that have been defined, they are likely to say there's no way that they can cope with that complexity. However, the question could be rephrased from "can we afford to monitor it" to "how frequently can

we afford to monitor these issues". There maybe are some areas that do not need to be monitored every month. There are probably many elements of service delivery that can be observed infrequently, and perhaps that frequency ought to be based on the result of the previous assessments.

How operations research and health information system could interface: Service delivery activities themselves are a frequent assessible event rather than infrequent, rare event like mortality. The nature of these activities lends themselves to verification. If a certain percentage of what is reported to have been done is verified, this serves as a management tool in its own right. There are lots of service statistic forms that are of low quality that are probably totally unreliable or reported late and not put to any use. But information about whether or not health center staff are providing quality care, has obvious intermediate application from a management point of view.

Eventually, OR could lead to the incorporation of this kind of analysis into the systematic management information system for decision makers and managers in these service systems. So that they get just the information they need on a regular basis, whatever that basis is. It may only be once a year. Some of it may be twice a year, some may be twelve times a year. But they should get the information they need to be able to assure themselves that the system is functioning the way it was designed to function.

Incorporation of operations research into ARI programming: In the three country study for UNICEF, what is emerging in each of the three countries has been a distinction between the OR component as done at the beginning or periodically in the study as compared with the need for a continuing OR activities center or several such centers in a country. In the former, a study is done and then one goes back and does another study with whatever sampling device is available. In the latter, the capacity to maintain an operations research activity in the country can be developed. Ideally, there should be an area designated where the most intensive data gathering procedures are done. The results of the initial operations research systems analysis done in this specific area can yield the simplest possible combination, both of program activities and of the information system, that then can be applied on a general basis in the country as a whole. This process is not likely to be uniform in all countries, and will be modified by local conditions and health infrastructure.

Behavioral Aspects of Acute Respiratory Infection in Children

Gretel H. Pelto, Ph.D.
University of Connecticut

Carl Kendall, Ph.D.
The Johns Hopkins University

Introduction

Behavior and beliefs of parents and practitioners are significantly involved in the management of acute respiratory infection in children and the prevention of deaths from pneumonia. The types of parental or caretaker behaviors of importance include recognition and interpretation of ARI signs and symptoms, home management practices, the selection and seeking of health care, and the interpretation of practitioner advice and instructions. From the practitioner side, the behaviors of interest include management and prescribing practices and modes of communication with caretakers of sick children. At present, the serious lack of behavioral research on ARI precludes the possibility of reviewing current behaviors and their determinants. In the absence of such data, our reports lays out a framework for approaching this critical research area.

Background

In the past decade there has been a substantial growth of social science research on behavioral aspects of infectious disease in developing countries, focused particularly in medical anthropological studies of diarrhea (1). At the same time, the development of medical anthropology and medical sociology, as specialties within these disciplines, has led to a substantial body of theory that serves to underpin behavioral research on medical issues. We draw from this literature and previous research on diarrheal disease as the basis for our discussion here.

Definition of Behavior. We are using the term "behavior" very broadly to refer to the social and cultural ideas, activities and arrangements that influence risk, diagnosis, treatment and outcome of respiratory infection. These include factors on the biomedical side, as well as those that are relevant to households and communities. From the

perspective of the health care system, behavioral factors include those having to do with the organization and delivery of medical services and patient-provider interactions. Here, however, we have chosen to focus primarily on social and cultural factors operative at the local level in the communities and households within which infection occurs.

The Concept of "Explanatory Models". At the core of any medical system is a theory of disease. "Western medicine" is based on a very complex, multi-faceted theory derived from modern biological sciences, and it contrasts sharply with the general explanation of health and illness in traditional Chinese medicine, for example. For practitioners trained in modern biomedicine, the relationship between theory and medical practice is intuitively obvious. What is perhaps not as immediately obvious is that in all cultures, in all communities, people have theories of disease that provide the basis for their "case management."

Medical anthropologists often use the term "explanatory model" to refer to people's belief systems concerning the characteristic symptoms, etiology, preferred modes of treatments and expected course of development of specific diseases. For example, field research may be directed to identifying the explanatory model of diarrhea in a particular cultural setting, by which we mean the organization of cultural ideas -- knowledge and concepts that people have about the causes, characteristics, and treatment of diarrhea (2). Explanatory models of specific pathologies in any given community make up a composite system -- the "folk theory" of disease in the culture. Sometimes the folk theory is referred to as an "emic model."

The Concept of "Household Management of Illness". A primary aspect of field research in medical anthropology is the identification and description of patterns of case management in families within a community. Increasingly, medical anthropologists are using the term "household management of illness" to refer to these management strategies (3). Household management covers the entire process of household activities associated with a disease episode and is not limited to the application of home remedies.

The Interface Between Case Management and Household Management

At present, considerable attention is being devoted to the development of programs to reduce mortality from pneumonia and other acute respiratory infections. A main component of these programs is improved case management; however, management protocols can only be effective if practitioners have the opportunity to utilize them in the community. The introduction of an ARI program into a region or community is, in a sense, a community development problem. Whether one is introducing new agricultural technology, public health interventions or any other action that involves behavioral change, one of the most critical challenges that development agents face is to identify and understand the patterns of behavior associated with particular, local folk theories and management

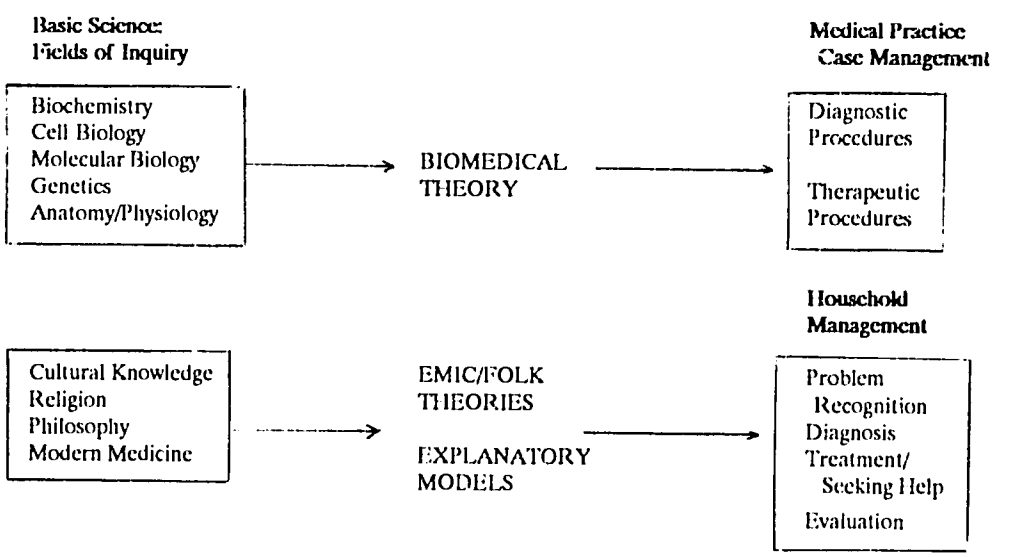
systems.

In the case of infectious diseases, such as pneumonia, people already have explanatory models and strategies of household management. New case management strategies emanating from ministries of health or non-governmental organizations are introduced into this already existing structure. Thus, the success of a new strategy in reducing mortality or morbidity depends very much on how well the two templates can be made to fit together. Therefor, the description and analysis of the community template should be an essential component of program development activities, along with the development of the medical infrastructure.

Household Management of Acute Respiratory Infection

As outlined in Diagram I, the process of household management can be divided into several stages: problem definition, diagnosis, treatment, and evaluation.

Diagram I. Parallels Between Biomedical and Community-Based Approaches



1. Problem Definition. A critical step in effective case management of pneumonia is getting caretakers to recognize signs and symptoms of ALRI and seek medical help promptly. The recognition of specific symptoms of severity, such as rapid breathing or chest indrawing is, however, part of a larger issue -- the process of caretaker "problem definition."

Some medical conditions are very clear cut, and there is little or no ambiguity in recognizing a departure from normality. Physical trauma with external bleeding is an obvious

example. Continuous vomiting is another. But many diseases present a more ambiguous picture. When, for example, do caretakers define soft stools as "diarrhea?" At some point, the frequency, consistency and appearance of a child's feces cross a culturally defined point, at which time the caretaker and/or other members of a household will agree: "This child has diarrhea." Once that occurs we can say that there is recognition of a problem.

Compared to diarrhea, respiratory symptoms, as a class, appear to be more problematic. Chronic cough and runny nose may be regarded as normal childhood conditions. Their presence doesn't signal a departure from "normal health," and they may go unnoticed. Problem definition by the caretaker may, in many instances, be influenced by the course of onset of symptoms. When the symptoms are preceded by a period of URI, as contrasted with sudden acute appearance of ALRI symptoms, the process of problem recognition may be quite different. At this time, very little is known about variations in the recognition of symptoms of acute respiratory infection, either cross-culturally or intra-culturally.

2. Diagnosis and Explanatory Models. Diagnosis of the problem by the mother and/or the household can be thought of as the interpretation of a symptom or set of symptoms, which is made on the basis of an explanatory model -- the organization of ideas about illness. Within a community there tends to be a considerable sharing of explanatory models, but there will also be intra-group variation.

At present there are, to the best of our knowledge, no published studies of the explanatory model of acute respiratory infection in a specific cultural setting. However, a number of examples can be drawn from medical anthropological studies of diarrhea, which illustrate key features of explanatory models (1).

In studying explanatory models, anthropologists find it useful to begin by developing a taxonomy of categories of illness and types of illness within each category (4). With a taxonomy in hand, one can then further describe the associated symptoms, causes, treatments, and other features of the categories. The categories and types are elicited from informants and are thus culturally rather than biomedically defined; thus, they are "emic models." Typically, KAP studies use pre-defined categories, which can distort the picture and reduce the validity of the results.

Often, there is considerable overlap between the biomedical taxonomy or classification and the emic or folk classification. However, local cultures may use biomedical terms to label an illness for which the content -- people's ideas about the cause and treatment -- may be quite different from biomedical theory. Also, explanatory models usually contain some categories that have no clear counterpart in biomedical theory. The concept of "empacho" in Mexico and Central America is an example of an emic illness category related to diarrhea that has no equivalent in biomedicine (5).

Judgments of severity are part of the explanatory model, and specific symptoms are often a trigger for regarding an illness as severe, even when the duration has been very short. For example, Bentley reports from North India that mothers consider blood in the stool as an indication of serious illness and rapidly seek medical attention (3).

In acute respiratory infection, the relationship of caretaker assessment of severity to the seeking of appropriate health care has received very little attention, but it may vary quite widely from one community to another. For example, in his research in South India, Nichter found that any illness in young children that was accompanied by convulsions or tremors, associated with a rapid increase in temperature, was interpreted as a sign of spirit possession and led to immediate consultation with an exorcist rather than in taking the child to a health clinic (6). On the other hand, in a KAP study in the Philippines, Tupasi reports that "mothers claimed they brought their children to the hospital when the cough was accompanied by fever or when their child looked weak, was unable to eat, slept most of the time and/or was bluish in color" (7). Less severe symptoms were treated at home or taken to a traditional healer.

3. Treatment Strategies. Anthropologists derive the elements in an explanatory model through intensive interviewing, first with key informants, then with relatively small samples, usually of mothers. For the description and analysis of actual treatment behaviors, active "case following" probably yields the most valid data. Recall of recent past cases may also be very useful, whereas generalized questions about "usual patterns of treatment" can produce fairly distorted accounts.

Health seeking behavior -- or "patterns of resort" as this feature of household management is sometimes referred to -- is a very complex matter. With respect to treatment alternatives for infectious disease, it is usual to find substantial variation within a community (8). Faced with the same set of signs and symptoms in a young child, households within a community will behave in very different ways. Depending on a variety of social and cultural factors, some households will engage in an extended period of home-based management procedures; others will take the child to a health clinic, while still other households will seek help from a private practitioner, a pharmacist, or various types of traditional healers.

The self-treatment strategy is often not limited to home remedies, but usually involves pharmaceuticals obtained from a street stall or shop. With respect to the household management of diarrhea, there is now considerable documentation demonstrating an extraordinary range of use of pharmaceuticals as well as home-prepared remedies (9). Some of this use comes about through household self-prescribing; much of it, however, occurs as a consequence of seeking help outside the household. The general picture that emerges from community-based studies is that household management of diarrhea in children is a trial-and-error process in which people quickly shift from one mode to

another when the problem doesn't resolve as quickly as they expect. It is very likely that a similar situation exists with respect to respiratory illness.

There are several reasons for the complexity and for the diversity in health seeking behavior. Among the significant factors are:

1. The presence of multiple health care resources in the community. (All medical systems today are pluralistic.)

2. Variations in explanatory models.

3. Variations in resources, in the factors that facilitate or constrain the use of one resource over another.

4. Variations in household decision-making and social organization.

5. Differential treatment based on characteristics of the sick child (i.e. gender, age or birth order.)

Conclusions

There is a clear need for research on the social and behavioral aspects of ARI. As a first step, detailed studies in several different geographic settings would provide an overview of the main dimensions of ARI from the community perspective. These studies should include people's perceptions of signs and symptoms associated with ALRI and the relationship of these perceptions to clinically-defined disease. It is likely that caretaker recognition and interpretation of pneumonia and other ALRI will vary across cultural settings. Examination of folk explanatory models will also require information on cultural beliefs about etiology, expected course of the illness, treatments, and related features.

If the gap between the folk models and our biological model is large, programs for effective case management must develop culturally sensitive education strategies to accomplish their goals. Based on past research and the experiences of diarrheal disease control programs, it seems likely that different strategies for ARI programs will have to be developed in different kinds of cultural settings. However, only future research can resolve these issues.

