ACUTE RESPIRATORY INFECTIONS IN THE DEVELOPING WORLD:
PRIORITIES FOR PREVENTION, TREATMENT, AND CONTROL

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Acute respiratory infections (ARI) have received increasing recognition as an important cause of morbidity and mortality among children in developing countries. Of the estimated two to five million deaths each year due to ARI, 90 to 98% might be prevented if case-fatality ratios could be reduced to those observed in the industrialized world. However, efforts to address the problem have been hampered by the heterogeneity of clinical presentations and causative organisms. While specific strategies have been developed to reduce deaths due to diarrhea and dehydration, malaria, vaccine-preventable diseases and undernutrition, the other major causes of death among children under five, it is more evident for ARI that no single technical intervention available today will dramatically diminish mortality. Yet significant reduction of the still appalling infant and child mortality rates in the developing world will be difficult to achieve without a strategy to avert deaths due to ARI, now the leading cause of death among children under five (1).

In May 1979 the thirty-second World Health Assembly adopted a resolution recognizing the importance of respiratory infections as a cause of death in infancy and childhood. The Assembly further recommended the promotion and conduct of national control programs that would give high priority to research on simple and effective methods for preventing, diagnosing and treating ARI. Recent advances in our understanding of the etiology and epidemiology of ARI, combined with directed research to fill the gaps, may provide the basis for the design of intervention strategies to address this major cause of death among infants and young children.
AID currently has several activities addressing acute respiratory infections, with both direct interventions and research now in progress. The Agency's Child Survival Strategy, working toward the goal of universal immunization by 1990, provides hope of averting up to 25% of the infant and child deaths due to ARI through the delivery of measles, pertussis, BCG, and diphtheria vaccines.

Most of the remainder of the mortality due to ARI is due to the bacterial pneumonias, especially those caused by the pneumococcus and H. influenzae. The importance of improving the newly available vaccines against these bacteria for use in infants and children was underscored by the report of an Institute of Medicine Committee on Issues and Priorities for New Vaccine Development, which selected a pneumococcal vaccine as the highest priority. In addition to funding trials to improve the existing vaccines against measles and pertussis, AID's Vaccine Development and Health Research PASA with the Public Health Service is currently exploring the opportunity for investment in the vaccines against the pneumococcus.

The Board on Science and Technology in Development (BOSTID) of the National Research Council is conducting an AID-funded research program to investigate the epidemiology, clinical features and diagnosis of ARI in the developing world. Child survival projects in Egypt and Nepal have addressed the infant and child mortality in those countries by incorporating low technology ARI treatment algorithms and control programs into their primary health care activities. The information provided by these activities will guide the development and selection of future intervention strategies.
Given our current limited knowledge of the pathogenesis, prevention and treatment of ARI, we should use available technologies maximally to reduce infant and child mortality due to these infections, and provide resources for the necessary research. Directed research efforts should be selected which will improve our limited understanding of the epidemiology of ARI in the developing world, refine our strategies for the prevention and treatment of these infections, and ensure the development of new vaccines.

Any effort to reduce the death toll due to ARI would best emphasize program components which will fill gaps and complement or strengthen the ongoing efforts of WHO and PAHO. The campaign to improve child survival should not overlook the opportunity to significantly reduce infant and child mortality by alleviating ARI's "international tragedy of almost unprecedented magnitude (103)."

Even limited interventions in LDCs have resulted in ARI-specific mortality reductions of 36 to 84% (40, 53-54), suggesting that simple, readily transferable technologies may save literally millions of lives each year. ARI represents the next major challenge and hope of reducing the still unacceptable infant and child mortality rates in LDCs.
1. INTRODUCTION

Acute respiratory infections (ARI) have received increasing recognition as an important cause of morbidity and mortality among children in developing countries. Of the estimated two to five million deaths each year due to ARI, 90 to 98% might be prevented if case-fatality ratios could be reduced to those observed in the industrialized world. However, efforts to address the problem have been hampered by the heterogeneity of clinical presentations and causative organisms. While specific strategies have been developed to reduce deaths due to diarrhea and dehydration, malaria, vaccine-preventable diseases and undernutrition, the other major causes of death among children under five, it is more evident for ARI that no single technical intervention available today will dramatically diminish mortality. Yet significant reduction of the still appalling infant and child mortality rates in the developing world will be difficult to achieve without a strategy to avert deaths due to ARI, now the leading cause of death among children under five (1).

In May 1979 the thirty-second World Health Assembly adopted a resolution recognizing the importance of respiratory infections as a cause of death in infancy and childhood. The Assembly further recommended the promotion and conduct of national control programs that would give high priority to research on simple and effective methods for preventing, diagnosing and treating ARI. Recent advances in our understanding of the etiology and epidemiology of ARI, combined with directed research to fill the gaps, may provide the basis for the design of intervention strategies to address this major cause of death among infants and young children.
The classification and management of ARI in the industrialized world is founded upon radiologic and microbiologic data, in addition to the clinical history and physical examination. ARI syndromes, which are complex clinical conditions of varying etiology and severity, have been categorized primarily on the basis of anatomical location. Common diagnostic categories for uncomplicated ARI with etiologic and clinical correlates are detailed in table 1. Although acute upper respiratory infections, such as the common cold, are of great public health importance due to their high incidence, only the acute lower respiratory infections such as pneumonia and bronchiolitis are major causes of mortality. Although little information is available from developing countries, the available data suggest that over 75 percent of ARI deaths are due to pneumonia, both bacterial and viral (2).