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Mothers' Perception of ALRI: A Case Study in Lesotho

Dr. Ruth P. Wilson
Centers for Disease Control

Dr. Itumeleng Kimane
National University of Lesotho

I. INTRODUCTION

In 1988 the Ministry of Health of the Kingdom of Lesotho[1] noted a high incidence of cases of acute respiratory infections among children under the age of five and requested assistance from the Centers for Disease Control in the development of a national policy for the control of acute respiratory infections (ARI). This paper presents the preliminary results of our efforts to assist Lesotho in the development of a culturally appropriate and medically effective policy[2]. The Lesotho Ministry of Health (MOH) plans to combine the social science efforts with the clinical findings during a pilot intervention in early 1990.

II. PURPOSE

A three-phased study was designed to determine if there is a specific comprehension of ARI among mothers with children under five years of age in Lesotho. If ARI is present, the research sought to determine how care providers define, diagnose and treat acute

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[1] Lesotho is a southern African country of 1.6 million people. Its people are called Basotho. The term Sesotho is used to describe their language, and is used as an adjective to specify traditions and practices peculiar to Basotho. English is also an official language. The county is characterized by its political organization (it is one of the few kingdoms still in existence), its geographical terrain (mountainous), and by the fact that it is surrounded by the Republic of South Africa.

[2] The clinical research activities are being coordinated by Dr. Steve Redd, Centers for Disease Control; International Health Program Office, Atlanta Georgia.

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lower respiratory infections (ALRI). Finally, the study sought to elucidate the customs, traditions, beliefs, and behaviors surrounding Basotho-defined ALRI in order to make recommendations for health education and training.

III. METHODS

Phase I, completed during March 1989, used rapid anthropological research methods[3] to assess the local comprehension of ALRI (February 1989). These qualitative data were used to develop the questions and to design the survey instrument used in Phase Two (May-June 1989). Phase II used cluster sampling techniques[4] to survey ALRI beliefs and practices among child care providers and village health workers throughout Lesotho. Primary child care providers in households with children under five years of age were the target of our inquiry. Phase III will use participant observation to determine the relationship between what care providers say they do and their actual behavior[5].

IV. FINDINGS[6]

The presence of a clinical sign or symptom does not signal recognition of an illness. Illnesses are culturally defined. And when common, a disease may or may not be recognized as an illness. Once people recognize an illness, they classify and categorize the condition according to their perceptions of its severity, and their beliefs as to whether or not it is treatable with their available resources. The data from Phase I and II suggest that a specific comprehension of ALRI exists in Lesotho.

A. Phase I

Analysis of 39 Phase I, in-depth, open ended interviews with mothers, grandmothers, fathers, and village health workers in two villages in Lesotho led to three major insights: 1) Basotho nosology includes specific terms for ARI and ALRI; 2) the Basotho have specific beliefs and practices associated with treating children with ALRI; and 3) questions about breathing difficulty were those most likely to elicit disease names with the signs and

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[3] Scrimshaw, Susan and E. Hurtado, Rapid Assessment Procedures, UCLA 1987. Bentley, Margaret E. et al, Rapid ethnographic assessment: applications in a diarrhea management program, Social Science & Medicine 27(1): 107-116, 1988.

[4] Henderson, R.H. and Sundaresan, T., Cluster sampling to assess immunization coverage: a review of experience with a simplified sampling method. Bulletin WHO 60(2): 253-60, 1982.

[5] Phase III is scheduled for completion by September 1990.

[6] These are preliminary findings. Our final results will be available December 1989.

symptoms associated with ARI.

To talk about ARI in Lesotho requires referring to the chest; the chest is "sefuba" in the local language. Sefuba also refers to general illness (being sick), but in children it refers specifically to the common cold. There are different types of sefuba, but the one most frequently associated with breathing difficulty is "letsoejana" (Table 1, pg. 158), which when literally translated means "little heart jumping". Sixty-six percent of the mothers and other child care providers cited "letsoejana" when asked about illnesses associated with breathing difficulty. We used this findings and other health beliefs and practice data found among the villagers to develop questions for the Phase II community-wide study.[7]

B. Phase II

Phase II data surveyed 660 individuals, with a response rate of 92% (603/660). Key findings are summarized here.

1. Sesotho Childhood Illnesses

Respondents were asked to name the most common childhood illnesses, the serious childhood illnesses, and the illnesses that cause death among the children under five years of age in their village (Table 2). Approximately 60 different Sesotho terms were cited as common illnesses for children under five. Letsoejana, the disease of interest, is not as common as sefuba (the common cold), but unlike sefuba, it is considered very serious, and is associated with child mortality.

Respondents were also asked to name the childhood illnesses associated with breathing difficulties and whether or not there were any children in the household with a present case of any of the named breathing difficulty illnesses. If a case was present, the respondent was asked to the name the child's illness, the age of the child, the method used to diagnose the illness and the steps taken to cure the child.

2. Sesotho ARI Terms

Table 3 summarizes the names and frequencies of Sesotho terms used to describe illnesses associated with breathing difficulty. Although a number of Basotho illnesses are associated with breathing difficulties, ninety percent of the responses refer to two illnesses: sefuba and letsoejana. The other illnesses cited by the Basotho care providers represent a small minority of the responses. Since Phase II data confirm Phase One respondents' belief that

[7] A preliminary summary of results from Phase One is available from Dr. Wilson at the Centers for Disease Control, IHPO, (F03), Atlanta, GA, 30333.

sefuba is but a common childhood cold, we focused our research on letsoejana, cited by more than sixty percent of the respondents when discussing childhood illnesses associated with breathing difficulty.

3. Care Providers' Diagnosis of Letsoejana

We used crude odds ratios to determine the likelihood of a symptom being used to diagnose letsoejana when compared to its being used to describe one of the other childhood illnesses. Respiratory symptoms significantly associated with the care provider's diagnosis are difficulty breathing, rapid breathing, cough, nasal flaring, runny nose, and noisy breathing (Table 4). A provider's perception of fever does not distinguish itself as a symptom significantly associated with letsoejana.

Care providers also use non-respiratory symptoms to diagnosis letsoejana. The other symptom associated with the care provider's diagnosis is difficulty drinking or sucking. Analyses to date show no significant association between a diagnosis of letsoejana and the following symptoms: problems eating, diarrhea, convulsions, sunken fontanel, the presence of "red anus"(kokoana)(Table 5).

4. Health Behaviors Associated with Letsoejana

When all health behaviors were analyzed, a few were significantly associated with letsoejana (Table 6): taking the child to the hospital, consulting with the mother-in-law, treating the child with Sesotho herbal medicines and non-prescription medicines, visiting the traditional doctor, consultations with the child's father, the chief, the village health worker, and some other person (usually another mother in the village whose child has had the condition, or the child's maternal grandmother). The care provider might also increase or decrease the amount of clothing the child wears and wrap the child's chest with cloth. Behaviors that may be most effective in reducing childhood mortality are addressed here.

The Basotho have already incorporated aspects of the Western health care delivery system into their modern health practices. Data presented in Table 7 show that the Western health care system (clinics, hospitals, pharmacies) and its practitioners (village health workers, physicians, nurses) figure prominently in villagers' efforts to find a cure for children with letsoejana. If current staff were trained to accurately diagnose ALRI and administer the appropriate treatment, any MOH ALRI control program could bring about a sustained decline in deaths of children under five years of age.

Traditional Sesotho medicine and its practitioners are an integral part of modern health practices in Lesotho. Home treatments include an array of herbal and medicinal teas and practices intended to restore normal breathing patterns to the child with letsoejana. Phase II data show little evidence of widespread support of Sesotho medicine practitioners for

letsoejana. Less than 5% of the care providers of children with letsoejana at the time of this study admit using the herbalist (0/104), religious healer (1/104), or the Sesotho doctors (8/104) to treat children with letsoejana.

Chest Binding

Analysis to date indicate two practices that may compromise chances for the survival of children with ALRI: chest binding and the widespead use of over-the-counterdrugs. The Basotho practice of chest binding is associated with their beliefs about the causes letsoejana. Basotho believe that the child is having pain in its chest. Some state that there are sores in the child's lungs. Others mention that they can see the heart "jumping", rapidly beating as the child struggles to breathe. By wrapping the child's chest with strips of cloth, care providers feel that they are easing the child's discomfort. Health education messages should build on the Basotho beliefs about sores in the lungs and teach the importance of the lungs having adequate space to expand and bring in clean air. (However, chest binding retricts the lungs' ability to bring fresh air to the sick child. Although the bound chest may appear more "normal" and ease the distress of the parent, it does not relieve the child.)

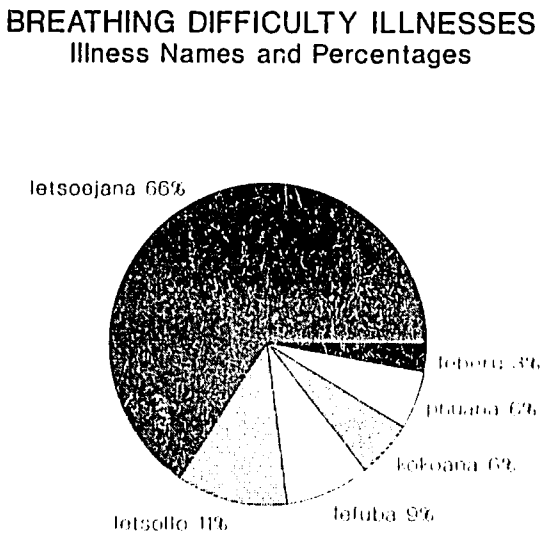
Over-the-Counter Drugs

Many over-the-counterdrugs are used by the Basotho. The majority of those named in this study are the equivalent of baby aspirins and cough mixtures. Although these may or may not be appropriate when a child has "sefuba", ALRI requires a more specific medical treatment. Health educators should build on the Basotho's beliefs in the efficacy of Western medicines but underscore the importance of specificity. Common medicines for common colds, strong medicines for strong, serious diseases like letsoejana. Children with letsoejana require a rapid medical assessment (from the village health worker or nurse clinician, and maybe even a doctor) and perhaps an antibiotic that must be given to the child according to the nurse's instructions. Even though the child may appear to be better after the first or second day of the medicine, the mother must keep treating the child with these "strong" medicines until the treatment is complete. Once the health practitioners are trained to recognize ALRI, the Lesotho pharmacy can produce and distribute antibiotics to meet national needs.

V. Summary

Anthropological research has been used to identify the body of illnesses representing ARI, classifying those illnesses, and identifying those most likely associated with mortality. Further, these methods have permitted the identification of practices that are detrimental, beneficial, or benign to the health of children under five. These data will be used in developing recommendationsfor health education and training in the Kingdom of Lesotho.

Table I



Phase I/39 interviews (missing=4)

Table 2

Perceived Seriousness of some Common Childhood Illnesses in Lesotho

Illness	Common		Serious		Cause Death	
	#	%	#	%	#	%
Letsoejana	289	14.8	191	15.7	209	17.8
Sefuba	429	22.0	76	6.3	39	3.3
Measles	139	7.1	96	7.9	65	5.5
Diarrhea	374	19.2	319	26.3	328	28.0
Vomiting	245	12.5	188	15.5	180	15.3
Other Illnesses	475	24.4	344	28.3	353	30.1
Totals	1951	100.0	1214	100.0	1174	100.0

Frequencies of illnesses cited as common, serious, and causing death in children under five years of age. Five common illnesses, 3 serious illnesses and 3 illnesses causing death were analyzed for each respondent. Missing data are excluded. The "other" category includes illnesses cited by less than fifty respondents in more than one category.

Table 3

Names and Frequencies of Illnesses
Associated with Breathing Difficulty

Name of Illness	Frequency	Percent
Feberu	1	0.65
Phuana	1	0.65
Kokoana	1	0.65
Lefuba	2	1.30
LETSOEJANA	104	67.53
SEFUBA	35	22.73
All Others	6	3.90
Missing	4	2.60
Total	154	100.00

Sesotho illness terms associated with difficulty breathing.

Table 4

LETSOEJANA
Respiratory Symptoms Associated with Diagnosis

Symptom	Odds Ratio	95% Confidence Limits
Difficulty Breathing	1.9	1.3, 2.9
Noisy Breathing	2.3	1.1, 5.1
Rapid Breathing	2.8	1.8, 4.5
Nasal Flaring	4.5	2.2, 9.2
Runny Nose	2.9	1.6, 5.5
Cough	1.8	1.2, 2.8
Fever*	1.5	0.9, 2.3

Table 5

LETSOEJANA
Other Symptoms Associated with Diagnosis

Symptom	Odds Ratio	95% Confidence Limits
Difficulty Breathing/ Sucking	2.1*	1.1, 3.8
Difficulty Eating	1.8	0.4, 8.9
Diarrhea	0.9	0.4, 2.3
Convulsions	0.3	0.1, 1.3
Sunken Fontanelle	2.8	0.9, 8.3
Cough	1.8	0.9, 314.4**

*The only significant "other" symptom ($p<.05$).
**Due to presence of zeros in some cells.

Table 6

LETSOEJANA
Associated Health Care Seeking Behaviors

Behavior	cOR(95% CI)	Xsq	p-value
Took the Child to			
Clinic	1.4(.9-2.3)	2.3	.1
Physician	1.1(.7-1.9)	.3	.6
Hospital*	6.2(3.4-11.1)	36.3	.000
Consulted with			
the Mother	1.6(.2-15.5)	.2	.7
the Mother-in-Law*	5.0(1.4-17.9)	6.2	.013
Trad. Doctor*	2.9(1.2-6.9)	6.0	.014
Herbalist	0.9(.05-20.9)	.4	.5
Healer	4.9(.4-60.6)	1.5	.2
the Father*	4.4(1.6-12.2)	7.9	.005
the chief*	3.3(1.8-5.8)	16.7	.000
the VHW*	2.2(1.1-4.1)	5.4	.020
Other person*	2.7(1.8-4.3)	20.3	.000
Treated Child w/			
Herbal Medicines*	2.6(1.3-4.9)	7.9	.005
Over Counter Meds*	6.4(4.2-9.7)	73.4	.000
Changed Dress*	4.6(2.8-7.4)	40.0	.000
Wrapped Chest*	2.6(1.7-4.0)	19.3	.000

* indicates significance at $p<.05$).

Table 7

LETSOEJANA
Frequencies of Associated Health Care Seeking Behaviors

Behavior	Frequency	Percent
Took the Child to		
Clinic	29	27.9
Physician	24	28.1
Hospital	21	20.2
Consulted with		
the Mother	1	1.0
the Mother-in-Law	4	3.8
Trad. Doctor	8	7.7
Herbalist	0	0.0
Healer	1	1.0
the Father	6	5.8
the Chief	20	19.2
the VHW	14	13.5
Other person	41	39.4
Treated Child w/		
Herbal Medicines	14	13.5
Over Counter Meds	55	52.9
Changed Dress	82	78.8
Wrapped Chest	68	65.4

(n=104 care providers of a child with a present case of letsoejana.)

Behavioral Research in the Development of ALRI Communication Strategies

Judith A. Graeff, Ph.D.
HEALTHCOM

In discussing ARI management in developing countries at this workshop, the critical effect of behavior on health outcomes and service delivery has been mentioned repeatedly. What is striking about work in child survival is that although the primary concern is the health of children, the primary target of behavior change must be the adults responsible for children: parents, health workers, and physicians. As professionals involved in the design and implementation of child survival programs, we must therefore directly address the behavior of those adults in order to have a positive impact on the health of their children. In the context of a health communication project in child survival, we have had to confront a broad range of behavioral issues when designing and disseminating effective messages to health workers and mothers. Today, I want to share with you a methodology and some results from our efforts to document behavior change in an ARI communication program.

In designing and implementing a communication strategy, the first step is assessment of behaviors related to a particular health outcome. We assess the behaviors of both health workers and mothers because we are interested in maintaining appropriate practices in both groups of adults. Behavioral research provides a systematic way of documenting the complexity and pervacity of critical behaviors of both health worker and mother alike. Specifically, (see Figure 1, pg. 166) behavioral research helps to identify appropriate behaviors already being practiced. These practices we attempt to encourage. For example, if we found that most women continue to breast feed during diarrhea, we would design a communication strategy that encourages that practice. Behavioral research can also identify important skills that are missing, such as effective teaching methods in health workers. We would design training opportunities to teach these skills. This type of research can also identify inappropriate practices in a target group. These behaviors should be replaced by training new behaviors or encouraging existing appropriate practices.

Behavioral research also focuses on the larger context in which these behaviors occur: it

identifies factors that act as antecedents, in other words, those events which trigger current practices. In the case of ARI, we are attempting to identify the symptoms in a child that trigger current practices (appropriate and inappropriate) in mothers. Lastly, behavioral research identifies factors that act as consequences. Consequences are positive or negative events following a behavior that increase or decrease the likelihood that the behavior will be repeated. The real and perceived consequences to appropriate health practices influence, to a great degree, the extent to which they will be maintained in a population. For example, a mother's positive or negative experiences with clinic staff can influence her decision to return to the clinic on a regular basis.

Some examples of behavioral research we are currently conducting to support health communication efforts are:

- In the Philippines, the study compares the WHO protocol for ARI with the symptoms a mother recognizes in her sick child.

- In Nigeria, the study measures whether mothers' return rates for immunization will increase after health workers change clinic procedure and health education practices on immunization days.

- In Indonesia, the study explores how to motivate kader (volunteer health workers) to remain active and accurate communicators of ORT after their training. Specifically, it will document whether direct mailing of a newsletter and periodic airing of radio spots will decrease kader drop out rate.

These examples illustrate research that looks closely at the behavior of individuals. Two research methods well suited to research of this type are structured observation and multiple baseline. Detailed observations of a small sample give data of actual practices that complement information from verbal responses to questionnaires. Observations are usually structured, in that target behaviors are recorded on a check list of possible behaviors so that observations can be reported quantitatively. This approach is particularly useful, for example, in observing the health education efforts of health workers. Usually, both the content of the talk and the techniques for effective teaching are already established, so it is possible to design an observation sheet with codes for specific target behaviors. This approach allows us to quantify the level of health worker communication effectiveness before and after training by serving as both a baseline and a post intervention measure. It can also be a planning tool for designing health worker communication training by identifying existing skills and skill deficits.

Figure 2 is an example of an observation check list for an EPI health talk from a study we conducted in Nigeria. As you can see, there is room at the top to record selected behaviors of both health workers and women in the audience as well as room at the

bottom to check off which content items on EPI the health worker mentions. Measuring mothers' behavior after training is another way we used structured observation. In Mexico, health workers visited homes 24 hours after mothers had received ORS mixing instructions at the clinic. Rather than rely on mothers' recollection and estimate of how much solution they had administered, the health worker actually measured, in the home, the amount of solution remaining and then watched the mother mix a new solution. With some modification, we are replicating this study in Lesotho.

Multiple baseline (staggered control group time series design) is a research design particularly well suited to the measurement of individual behavior change in field settings (see Figure 3). It allows plotting behavior (of an individual or a group of people) at a site before and after an intervention occurs. The intervention is staggered over time from site to site. Data can be analyzed horizontally, looking at behavior change from baseline to post intervention at an individual site. Data can also be analyzed across sites, looking for a jump in the level of performance at each site from baseline to post intervention. The consistency of this phenomenon suggests that the intervention and not other events occuring in the environment produced this effect. Because each site functions as its own control, a multiple baseline can show an intervention's effect without using a separate control group. This is particularly useful when measuring program impact because logistics often prohibit simultaneous start-up at multiple sites; and no site needs to be without an intervention in order to serve as an experimental control.

Let us see how these two methods were used to monitor the pilot of an ARI communication program in Honduras. After conducting preliminary research (as described in the following paper by Patricio Barriga), the Honduran Ministry of Health designed a communication strategy for ARI which integrates face-to-face communication between health workers and mothers, with print materials and radio broadcasts. As part of this strategy, health workers were trained both to communicate a basic educational message on ARI and its treatment, and to use participatory teaching methods and a flip chart specially designed for these talks. Figure 4 summarizes the content of the ARI messages, and Figure 5 shows the list of participatory methods health workers learned.

Health workers then used these techniques and the message content whenever they taught mothers about ARI. On a specified day, which was also announced over the radio in some regions, a special contest was held in each clinic to reinforce mothers' new knowledge and skills on ARI management. In front of the group, individual mothers were asked four questions on ARI. If their answers were correct, they were applauded and entered into a drawing for a prize. Three women in each group were winners, and everyone present received a comic book and calendar both of which reinforced the ARI messages heard at the meeting.

The MOH selected eight clinics in four regions to participate in piloting this communica-

tion program before considering doing it nationwide. The research therefore attempted to answer the following questions:

> Did training change how health workers communicated on ARI?
>
> Did the new approach of health workers have any impact on mothers' knowledge of ARI symptoms and management?
>
> Did any information leak into the community and change community awareness?

Health worker training, which was the study intervention, was conducted in one region every month, thus following the multiple baseline design described earlier. In addition, participating clinics received observers monthly to measure health worker communication skills before and after training. The observers also measured changes in mothers' knowledge of ARI with a brief interview before and after health education sessions. Following the clinic sessions, the observers went into the community and requested brief interviews with approximately 20 women, selecting them from every third (town) or every second (village) residence. This assessed the extent to which information had spread informally to women in the community not attending the clinic sessions.

What effect did training have on the health workers' communication skills on ARI? Some data are presented in the following figures. Figure 6 portrays the effect of training on ARI content covered by health workers. Areas 1- 4 on the graph are the 4 regions, 2 clinics each, involved in the pilot. These data points represent the average number of content items observers recorded during health worker ARI talks. Health workers in Areas 1, 2, and 4 show clear and notable increases in the number of appropriate subjects covered in their talks when comparing the baseline (BL) with post-intervention (PI) scores. Area 1 increased from a BL score of 5 to PI scores of 10 and 13. Content increases were particularly marked in the management of mild ARI and the recognition and management of worsening ARI. Area 2 increased from BL scores of 2 and 4 to PI scores of 13, 13, and 12. Area 4 increased from BL of 4, 6, and 7 to PI of 13 and 11. In Area 3, BL scores were 7, 5 and 9 and PI scores of 10 and 13. So the "jump" between baseline and post-intervention in Area 3 was only one point compared to an average across settings of 5.5 for baseline and 11.8 for post-intervention. Nevertheless, the absolute post-intervention scores in Area 3 were on par with the other areas' scores.

Training in interactive teaching techniques were scored in a similar manner and produced similar results even though these behaviors are harder to train (See Figure 7). All areas showed marked increases from baseline to post intervention observations. There were approximately 15 teaching behaviors on the checklist. Health workers scored no more than 4 during BL and scored up to 12 during PI observations. The dip in PI scores seen

in Area 4 was due to a personnel change at one clinic, and one health worker who seemed unaffected by training.

These data suggest that health workers were delivering more information on ARI in a more interactive way, but did such an approach have a discernable impact on mothers' knowledge and practices? Four hundred and fifty-two mothers attending clinic health education talks were given a short pre- and post test. Figure 8 shows the average difference between each mother's pre- and post test. The low difference between their scores during baseline indicates that before the health workers were trained, mothers did not retain much information from ARI sessions.

Post intervention scores however, suggest that the new health talks were communicating more information on ARI than before. Results are most striking in Areas 2, 3, and 4. Average difference in mothers' pre- and post-test scores during BL for Area 2 were 1 and 2, and PI average differences were 8, 7, and 8. Areas 3 and 4 show similar patterns. Results from Area 1 are ambiguous: BL score of 2 and PI scores of 3, 4, 7, and 8. Although there was no dramatic jump in mothers' scores immediately after health worker training, over time their scores were comparable to those in the other areas. Taken together these scores show that after hearing the new health talk, mothers' post-test scores were on average 7 points higher than their pre-test scores. During baseline, this difference was only 2.

The other intended result of the communication strategy was for information on ARI to reach mothers in the community who do not frequent the clinic. Figure 8 shows the changes in community awareness of ARI during the communication program. All areas show gradually increasing scores over time. We would not expect a dramatic jump between baseline and post- intervention conditions in this case because we are measuring the communication effect on a secondary audience, and it takes time for word to spread. Nevertheless, community awareness of ARI symptoms and management does show an increasing trend during the measurement period. Average BL score for all areas was 3 and PI was 7 out of a possible 15 points. This suggests that mothers coming from the clinic were talking about what they had learned and perhaps were showing neighbors the print materials distributed at the ARI educational session. A possible refinement in the communication strategy is to find ways to encourage mothers to "spread the word" to their friends and neighbors.

This pilot of the communication strategy in Honduras provides an example of how training and measurement of important behaviors in both health workers and mothers can be integrated into an ARI communication effort. Other studies demonstrate how behaviorally focused research can be used during assessment, planning and implementation phases of health communication programs.

Let me conclude with the following points:

1. We need to recognize that appropriate adult behavior is critical to saving lives of children with ARI. Therefore, the behaviors of health personnel and parents need to be addressed directly in the design of public health interventions.

2. It is particularly important in ARI communication programs that messages to health personnel and parents be simple and clear, yet address the complexity of symptoms and behaviors necessary to combat ARI.

3. There is a methodology that can help to identify those adult behaviors that need to be encouraged, changed or trained. This methodology allows us to look at the "soft" area of health practices in an empirical fashion, to measure the changes produced by interventions, and to modify communication programs to enhance desired changes.

FIGURE 1

ASSESSMENT OF BEHAVIORS

Conduct Research to Identify:

- Existing Appropriate Behaviors
- Missing Skills
- Existing Inappropriate Behaviors
- Antecedents: What Triggers Practices?
- Consequences: What Maintains Practices?

OBSERVATION OF HEALTH TALK

EPI TALK

Time talk begins _____

Circle each language used in health talk: Gwari Hausa Nupe

Measures of Mothers' Involvement

Q=Question A=Answer S=Song D=Demonstrate (circle if group)

Time		Time	
__:00	_____	__:00	_____
05	_____	:05	_____
10	_____	:10	_____
15	_____	:15	_____
20	_____	:20	_____
25	_____	:25	_____
30	_____	:30	_____
35	_____	:35	_____
40	_____	:40	_____
45	_____	:45	_____
50	_____	:50	_____
55	_____	:55	_____

Check each item mentioned or demonstrated by health worker:

_____ EPI is for Prevention of disease

_____ Pregnant woman gets immunization

____ at 4 months ____ at 5 months ____ other _____

_____ 5 immunizations needed to complete EPI

Parts of body where immunizations given:

____Forearm ____Thigh ____Mouth ____Upperarm

Age of child when immunizations given:

____Birth ____2 mo. ____3 mo. ____4 mo. ____9 mo.

Names of diseases:

____Tuberculosis ____Diptheria ____W. Cough ____Tetanus

____Measles

Side effects of immunizations:

____fever ____discharge ____swelling ____other_____

Treatment of side effects:

____cool fever with water ____give medicine

____wipe discharge ____cool to reduce swelling

____other_____.

_____ Use of vaccination card explained

_____ Mothers encouraged to tell others about EPI

_____ Mothers encouraged to bring others to the clinic

Visual aids used by Health worker:

____flipchart ____brochure given to mothers

____other(s) _____

Time at end of EPI talk _____

FIGURE 3

DIAGRAM OF MULTIPLE BASELINE DESIGN

	Observation Period				
Area	1	2	3	4	5
1	BL	X PI	PI	PI	PI
2	BL	BL X			
3	BL	BL	BL X		
4	BL	BL	BL X		

BL = Baseline Observation X = Intervention PI = Post-Intervention Observation

FIGURE 4

HEALTHWORKER TRAINING

Educational Techniques

- Ask Questions
- Answer Questions
- Personalize the Message
- Instruct
- Demonstrate
- Practice
- Give Feedback
- Reinforce
- Use Flip Chart
- Distribute Print Materials

FIGURE 5

HEALTHWORKER TRAINING

Message Content

Mild Case =
- Recognize Symptoms
- Treat at Home

Aggravated Case =
- Recognize Symptoms
- Take to Clinic or Private Physician

FIGURE 6

MESSAGE CONTENT OF HEALTHWORKER ARI PRESENTATIONS, BY AREA AND OBSERVATION PERIOD;

ARI Control Program Pilot Study, Honduras, 1988

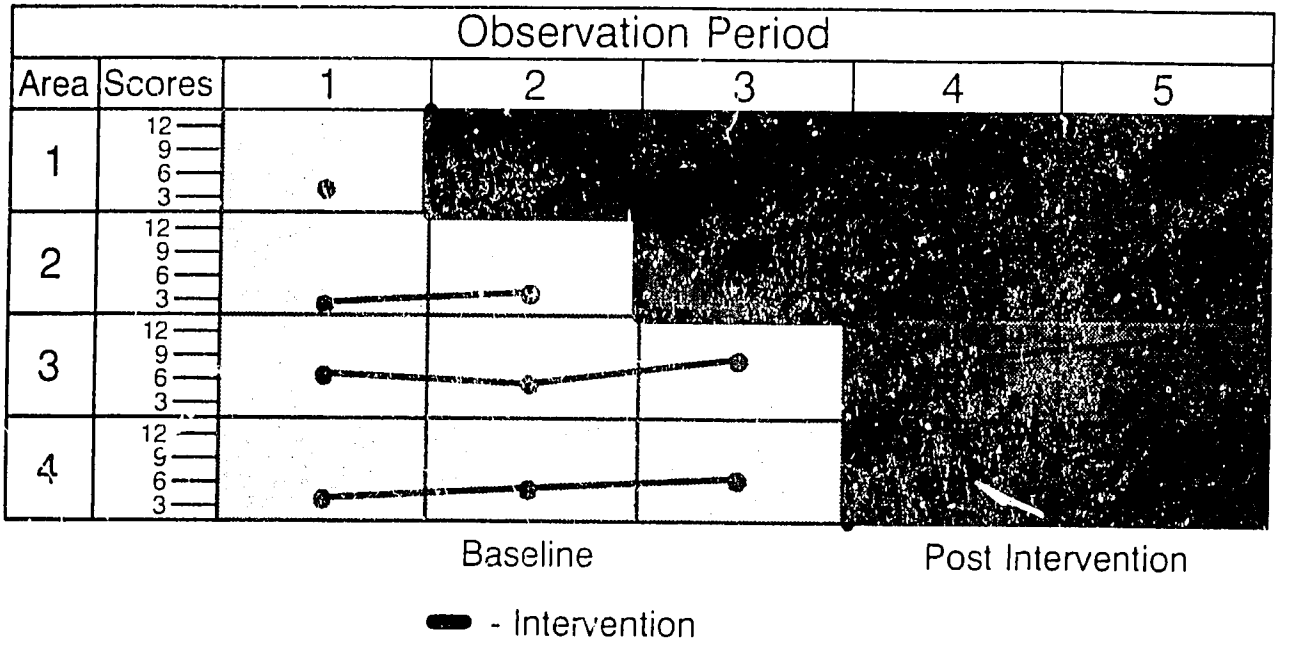


FIGURE 7

EDUCATIONAL TECHNIQUES OF HEALTHWORKER ARI PRESENTATIONS, BY AREA AND OBSERVATION PERIOD;

ARI Control Program Pilot Study, Honduras, 1988

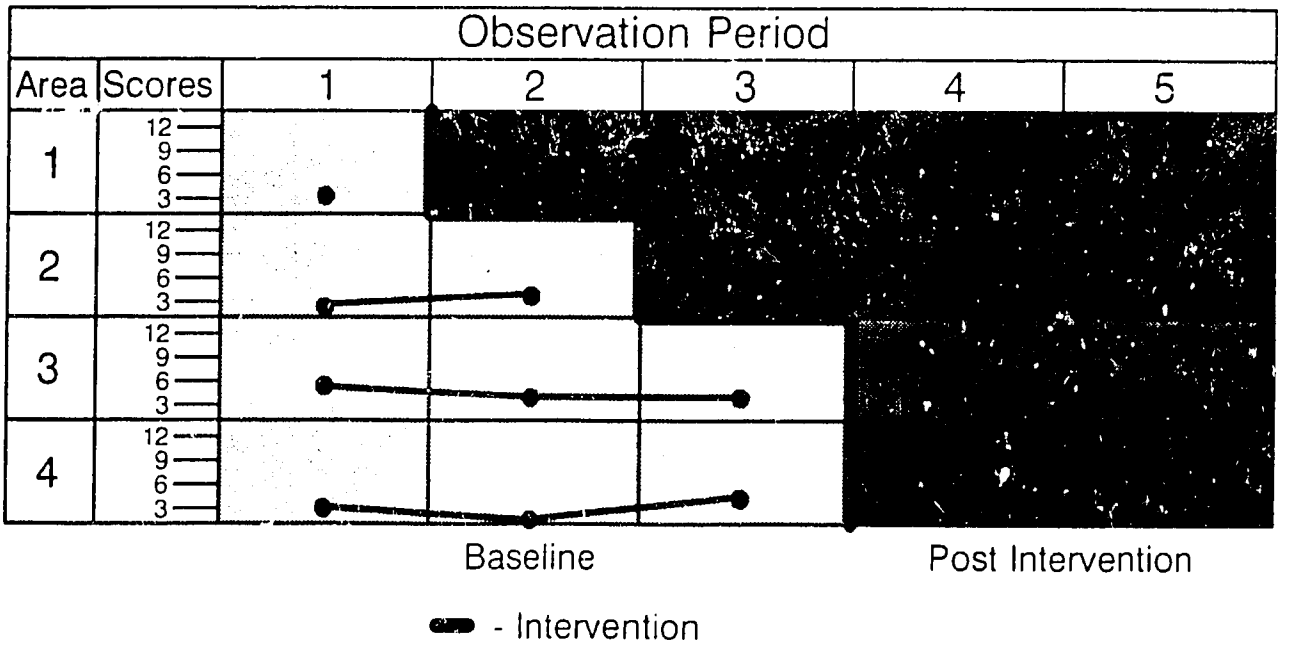


FIGURE 8

MOTHERS' PRE/POSTTEST AVERAGE DIFFERENCES AFTER HEALTHWORKER ARI PRESENTATIONS, BY AREA AND OBSERVATION PERIOD;

ARI Control Program Pilot Study, Honduras, 1988

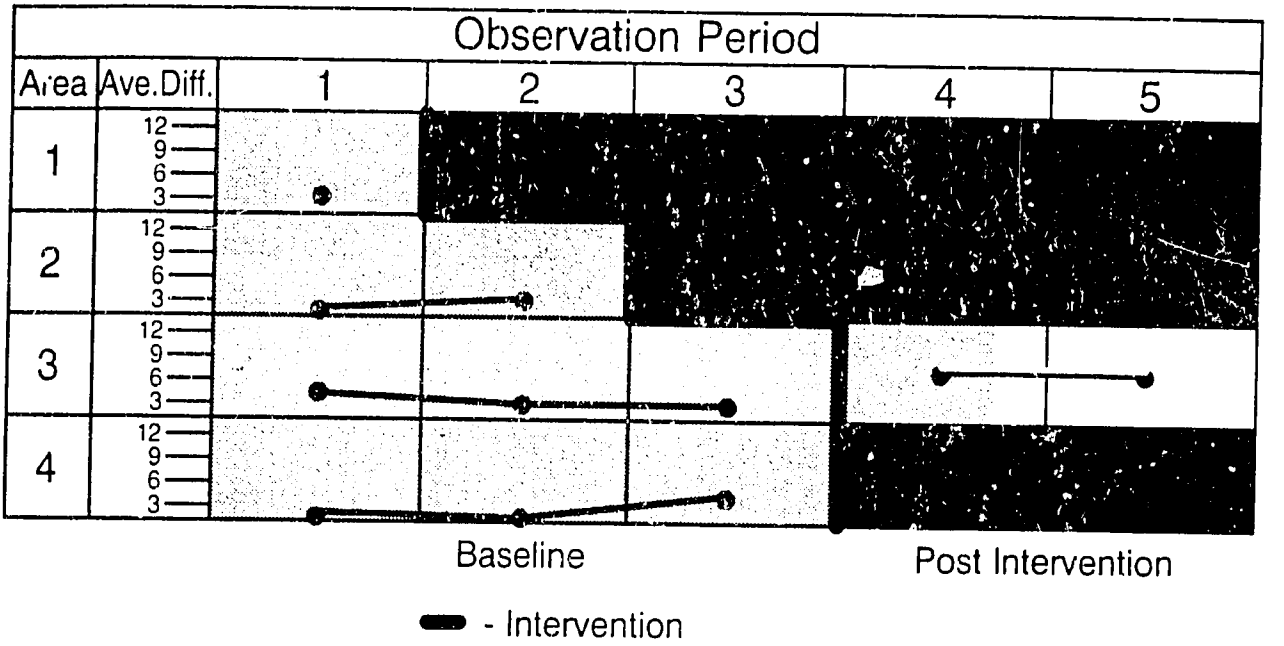
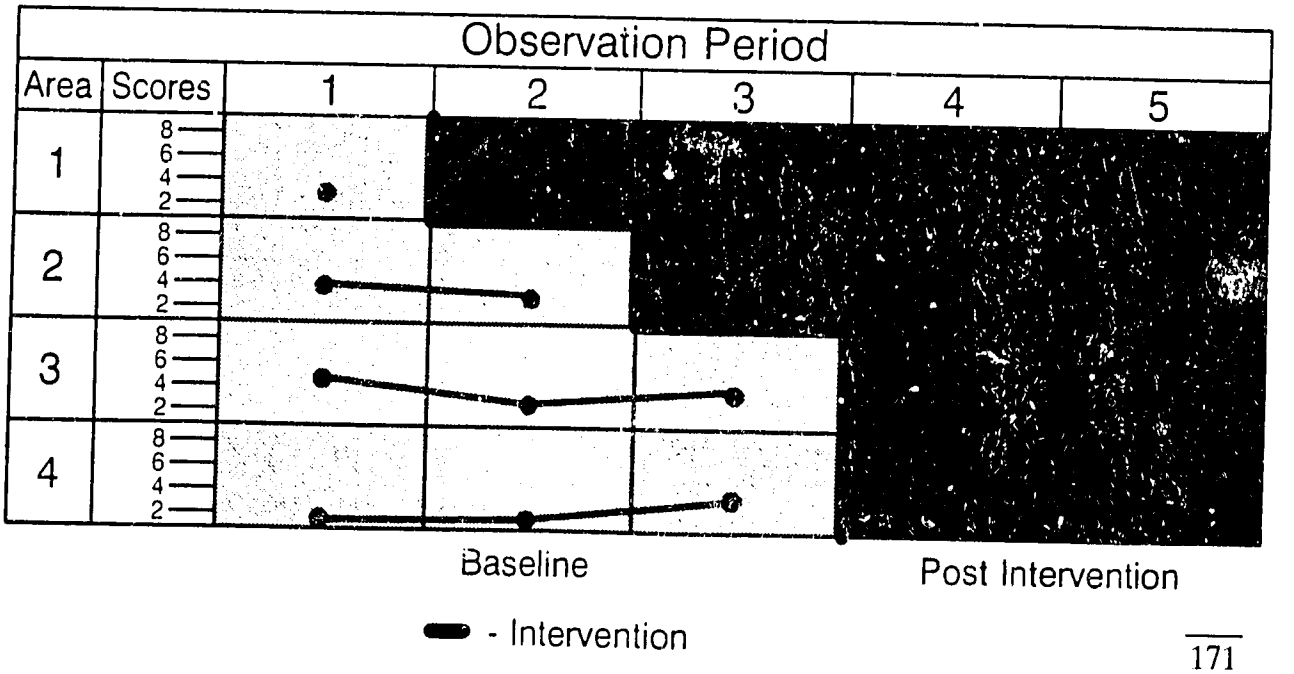


FIGURE 9

RECOGNITION OF SIGNS AND MANAGEMENT OF ARI, COMMUNITY SURVEY BY AREA AND OBSERVATION PERIOD;

ARI Control Program Pilot Study, Honduras, 1988



Field Perspectives on Implementation of an ARI Communications Program in Honduras

Patricio Barriga, Ed.D.
HEALTHCOM

Honduras Context

ARI became the leading cause of death of Honduran children under one year of age in 1987. One third of total deaths of children under five is due to ALRI. In the Nutrition Survey (1987) of 3,406 respondants, 69.6% of the sample referred to an episode of ARI in their children under five in the 15 days preceeding the survey interview. A child suffers an average of five to seven ARI episodes per year, and 30% of the cases treated at hospitals are related to ARI.

The Ministry of Health recognized this problem and asked HEALTHCOM to assist in developing an ARI communication strategy to train health personnel and educate mothers. The first stage of the strategy was to conduct a rigorous assessment of the behavior of mothers as well as that of health personnel.

ARI Developmental Investigations

The health communications (HEALTHCOM) methodology bases decisions on reliable and updated data. So, for the design of the ARI communication strategy, several investigative research activities were conducted. They were as follows: 1) Qualitative research: ethnographic research, focus groups and health workers interviews 2) Quantitative survey (mothers and health personnel); 3) Preference study. While the qualitative research gave the MOH a better idea of the shape of the ARI problem, the survey showed its magnitude. (See Figure 1, pg. 177.)

Qualitative Research: Important questions about mothers' knowledge and practices needed to be answered such as:

- How do mothers perceive infant ARI?
- What kind of signs and symptoms do they recognize?
- Which signs of severity do mothers recognize?
- How do they feed infants with ARI?
- Whom do they consult with when a child has ARI?

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Ethnographic Research: The ethnographic research was conducted in six culturally different communities with a total of 85 informant mothers. The ethnographic research method uses two main instruments: the open interview, which allows the researcher to go as deeply as necessary into a topic, and direct observation, which permits identification of actual behaviors. In this way the MOH was able to establish a popular taxomony for ARI, with a terminology that is shared by almost all Honduran mothers.

Some findings from the ethnography were that most mothers do identify mild ARI even if they do not do much about it. The majority administer inadequate treatment, if any. Some women thought that a runny nose and cough were normal, and stated that the "child was born with a cold". It was also found that mothers tend to consult with traditional healers, older-aged neighbors and pharmacists, before consulting physicians. They lose valuable time in this way, and children can die before entering the health system. (See Figures 2 and 3.)

Focus Groups: Thirty-one focus groups were conducted to identify home treatment and feeding habits during ARI episodes. The groups validated the fact that mothers do very little about ARI and do it too late. Treatment at home seems to be rather a middle and upper class behavior in Honduras.

Almost all informant mothers, both in the ethnographic study and in focus groups, reported that some types of foods are eliminated from an infant's diet when an ARI episode occurs. They basically withdraw food staples that belong to the "cold" food group, among others: beans, rice, avocado, oranges, lemons, grapefruits, butter, and in some cases, fish, pork and beef. They systematically stop the administration of these food items when the child shows any kind of ARI symptoms. They also discontinue the intake of low temperature foods such as ice-cream and cold beverages.

Interviews with Health Personnel: During the ethnographic research, 39 health workers, both traditional and clinic-based, were interviewed. One of the most striking findings from these interviews was that health workers' knowledge and case management skills were not much different from what mothers reported in the community.

During the survey, 84 health workers in clinics were interviewed. Here, the most striking finding was the tendency to use antibiotics when available regardless of symptoms. The mothers reinforced this practice.

Data Utilization

In order to utilize the data collected for program design and message development, we compared the observed behaviors with lists of ideal behavior as specified by pediatricians, and PAHO norms. The results of the comparison produced ideas for behaviors to support

and other behaviors to introduce or modify. A list of ideas and practices was developed and became the basis for the communication plan, described below and was used to develop the content for graphic material, radio spots, and training courses.

The ARI Communication Plan

The ARI communication plan outlines the messages on ARI and the strategies for their dissemination. It also includes the management, logistic and financial aspects that need to be foreseen in order for the ARI communication project to be succesful.

Messages: The thrust of the messages are to teach symptom recognition and a simple appropriate reaction on the part of parents: When to treat at home and when to seek help from the clinic or a private physician. (See Figure 4 for more detail.)

Lottery: Mothers' effort for learning ARI messages and new practices is rewarded through a lottery and educational quiz game at the clinic. All mothers who demonstrate their new learning receive a small prize such as the ARI calendar, the ARI handkerchief, or food staples from the complementary feeding program. During the lottery event, which can take place any where in the community, mothers have also had the opportunity to practice new behaviors like nose cleaning. (See Figure 5.)

Graphic materials and radio spots:

ARI flipchart: A collection of 24 cloth pages serves as a teaching aid for health workers. It contains all the basic messages and related content areas.

ARI brochure for mothers: an eight-page comic-book style hand out with illustrations and simple wording containing the basic messages.

ARI fact sheet for health personnel: the communication strategy is described as well as the main messages they are to deliver.

ARI radio spots: (30 seconds each) contain risk factors, some treatment instructions, and what signs warrant a doctor's referral.

Printed handkerchief: to remind mothers about nose cleaning, an important practice when an infant has a stuffy nose and cannot breathe or eat well.

ARI Program Policy Issues

Developing an ARI communication plan in Honduras has been a learning experience in many respects. Both methodology development and institutionalization were factors that needed a lot of attention before and after the plan was designed. The relationship among international institutions was particularly challenging. While PAHO in Washington was

very suportive from the beginning about the ARI communication strategy, PAHO in Honduras was less enthusiastic. Later we learned that PAHO had a long history of trying to update the Honduras ARI norms without much success. At present, PAHO has provided two short term consultancies to the ARI program. They have agreed that the communication plan is viable but the ARI norms for Honduras need to be revised as a prerequisite for the present communication program to be implemented nation-wide.

UNICEF provided logistical and/or funding support but has not been involved in technical aspects.

The main difficulties that the team had to deal with in terms of policy issues are the following:

1) Lack of adequate communication on sector policy between participating parties (USAID, UNICEF, PAHO and MOH).
2) Lack of technical leadership for this communication process to take place in a productive way.
3) Child Survival programs competing for the use of available resources (funds, vehicles, installed hardware, etc.)
4) Access to PHC personnel (sometimes too busy participating in other types of training and research activities considered to be more important.)
5) Lack of appropriate research skills for developmental investigation and lack of research perspective for data to be used as decision-making input.

The main favorable factors for the development of the ARI communication plan were the following:

1) Previous successful experience of MOH in the development of the ORT communication plan.
2) Presence of a core group formed by physicians and communicators.
3) Support from the MOH political level.
4) Some available financial resources.
5) Basic MOH openness to try out new approaches.
6) Development of a learning community approach as a design and impementation mechanism.

There have been institutional fears and professional reluctancies during the entire process of planning and testing the communication plan. ARI is a new area for systematic health communication to be applied, and so our learning process has not always been easy. The reward nevertheless, will be preventing the deaths of hundreds and thousands of infants due to ARI.

DEVELOPMENT OF THE ARI COMMUNICATIONS PLAN

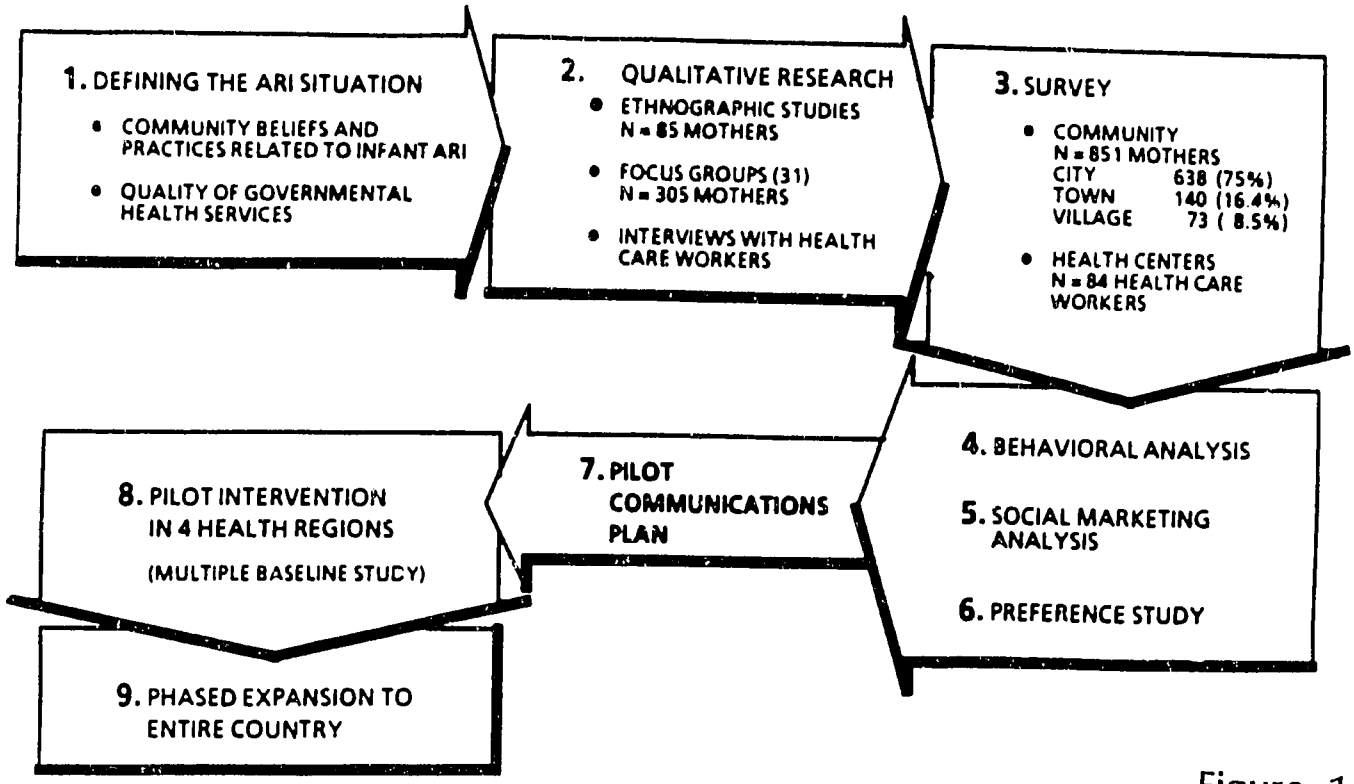


Figure 1

ARI ETHNOGRAPHIC RESEARCH

KEY FINDINGS OF MOTHERS' BEHAVIOR WHEN CHILD HAS AN ARI EPISODE

1. DECREASE FOOD INTAKE
2. DECREASE QUALITY OF DIET
3. STUFFY NOSE LEADS TO LESS DEMAND FOR BREASTMILK / PREMATURE WEANING
4. ADMINISTRATION OF VARIOUS TYPES OF OILS (SOMETIMES FORCING THE INFANT TO TAKE IT)

Figure 2

ARI ETHNOGRAPHIC RESEARCH

PERCEIVING SERIOUSNESS OF INFANT ARI

RESPONDENT MOTHERS: 85

(-) FROM LEAST SERIOUS → TO MOST SERIOUS (+)

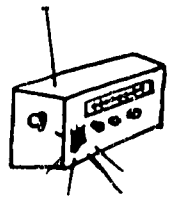
1 2 3 4 5 6 7 8 9 10

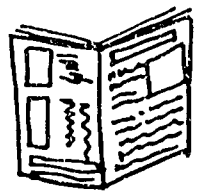
- SNEEZING
- RUNNY NOSE
- BODY PAIN
- STUFFY NOSE
- WATERY EYES
- IRRITABILITY
- UNEASINESS
- MALAISE
- COUGH
- MILD FEVER
- RAPID PULSE
- LISTLESS
- PALE
- LACK OF APPETITE
- "JIR JIR" CHEST NOISE
- DRY COUGH
- MILD EARACHE*
- RASPY VOICE
- RESTLESS SLEEP
- TIREDNESS
- STRONG AND PERSISTANT COUGH
- EARACHE*
- EAR SECRETION*
- TONSIL INFLAMMATION
- "ATAQUE DE PECHO"
- HIGH FEVER
- VOMITING
- DIFFICULT BREATHING
- "AMONIA" PNEUMONIA
- "OGIDO DE PECHO" ASTHMA-LIKE CONDITION
- SUFFOCATION
- DOESN'T URINATE
- "HERVOR BAJO" LOWER CHEST NOISE
- NECK AND STOMACH IN DRAWING
- LIPS TURN BLUE

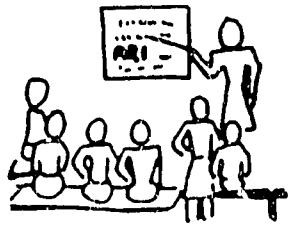
*GENERALLY NOT CONSIDERED TO BE ARI SYMPTOMS

Figure 3

ARI BASIC MESSAGES







- **CUE TO BEGIN CHILD CARE AT HOME**
  - RUNNY NOSE
  - COUGH
- **CARE FOR CHILD AT HOME MEANS:**
  - GIVE A LOT OF LIQUIDS
  - CONTINUE WITH FEEDING
  - CONTINUE WITH BREAST FEEDING
  - CLEAN THE NOSE
  - TO LOWER FEVER, APPLY LUKEWARM COMPRESSES
- **CUE TO SEEK HELP:**
  - PERSISTENT COUGH
  - HIGH FEVER
  - DIFFICULTY BREATHING
  - PUS AND PAIN IN THE EARS
- **IF CHILD GETS WORSE**
  - TAKE CHILD TO THE HEALTH CENTER OR PRIVATE PHYSICIAN

Figure 4

CREATIVE STRATEGY: ARI COMMUNICATIONS PLAN

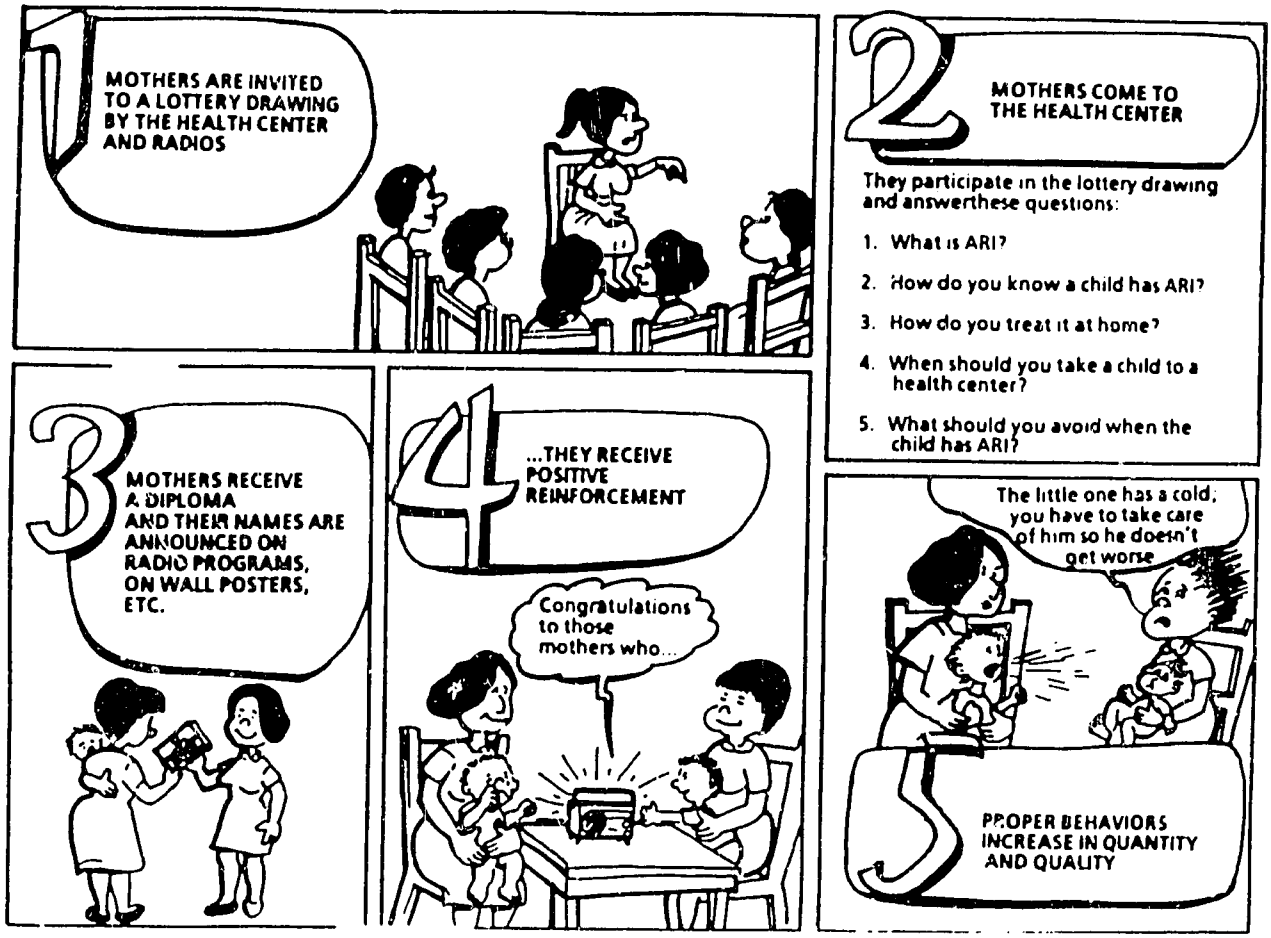


Figure 5

Behavioral Aspects of ALRI Research and Programming

Discussion Summary

The following major points were underscored during the discussion: 1) it is important to focus on the household management of ARI, 2) it is important to develop communication as well as face to face methods to change behavior of both caretakers and health care providers, 3) the difference between the community's explanatory model and the scientific or health provider explanatory model was underscored, 4) there is a need to achieve a better fit between these two templates in order to improve health care outcomes, 5) there are many factors that determine the use of the multiple sources of care available in the community, and program developers should be cognizant of these.

Cultural diversity in explanatory models of disease: One lesson learned pertains to the diversity of the disease models that are found in the different cultures. This is not necessarily discouraging because fairly simple methods can be employed in each situation to clarify what the local explanatory models are. This will involve an understanding of the taxonomy of ARI and require a local research effort. Essentially, ARI recognition and problem solving need to be defined at the household level. This information should be integrated within the general process of implementation of ARI programs.

Gaps in behavioral science as it pertains to ALRI: There are many. What is needed is some simplification and some more specific guidelines of when mothers should seek health care for ARI. Obviously, given the average of 6 ARIs/child <24 mos old/year, there must be some way of identifying the child with more serious disease that needs to be seen by a health worker. What ought to be transmitted to mothers are the recognizable signs of illness that they should be seeking care for, so that they can self refer when they recognize these signs and symptoms (S&S). The medical knowledge is still not available as to what social scientists should be asked to focus on in the behavioral research. The medical and epidemiological scientists should be trying to guide the social scientist toward focusing research on the key S&S.

There are no answers on how to move from general lessons learned in behavioral sciences to the national implementation process. From a research perspective, one of the problems in the interface between the behavioral scientist and health workers is that behavioral scientists tend to have their own personal preference in methods that they use. Behavioral scientists, just like any other scientist, usually develop their methodology and look for a problem to solve with the method that they know. The question for the health worker that is trying to develop an affiliation with a behavioral scientist is how to choose the appropriate scientist for a specific problem. The problem of the choice of specific methods gets even more complicated as the process moves from a descriptive behavioral study at the initial baseline level, to what is required to evaluate an intervention.

Lessons learned in EPI: In most cultures, but particularly in Asia, it is believed that illness is something that the caretaker can do nothing about. It pertains to a different realm, a world of ghosts and ghouls. Measles, again in the subcontinent, is a disease of the

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mother, not a disease of a child. This type of information should be used when attempts are made to improve coverage or management measures. Even if vaccines become available in the near future to prevent serious ALRI, the efficacy of the technology does not ensure its acceptance by the community.

The difference between ALRI and EPI diseases is the time factor. ALRI, particularly in neonates, is an emergency and something has to be done quickly.

Determinants of health seeking behavior: What we know about the patterns of health seeking behavior is that we see children in clinics late. When the child is sick, advice is sought from the mother-in-law, from the neighbors, from the local practitioner, and eventually the child is delivered to the health system. Delays are less affordable with serious ALRI. Why did that mother not use the services? In some cases this may be due the fact that the community does not believe that Western medicine, as it is practiced in these settings, is competent to handle that particular illness.

Bringing templates closer together: The process of learning how to fit together the explanatory models of the community and the health system should be an active area of research. Achieving a fit between western and local templates of illness and response to illness becomes very difficult. Research should focus on what things can be re-interpreted within the local cultural situation to fit with the scientific template and those things which just cannot.

People receive information into an organized perspective on the world. It will not be enough just to say "let's teach them when you see X or Y, then go seek care", because that information X or Y is processed in relation to a whole set of ideas about what to do. Even if successful in teaching people to recognize particular signs and symptoms, the "you go there" part of it does not follow automatically. What ultimately happens depends on how the whole system in which the decision-making is made influences the caretaker's behavior. It may not be up to the caretaker to "go there" if they are part of an extended family, and it is not their decision rather it is up to the head of household. Additionally, one must consider medical pluralism. Why "go there" if there are more attractive alternative sources of care. Why go to the CHW when you could go to the pharmacist, traditional healer or to a neighbor. Day to day issues influence these decisions. Social scientists are not reluctant to focus on them, but place these decisions within a certain cultural framework which needs to be understood as a first step.

Interaction between mother and health provider: Clearly the issue of "why go there" could be examined in a different way, i.e. "why don't they go there?" There is a need to acknowledge and examine what happens between the mother and health provider. Often mothers are offended by many of the things that they have to encounter when they go to the health center. Mothers do not like to go to the hospital in their area, in some cases, simply because they do not like the way they get treated. So they will go there as a last resort, when the disease is later in its course.

Health workers often have the attitude that they have the answer with the one or two things that they need to know and they want to focus only on that. Additionally these practitioners appear to develop negative attitudes or intolerance of cultural practices. For example, they do not see the significance of the charm around the child's neck, instead they rip the charm off the child's neck offending the mother. There is little recognition of the benefits of traditional medicine among the Western health providers

because most likely, they tend to only be exposed to the failures of traditional medicine, that come in late in the course of disease. What they do not see are the traditional healer's successful cases. The emphasis should not only be on about how to educate the mother, but also, how to make physicians, nurses, health educators and village health workers culturally sensitive.

Role of behavioral science studies as a problem solving tool in program implementation: Behavioral studies are generally done in retrospect to identify the obstacles that programmers wish they had known about when the program was being designed. Program managers who have to work on developing and implementing programs, have to be mechanical to solve logistic problems and go from point A to point B. They can find it frustrating to deal with a conceptual system with abstract theories of causality and issues of what people believe makes them sick. Rather than mystify the program manager, the social scientist can collect the necessary information, and work in conjunction with program managers to plot program strategy.

Rather than have anthropologists bring program managers the stories as to why the program did not work, there is a need for a strategy to identify some of these facts before the program is implemented. Taking a proactive approach to cultural beliefs and practices would be a very constructive lesson to draw from the experiences in the implementation of other direct interventions such as malaria or diarrheal disease control. Data gathering needs to be done before or the program is designed. As in marketing a commercial product, the appropriate treatment of ARI needs to be positioned within the socioeconomic context and within the context of local belief systems.

Where CDD and behavioral science seemed to fit together well is in the process of program implementation. This merger often occurred in field settings where training and education materials had to be developed, and words chosen to bridge the gap between the provider and the child's caretaker and community. In that context, there is a shared perception of the problem enabling the different templates to come together.

Cost and Cost-Effectiveness Issues for ARI Case Management

Logan Brenzel, M.S.
Resources for Child Health Project

I would like share with you several thoughts about the cost of treating moderate and severe lower respiratory tract infections (LRTI) and pneumonias and provide some projections about global program costs to the year 2000.

I. What are Cost-Effectiveness Studies and Why are They Important?

Economic and financial analyses are becoming of growing importance in the health sector as the total amount and real value of resources are declining most notably in Africa and Latin America. In some African countries, less than one percent of total government resources is allocated to the health sector. Of the resources available to the health sector, over half is devoted to the curative, hospital sector. The lack of resources for preventive services poses severe constraints on what types of promotive health programs can be implemented and how successful they will be in reaching the target population and reducing the disease burden.

Cost-effectiveness analysis is a tool that can be used to make decisions regarding the allocation of scarce health resources between preventive and curative services, between different health programs or between alternative strategies to delivery the same service, such as immunization services. Those programs or strategies which achieve the greatest outcomes for the least cost are the most cost-effective and are preferable, in economic terms, to those which are less efficient.

Cost and cost-effectiveness analyses are important not only for decision-making about the allocation of health resources, but also for determining the magnitude of recurrent costs that are required each year to maintain the same level of program activities and

I would like to thank Drs. Pierre Claquin and Mark Steinhoff for their comments and suggestions on earlier versions of this document.

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outcomes. The results from cost and cost-effectiveness analysis can be used to plan government, local and donor financing of a health program over time to ensure its sustainability. In addition, these studies may be used by program managers for monitoring and managing program resources by identifying where inefficiencies in service delivery exist and determining which program components utilize a disproportionate share of total program resources and could be managed better and made more efficient.

Within the last decade, cost and cost-effectiveness studies have been undertaken in selected countries for the Expanded Program on Immunization (EPI) and for Control of Diarrheal Disease Programs (CCD). Several manuals and guidelines exist that describe how to collect cost information and how to make cost calculations. USAID has developed a "Guidance for Costing of Health Service Delivery Projects," which has been used in the Philippines to determine the cost of both an EPI and ARI project.

II. Cost and Cost-Effectiveness Analysis for ARI Programs

Acute respiratory infections (ARI) are recognized as one of the leading causes of child morbidity and mortality in developing countries. It is estimated that each child less than five years of age will experience between four to eight infections per year. Moderate and severe pneumonias account for nearly 10% of all cases (4,5,7,11), and the case fatality rate ranges from 13% (Bangladesh) to three percent in Malaysia (7). Control efforts focusing on community-based case management of pneumonia have been undertaken in selected countries within the last few years (Nepal, Tanzania, Kenya, Indonesia, Pakistan, Bolivia and the Philippines). Their impact on childhood mortality rates has been documented, though the extent of these programs' influence on ARI mortality varies (4,11).

Given the encouraging results from field studies, it is likely that a global control program will be launched in the near future. In an age of declining health resources and the inevitable competition for limited resources among other global programs, such as EPI and CDD, it is imperative that cost and cost-effectiveness analysis for ARI control be undertaken in order to ensure that adequate resources are available to begin and maintain achievements at country-level, and that appropriate strategies are selected which will be economically sustainable.

III. What is Known About ARI Costs?

In preparing this presentation, the most striking finding was the paucity of information on the cost of treating a childhood pneumonia or the cost of preventing a death due to LRTI. One field study has been undertaken to date (Bohol, Philippines) and three estimations of program cost have been made (Philippines, Indonesia, and Nepal). The results of these studies are presented in Table 1.

Table 1
Cost Estimations for ARI Control Programs

COUNTRY	COST PER CASE TREATED	COST PER DEATH AVERTED
Bohol, Philippines (a)	$5.15	
REACH, Philippines (b)	$4.37	$131
Indonesia (c)		$ 14
Nepal (d)		$350

(a) as referenced in Turner, Pamela, 1988.
(b) from Turner, Pamela, 1988.
(c) from Frerichs, R.R., and Miller, R.A., Operations Research in Indonesia on diagnosis and management of acute respiratory Infections. Center for Child Survival, University of Indonesia, USAID, unpublished.
(d) personal communication, Nils Daulaire, M.D.

The estimates for the cost per case treated are very similar; although, the Philippine estimate was for a future project with a large training and IEC (information, education and communication) component. Among these three country studies there is a 25-fold difference for the cost per death averted. The high cost estimated in Nepal may be attributable to the use of a cotrimoxazole suspension which was purchased in the U.S. rather than locally, and the high costs associated with providing services to a remote population. Information on the average cost of care for ARI cases was not available in Indonesia, and the researchers based their estimates on discussions with physicians and values published in the international literature. This figure may be low because costs of service delivery were not actually measured (1). The estimate by Turner in the Philippines was developed using "The Asia/Near East Bureau Guidance for Costing of Health Service Delivery Projects" (2,3). This is a comprehensive method for calculating costs and quantifying inputs into the project. This study estimated that an average health worker would spend 12% of their time managing ARI cases in a health facility.

Few field studies have been undertaken on the cost of treating and managing ARI, particularly pneumonias, and the studies which have been conducted do not use the same methods for quantifying program inputs and calculating total costs. Clearly, more detailed analyses using a standard methodology are needed to determine the cost of an ARI treatment program.

IV. Projections of Global Costs by the Year 2000

Crude projections were made to estimate the range in total cost between 1987 and the year 2000 for ARI case management based on what is known so far. These figures should be regarded as estimates, the accuracy of which will improve with more systematic and frequent data collection.

Tables 2 and 3 present the findings of projections of total costs for treating all moderate and severe ARI cases and reducing mortality from LRTI from between 25% to 100%.

The projections were based on demographic data from WHO and UNICEF for 1987 and projected forward until 2000. To estimate the cost per LRTI death averted, it was assumed that ARI deaths accounted for 27% of all childhood mortality and that 70% of all deaths were due to pneumonias (4,5,7,11), resulting in 19% of the child mortality rate from pneumonia in children less than five. The base scenario uses the Philippine data on cost per death averted of $131. The high estimate uses the Nepal data of $350 per averted death and the low estimate is based on an average of the Indonesia data of $14 per death prevented.

Table 2

Summary of Cost per LRTI Death Averted by Region
for Children Less than Five Years of Age
1988-2000
(in million $U.S. 1987)

REGION	AFRICA	ASIA	LATIN AMERICA	MIDDLE EAST	TOTAL	ANNUAL
AT 25% REDUCTION OF LRTI DEATHS						
Base	$396	$925	$96	$347	$1,765	$147
Low	$42	$99	$10	$37	$189	$16
High	$1,058	$2,472	$256	$928	$4,715	$393
AT 50% REDUCTION OF LRTI DEATHS						
Base	$692	$1,851	$192	$695	$3,429	$286
Low	$85	$198	$21	$74	$377	$31
High	$2,116	$4,944	$513	$1,857	$9,430	$786
AT 100% REDUCTION OF LRTI DEATHS						
Base	$1,584	$3,701	$384	$1,390	$7,059	$588
Low	$169	$396	$41	$149	$754	$63
High	$4,231	$9,888	$1,026	$3,714	$18,859	$1,572

FOOTNOTES: Figures based on population data and child mortality rates (0-5 years) found in UNICEF,"State of the World's Children, 1989". Base scenario from Philippines data of $131/death averted. Low scenario from Indonesia data of $14/death averted. High scenario from Nepal estimates of $350/death averted.

Table 2 shows that to reduce deaths from LRTI by 25% until the year 2000, country programs will cost $1.7 billion on average. A reduction of 50% of deaths will require $3.4 billion on average, and to eliminate ARI deaths, an estimate of $7 billion was made. Because of the wide range and sensitivity of total costs to the estimate of the cost per death averted, these figures should be regarded with some degree of caution. On an annual basis, a global ARI program that reduced LRTI deaths by 50% would cost between $286 and $761 million.

A similar projection was made for the cost per case treated of a global program. These estimates were based on the assumption that each child less than five will have between five and eight episodes of ARI per year, and that 10% of those will meet the criteria for

treatment with oral antibiotics (4,5,7). Cost figures per case treated are based on both of the Philippines estimates of $4.37 and $5.15 (high and low scenarios).

Table 3

Summary of Cost per LRTI Case Treated
Children Less than Five Years of Age
1988-2000
(in millions of $U.S. 1987)

REGION	AFRICA	ASIA	LATIN AMERICA	MIDDLE EAST	TOTAL COST	ANNUAL COST
ASSUMING 0.5 LRTI CASES/CHILD/YEAR,50% COVERAGE						
High	$1,478	$4,76[illegible]	$897	$822	$7,962	$664
Low	$1,742	$5,616	$1,058	$969	$9,385	$782
ASSUMING 0.8 LRTI CASES/CHILD/YEAR,50% COVERAGE						
High	$2,365	$7,724	$1,436	$1,315	$12,740	$1,062
Low	$2,788	$8,985	$1,693	$1,550	$15,016	$1,251

FOOTNOTES: Figures based on population data and mortality rates for children less than five years from UNICEF, "State of the World's Children, 1989". The "High" scenario was based on Bohol data cost/case of $5.15 and the "Low" scenario was estimated from Philippine data of cost/case of $4.37. Moderate and severe ARI infections were assumed to occur in 10% of cases, with a range of 5 to 8 episodes per child under five years per year.

Table 3 shows that to treat 50% of cases with oral antibiotics, a global program would cost between $8 and $15 billion for a twelve-year period assuming five to eight episodes per child per year. On an annual basis, a treatment program would cost $664 million to $1.2 billion per year. The analysis assumes that the probability of having ARI does not change between age groups (though we know children in their first year of life have more episodes than older children, and that the incidence of disease does vary by region.)

These results suggest that a global effort to control ARI and to reduce mortality from LRTI will require proper planning and securing of adequate resources. There are few countries that could currently afford the incremental costs of a national treatment program, though initial investment costs such as those for oral antibiotics, could be financed through international sources. These data also highlight the need for more in-depth and careful studies on the cost of treating moderate and severe ARI episodes.

V. Future issues

Clearly, there is a need for more research and field studies in this area. Cost and cost-effectiveness analysis can be used to help determine which approaches to ARI control will be the most economically feasible for a particular country. Specifically, cost-effectiveness analyses could be used to answer the following questions:

1) Is clinic-based or home-based treatment more cost-effective?

2) Which type of oral antibiotic is more cost-effective?

3) What types of supervision strategies are more cost-effective?

4) Which alternative approaches to maternal and parental education are the most cost-effective?

5) What will the incremental cost be of adding ARI control programs to existing preventive programs, such as CDD or EPI?

6) What are the different costs to the household of alternative case management and treatment strategies?

7) What are the potential cost savings for a global program of procuring antibiotics through alternative sources?

8) What is the cost of treating all suspected LRTI with antibiotics, including viral infections, and what potential cost savings would result from better diagnostic capabilities?

The methods developed specifically for analyzing the costs of health programs are available and should be adopted and applied in future studies. It is not acceptable at this point, given the wealth of experience with EPI and CDD evaluations, to conduct studies that do not use established methods. Evaluation of program costs will require data collection on the numbers of inputs used to provide services and the unit price of these inputs. Data on the cost of antibiotics and other inputs do exist at country level. However, information on the quantity of time spent by health and community workers for case detection and management needs to be assessed.

In the WHO handbook on Acute Respiratory Infections: A Guide for the Planning, Implementation, and Evaluation of Control Programmes Within Primary Health Care, a budget format is proposed for ARI programs which does not conform to other accepted costing methods and needs updating. In addition, more direction as to how cost informa-

tion could be used for planning and monitoring an ARI control program needs to be provided.

Often the weakest aspect of cost-effectiveness studies is an accurate measure of program outcomes. For ARI case management strategies, it will be necessary to measure and monitor changes in mortality and the number of cases treated in a more systematic way in the future.

Finally, one possible outcome of this working group could be identification of possible countries where cost-effectiveness analysis of ARI control strategies could be conducted. In addition, a strategy on how the results of these studies will be used by managers to strengthen and improve the operation of the program and to make decisions among alternative approaches remain to be discussed.

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Potential Savings Through Reduction of Inappropriate Use of Pharmaceuticals in the Treatment of ARI

Sally K. Stansfield, M.D.

In areas where little health infrastructure has been developed, there will clearly be new costs incurred as antimicrobials are made available through implementation of ARI control programs. In many developing countries where pharmaceuticals are currently available, however, it is intriguing to consider that a net cost savings may be realized in the reduction of their inappropriate use. This paper reviews the available data regarding the current costs of pharmaceuticals for the treatment of ARI, identifies potential cost savings with improving use patterns, summarizes the evidence that pharmaceutical use patterns can successfully be altered, and identifies priorities for program implementation and operational research.

Inappropriate use of pharmaceuticals may be due to 1) poor prescribing practice, or 2) poor compliance with the medication regimen (including inappropriate self administration, which is widespread in the developing world). Inappropriate prescription practice has been categorized (MSH, 1982) as 1) extravagant prescribing, 2) over-prescribing, 3) incorrect prescribing, 4) multiple prescribing (polypharmacy), and 5) underprescribing.

I. Costs of Inappropriate Use of Pharmaceuticals

Available data regarding the current patterns of pharmaceutical use provide support for the notion that ARI programs might achieve some cost savings. For example, global pharmaceutical expenditures were $94.1 billion in 1985, suggesting that an average of approximately $15 per person per year is spent on medications. However, three quarters of the world's pharmaceuticals are consumed by the one quarter of the population living in the industrialized nations. By comparison, the World Health Organization estimates the cost of an essential drug program at less than $1 per person per year.

In many developing countries, drugs consume up to 40% of the total health budget, with non-essential drug items exhausting a high proportion of resources, leading to inadequate supplies of essential drugs. Drugs for the treatment of ARI account for nearly half of the budget for pharmaceuticals in these countries, yet nearly half of that is spent on non-essential cough preparations.

Although only antimicrobial therapy is life-saving, multiple other drugs are frequently prescribed for episodes of ALRI. In Indonesia, for example, 60% of children with ARI are prescribed four or more drugs, and the average number of drugs per case for children under five is 3.8 (Quick, 1988). Although there are no data to document the effect of multiple prescribing on compliance, the Indonesia study also suggested that mothers were "distracted" by the non-essential drugs and less likely to take the antimicrobial correctly.

Although reduction of such inappropriate multiple prescribing would result in significant savings, reduction of the incorrect prescribing of antimicrobials represents an even more important opportunity to achieve cost savings. Studies in India, Thailand, Bangladesh, and Tanzania estimate that from 24% to 50% of the total pharmaceutical budget is spent on antimicrobial agents (Kunin, 1987). The majority of these antimicrobials are prescribed for problems for which they are not indicated. In Harare, for example, 54% of outpatients receive antibiotics, while 12.3% of those treatments were judged to be "inappropriate", with viral upper respiratory infections being the largest source of error (Stein, 1984). Among inpatients in Bangladesh, 67% of whom were treated with antibiotics, only half of antibiotic prescriptions were judged to be appropriate (Hossain, 1982).

Where data are available specifically for antimicrobial use in treatment of ARI, the conclusions are similar. Antibiotics were used inappropriately in most cases of URI, representing 54% to 61% of costs for URI treatment in Indonesia (Quick, 1988). In a private sector health services system in Peru (Foreit, 1987), it was determined that alteration of outpatient treatment for ("mild to moderate") ARI to conform to the WHO algorithm would result in an 89% reduction in the treatment costs. The excess cost incurred by inappropriate patterns of antibiotic use were calculated at $18.47 to $21.97 per child treated.

Oral antibiotics in Indonesia (Quick, 1988) are prescribed in average quantities of two days' supply, reflecting an inefficient use of drug resources which is also likely to contribute to the rapid evolution of bacterial resistance. Over 80% of children with ARI were treated with antibiotics, although only a minority of these were likely to require such treatment. Many were given injectable antibiotics, although injections were most frequently prescribed for skin, musculoskeletal and nutritional problems, reflecting the frequently inappropriate use of more expensive (and higher risk) parenteral routes of administration for treatment of non-life threatening conditions in developing countries.

The costs of antimicrobial use may be thought of simply as the aggregate of the costs of antimicrobial treatment in many individual episodes of pneumonia. This cost is related not only to the price of the antibiotic, but also to the risk of adverse effects to the individual treated with that antibiotic. However, the benefits of antimicrobial therapy clearly outweigh the risks of adverse effects when the treatment is appropriate.

Table 1
Potential Interventions for the Reduction of
Inappropriate Use of Pharmaceuticals in the Treatment of ARI

Strategy	Intervention
Regulatory	National formularies or essential drug programs Import duties on non-essential drugs Subsidy or tax reductions to encourage local production of essential drugs Regulation and licensing procedures to limit unauthorized sale of antimicrobials National legislation requiring tertiary care facilities to conform to standards for monitoring antibiotic resistance patterns
Managerial	Reliable procurement and distribution network for delivery of effective agents Health information systems which increase provider accountability by linking diagnostic, treatment, accounting, and patient flow data with antibiotic use patterns Control of contact between pharmaceutical representatives and prescribers
Educational	Training of health personnel regarding appropriate diagnosis and treatment Education of consumers to ensure that expectations are consistent with appropriate treatment practice, compliance with the treatment regimen is optimal, and that self administration of antimicrobials is discouraged

Of perhaps greater public health importance, although more difficult to quantify, is the incremental risk to society with each antibiotic use through the development of resistance to these antimicrobials. The evolution of antibiotic resistance is a natural consequence of antibiotic use, however when antibiotic use is "inappropriate" (whether as due to poor prescribing practice or poor compliance with the antimicrobial regimen) the risk of the development of such resistance is undoubtedly even greater.

Although attempts have been made to estimate or model these externalities of antibiotic use patterns (Liss, 1987; Phelps, 1989), the data are not adequate to calculate the external benefits or costs of changing patterns of antibiotic use to reduce the likelihood of the development of resistance. In many countries, policies regarding antibiotic use have been adopted to prevent the development of antibiotic resistance, although there is no clear evidence that any of these recommended policies and practices have been effective (McGowan, 1983; Liss, 1987).

It appears that in the U.S., costs of resistance (based on deaths due to resistant infections) are small relative to the savings attributed to appropriate antibiotic use (CDC, 1980; Liss, 1987). In the least developed countries, however, where the cost of the antimicrobial comprises the bulk of the cost of treatment, the need to prescribe a more expensive antimicrobial because of resistance to cheaper agents could greatly reduce access to lifesaving therapy. The "cost" of possibly hastening the evolution of antimicrobial resistance through inappropriate use should provide added stimulus to support programs to improve global patterns of antibiotic use.

Little is known about factors affecting patient compliance with antimicrobial regimens in either developing or developed countries. A recent review of compliance patterns in the U.S. (Hayes, 1988) suggests that approximately half of patients comply with the medication regimen as prescribed, while a study in Belgium found 40% of compliance patterns to be "potentially harmful". More information is needed from the developing world regarding current patterns of compliance, culturally-specific determinants of compliance behavior, and the effectiveness of interventions in enhancing compliance with medication regimens.

II. Evidence That Antibiotic Use Patterns May Be Altered

Three strategies for intervention to alter the use of pharmaceuticals include: 1) educational, 2) managerial, and 3) regulatory. Examples of interventions using each of these three strategies are provided as table 1. There are few studies documenting the success of interventions to improve pharmaceutical use patterns through improved patient compliance with medication regimens. Prescribing practice, however, has been successfully altered in both the U.S. and developing countries. Soumerai (1987) reviewed data on the effectiveness of programs to alter prescription practice, and concluded that effective interventions included face-to-face education, consumption analysis and feedback, and structured drug order forms. It was also suggested that essential drug lists and standard treatment schedules, when accompanied by education, may be effective in improving prescription practice.

Other studies from industrialized countries have suggested that some communications strategies (particularly print materials alone) to provide physician education have little impact on prescribing practice (Lewis, 1970; Haynes, 1984). However, the drug industry in the U.S. has provided documentation that its marketing strategies effectively alter physician prescribing behavior (Hemminki, 1975; Plumridge, 1973). Such profit-motivated pressures on prescribing practice represent a clear risk in developing countries where regulation of such practices is often weak or non-existent.

In Indonesia, where analysis of drug consumption patterns revealed overuse of six antimicrobials and two analgesics, feedback to the decisionmakers and providers resulted in a

reduction over a two year period from 42% to 25% of the total pharmaceutical budget for these medications (Quick, 1988). In another area in Indonesia (PRICOR, unpublished data), where interventions were undertaken to improve prescribing practice, none of 159 cases of URI received antibiotics, while 65-100% of patients in "control" areas continued to receive antibiotics for such infections.

Studies in the U.S. (Ray, 1985; Soumerai, 1986) have shown the effectiveness and durability of educational efforts to improve prescribing practice, and documented a cost to savings ratio of 1.8 to 3.0. Available evidence from Panama and Colombia (Avorn, 1987) suggests that such programs may be similarly cost-effective in developing countries.

In countries where there is little health infrastructure or regulation of pharmaceutical use, patient demand factors become the major determinant of the choice and regimen for antibiotic use (Van der Geest, 1984). Patients' expectations are also an infrequently documented (though likely very important) determinant of prescribing practice when a trained provider is present. In the U.S., for example, it is frequently suggested that despite efforts to assure that providers are educated, the prevailing expectation that patients will shun physicians who fail to prescribe antibiotics on demand continues to encourage inappropriate use of antimicrobials (Avorn, 1987).

There is also evidence that prescribing practice may be affected by drug shortages, leading to underprescribing and inappropriately low doses (Justice, 1986). Even when the formal health service delivery system is poorly supplied with pharmaceuticals, there are often medications available through other networks. It is clear that no program to improve the use of pharmaceuticals can neglect the importance of the informal and, occasionally, illegal networks of drug distribution, such as in the markets or through traditional healers (Weisberg, 1982; Ferguson, 1981; Van der Geest, 1984; Mitchell, 1985).

III. Priorities for Program Implementation and Operational Research

The issue of cost savings through reducing inappropriate use of pharmaceuticals in the treatment of ARI is best addressed in the operational setting of an ARI control program. Careful attention to program design will assure that the monitoring and evaluation systems are adequate to provide the required information. This "operational research" should be planned to address key issues, including:

- Strengthen the monitoring and evaluation of national ARI programs to document baseline and program expenditures for ARI treatment (including through traditional healers, illegal purveyors of antibiotics, local pharmacies).

- Compare the effectiveness of cost containment through improving pharmaceutical use patterns only for an ARI program with that due to improving pharmaceutical use for horizontal (primary health care) programs, addressing issues including:
  - the overlap of the clinical syndromes of ARI with other life-threatening infections in children as a barrier to the proposed "pneumonia medicine" labelling in an effort to limit the use of ARI program antimicrobials.
  - the threat that supplies of antimicrobials for ARI programs will be used inappropriately in treatment of other diseases unless such other inappropriate use is simultaneously addressed.

- Systematic examination of the impact of regulatory, managerial and educational interventions to improve antibiotic use patterns, such as:
  - efficacy of national formulary and essential drug programs in improving pharmaceutical use patterns and cost containment.
  - impact of import duties, subsidies, tax credits and other economic incentives on pharmaceutical use for ARI treatment.
  - effectiveness of single and combination interventions on prescribing practice.
  - impact of patient education and effectiveness of communications strategies in altering pharmaceutical use patterns, including methods to identify culturally-specific beliefs which alter patient expectations, service utilization patterns and compliance behavior.

- Investigate field methods for research use in assessing patient compliance, such as through interviews, special packaging of medications, or urine testing.

- Document baseline and improve national capacity to monitor antibiotic resistance patterns. Policies should be examined for their impact on prescribing practice and on the evolution of antibiotic resistance. Also of concern, however, is that policies designed to reduce the evolution of resistance do not interfere with the continuing availability of newer antibiotic preparations through providing economic disincentives to research and development.

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WORKSHOP AGENDA

Wednesday, August 2, 1989

Overview of Ongoing Research Activities and Plans
Moderator: James Heiby

9:15	Summary of AID activities	Pamela Johnson
9:30	Summary of WHO activities	Michael Merson
9:45	Summary of UNICEF activities	Nyi Nyi
10:00	Break	

Epidemiology of ALRI: State of the Art
Moderator: Beatrice Selwyn

10:15	ALRI Nosology and Standards	Mark Steinhoff
10:30	The BOSTID studies	Patricia Charache
10:45	ALRI in the first three months of life	Steven Berman
11:00	Hierarchy of Risk Factors: feasibility and status of primary prevention	Robert Breiman
11:15	Available and Potential vaccines for ALRI control	Neal Halsey
11:30	Discussion	
12:30	LUNCH (Conference Room)	

Community-based ALRI Treatment
Moderator: Harry Campbell

1:30	Population based epidemiology of ALRI deaths in developing countries	Claire Broome
1:45	Overview of the Six Case management studies	Robert Black
2:00	Review of the Operation of the Clinical Algorithm	Steven Redd
2:15	Field perspectives on implementation of an ALRI case management in Jumla, Nepal	Nils Daulaire
2:30	Discussion	
3:30	Break	

Dovetailing issues related to ALRI research and programming
Moderator: John Clemens

3:45	Therapeutic implications of the presence of wheezing in infants with ALRI	Robert Welliver
4:00	Antibiotic overuse and development of resistance	Thomas O'Brien
4:15	Field perspectives on Implementation of an ALRI communications program in Honduras	Patricio Barriga
4:30	Discussion	

Thursday, August 3, 1989

Operations Research in ALRI programs
Moderator: Steven Berman

9:15	Operational research framework	James Heiby
9:30	Operations research on service delivery	Stewart Blumenfeld
9:45	Operational difficulties in ALRI Control in Indonesia	Art Reingold
10:15	Discussion	
10:45	Break	

Behavioral Aspects of ALRI Research and Programming
Moderator: Carl Taylor

11:00	Overview of the anthropologic perspective	Gretel Pelto
11:15	Methodologic strategy for determining the caretaker's preception of ALRI	Carl Kendall
11:30	Case study in Lesotho: What mothers recognize as ALRI	Ruth Wilson
11:45	Behavioral studies for the development of ALRI communication strategies	Judith Graeff
12:00	Discussion	
12:30	LUNCH (conference room)	

Cost-effectiveness Projections:
Moderator: Robert Kim-Farley

1:30	Cost and cost effectiveness issues for an ARI case management program	Pierre Claquin
1:45	Potential savings in reduction in inappropriate antibiotic use	Sally Stansfield
2:00	Recent survey findings on drug and antibiotic use	John Tomaro
2:00	Discussion	
2:15	Summary of the BOSTID research program	Floyd Denny
2:30	Break	

Meeting Summary: Research and Implementation Priorities
Moderator: Ann Van Dusen

3:00	Presentation of workshop recommendations	Anne Gadomski
3:20	Modification and additions	

Meeting held at:
Stanford Research Institute, Suite 700
1611 North Kent Street
Rosslyn, Virginia 22209

WORKSHOP PARTICIPANTS

Patricio Barriga, Ed.D.
Resident Advisor - HEALTHCOM
Apartado Postal 140
Tegucigalpa
Honduras

Steven Berman, M.D.
Associate Professor, Pediatrics
University of Colorado Health Sciences Center
4200 East Ninth Avenue
Denver, CO 80262

Robert E. Black, M.D., M.P.H.
Professor and Chairman
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street, Room 5515
Baltimore, MD 21205

Stewart Blumenfeld, Dr.P.H.
Deputy Director, PRICOR Project
Center for Human Services
7200 Wisconsin Avenue
Bethesda, MD 20814-4204

Robert Breiman, M.D.
Chief, Epidemiology Section
Respiratory Diseases Branch
Division of Bacterial Diseases
Center for Infectious Diseases
Centers for Disease Control
1600 Clifton Road, N.E.
Atlanta, GA 30333

Claire Broome, M.D.
Chief, Meningitis & Special Pathogens Branch
Center For Infectious Disease
Center for Disease Control
Atlanta, GA 30333

Harry Campbell, M.D.
Programme Officer
Acute Respiratory Infection Control Programme
1211 Geneva 27
Switzerland

Patricia Charache, M.D.
Director of Microbiology
Johns Hopkins Hospital
Meyer B1 - 193
600 N. Wolfe Street
Baltimore, MD 21205

Pierre Claquin, M.D.
Associate Director for EPI
REACH/ John Snow Inc.
1100 Wilson Blvd., 9th Floor
Arlington, VA 22209

John Clemens, M.D.
Associate Professor
Center for Vaccine Development
University of Maryland
School of Medicine
Baltimore, MD 21201

Kathleen Cravero, M.D.
Project Officer ORT/CDD
UNICEF
3 UN Plaza
New York, NY 10017

Nils Daulaire, M.D., M.P.H.
The International Center for the
Prevention and Treatment of Major
Childhood Diseases
P.O. Box 168
Hanover, NH 03755

Floyd Denny, M.D.
Professor of Pediatrics
Program for Health Promotion and
Disease Prevention
University of North Carolina
Chapel Hill, NC 27599

Anne Gadomski, M.D., M.P.H.
Adjunct Assistant Professor
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205
and
Assistant Professor
University of Maryland
Department of Pediatrics
Western Health Center
700 West Lombard Street
Baltimore, MD 21201

Sandy Gove, M.D.
Programme Officer
Acute Respiratory Infection Control
Programme
1211 Geneva 27
Switzerland

Judith A. Graeff, Ph.D.
Senior Program Officer
HEALTHCOM
Academy for Educational Development
1255 23rd Street N.W.
Washington, DC 20037

Neal A. Halsey, M.D., M.P.H.
Director, Division of Disease Control
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205

Carl Kendall, Ph.D.
Assistant Professor
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205

Chris Kjolhede, M.D., M.P.H.
Assistant Professor
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205

Martita Marx, Ph.D.
Associate Technical Director
PRITECH
Suite 700
1655 N. Fort Myer Drive
Arlington, VA 22209

Michael Merson, M.D.
Director, Control of Diarrhoeal Disease Programme
World Health Organization
1211 Geneva 27
Switzerland

David Nichols, M.D., M.P.H.
Director, PRICOR Project
Center For Human Services
7200 Wisconsin Avenue
Bethesda, MD 20814-4204

Dr. Nyi Nyi
Director Program Division
UNICEF
3 UN Plaza
New York, NY 10017

Thomas O'Brien, M.D.
Associate Professor of Medicine
Harvard Medical School
Microbiology Laboratory
Brigham and Womens Hospital
Boston, MA 02115

Ellyn W. Ogden, M.P.H.
Project Administrator
STATISTICA, Inc.
1800 N. Kent Street
Suite 1050
Arlington, VA 22209

Gretel Pelto, Ph.D.
Professor
Department of Nutrition Science
University Of Connecticut
U Box 17
Storrs, CT 06268

Stephen Redd, M.D.
Medical Officer
Technical Support Division
International Health Program Office
CDC Building 16, Room 208, Mailstop F03
1600 Clifton Road N.E.
Atlanta, GA 30333

Art Reingold, M.D.
Associate Professor
University of California at Berkeley
Earl Warren Hall
School of Public Health
Berkeley, CA 94720

Beatrice J. Selwyn, Sc.D.
Associate Professor of Epidemiology
International Family Health Module
University of Texas
School of Public Health
P.O. Box 20186
Houston, TX 77225

Sally Stansfield, M.D.
Consultant
171 Minto Place
Ottawa, Ontario
Canada, KIM 0B6

Mark Steinhoff, M.D.
Associate Professor
Department of International Health
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205

Carl Taylor, M.D., Dr.P.H.
Consultant
The Johns Hopkins University
School of Hygiene and Public Health
Institute for International Programs
103 East Mount Royal Avenue
Baltimore, MD 21202

Robert Welliver, M.D.
Professor of Pediatrics
Division of Infectious Diseases
Children's Hospital of Buffalo
219 Bryant Steet
Buffalo, NY 14222

Ruth P. Wilson, Ph.D.
Anthropologist
Technical Support Division
International Health Program Office
CDC Building 16, Room 208, Mailstop F03
1600 Clifton Rd., N.E.
Atlanta, GA 30333

U.S. Agency for International
Development
Science and Technology
Office of Health
SA-18
Washington, DC 20523

Office of Health
Ann Van Dusen, Ph.D.
Robert Clay, M.P.H.
Caesar Gonzmart
Jeffrey Harris, M.D.
James Heiby, M.D., M.P.H.
Pamela Johnson, Ph.D.
Robert Kim-Farley, M.D., M.P.H.
F. Eugene McJunkin
Anne Tinker, M.P.H.

Office of the Science Advisor
John Daley, Ph.D.
Alexandra Fairfield, Ph.D.

Latin America and the Carribean
Paula Feeny, M.P.H.
Jack Thomas, M.P.H.
Mike White, M.D. (USAID/Haiti)