Bacterial pneumonias, which by far account for the majority of deaths due to ARI in the developing world, remain the most treatable of causes of severe ARI. They may also become, with emerging vaccine technologies, preventable. This review and the recommended strategy to avert infant and child deaths due to ARI will focus primarily on the prevention and treatment of the bacterial pneumonias. However, the probable role of antecedent upper respiratory infection in the pathogenesis of the bacterial pneumonias requires that consideration be given to the epidemiology of all ARI in the design of strategies.

II. ETIOLOGIES

Accurate data regarding bacterial and viral etiologies for ARI in infants and young children are lacking because of the difficulty in making clinical and microbiologic diagnoses.
Frequently children with pneumonia have few signs of pulmonary infiltrate or consolidation. The microbiologic diagnoses are often obscure because the young child swallows secretions and cannot produce sputum.

Cultures of blood, pleural fluid, or pulmonary exudate obtained by lung puncture yield the most reliable bacteriologic diagnoses. However, blood culture data may be positive in as few as 10% of cases of bacterial pneumonia (3), pleural fluid is most often absent, and clinicians are justifiably reticent to consider lung puncture for routine diagnosis because of the risk of serious complications of the procedure. Therefore, most epidemiologic studies of ARI in children have relied primarily upon cultures of the upper respiratory tract. Such culture data may be unrevealing or frankly misleading due to high rates of carriage of bacterial pathogens.

In addition, even minor variations in specimen collection and management will dramatically alter isolation rates and the range of organisms identified. Although a few studies in developing countries have reported culture data based on needle aspiration of lung, most have used techniques which would be expected to skew the culture results, for example by failing to use appropriate techniques for viral isolation or selective media which permit isolation of H. influenzae. Additional difficulties in establishing a single etiologic agent in a given infection arise with the frequent finding of multiple potential pathogens in a specimen of sputum, blood or even pleural fluid.

Table 2 presents a composite of the bacterial culture data from several etiologic studies of ARI in the developing world (2, 4-6). Since no direct data are available on the proportions of deaths due to the bacterial and viral agents of ARI, the
assumption was made in preparation of the table that the number of deaths due to each agent is proportional to the frequency of its isolation from acute lower respiratory infections. Mean values were used in the calculations where reported figures varied widely. The resulting disease burden estimates for ARI were employed by the Institute of Medicine in preparation of the report of the Committee on Issues and Priorities for New Vaccine Development (New Vaccine Development: Establishing Priorities, Volume II, Diseases of Importance in Developing Countries).

Shann (7) points out, in his review of 1011 previously untreated children studied in twelve lung aspiration studies of pneumonia in less developed countries, that bacteria were isolated in 632 (63%). The most frequent isolates in his study also were H. influenzae and S. pneumoniae, with S. aureus often isolated only after the child had received antibiotics. Twenty-eight isolates of S. pneumoniae from 25 cases were serotyped. The commonest serotypes were type 6 (24%), type 4 (12%) and type 19 (12%), which is consistent with data obtained among children in the U.S. (8). The high proportions of non-serotypable strains and the low proportion of H. influenzae type b observed in this study have not been reported by other investigators. In view of the potential importance of these findings, especially for prevention of ARI with vaccines, this study will need to be corroborated in other developing countries.

Further epidemiologic investigations will also be required to define the role of Chlamydia trachomatis, Mycoplasma pneumoniae, Ureaplasma urealyticum, and Pneumocystis carinii, which may be important causes of pneumonia among children in LDCs (9).

The most frequent viral isolates from the bulk of etiologic studies (2, 4, 7, 10-13) among patients hospitalized with acute
lower respiratory infection are RSV, parainfluenza viruses, adenovirus and influenza viruses. The role of cytomegalovirus, the isolation of which is associated with severe ARI, requires further definition as either a primary pathogen or reactivated infection in the setting of lower respiratory infection due to another organism. The isolation of viruses, particularly adenoviruses, herpes and enteroviruses, must be interpreted with caution as they are frequently found both in the absence of respiratory symptoms and in conjunction with other viral or bacterial pathogens (9).

Lepow et al. (14) suggested that the isolation of multiple pathogens may reflect the possibility that precipitation of bacterial pneumonia in patients without underlying disease may require multiple simultaneous infections to overwhelm normal pulmonary defense mechanisms. In general, a history of antecedent viral infection can be obtained from about one third of adult patients (15). Coincident viral and bacterial pulmonary infections, well known with influenza and measles, are probably more frequent than is commonly appreciated (16).

The undernourished and often chronically ill children of LDCs may well be more susceptible to the descent of bacteria from the upper to the lower respiratory tract to cause pneumonia, even in the absence of antecedent viral infection. Although cultures of the throat or nasopharynx are usually not a good reflection of the etiology of lower respiratory infection, the agents of bacterial pneumonia probably originate from among the potentially pathogenic commensals in the upper respiratory tract. The purulent nasal discharge so frequently seen among the children of developing countries bears some testimony to the suspicion that the carriage rate of these pathogens may be higher among these children. Indeed, one third of North
American children less than 5 years of age carry the pneumococcus (17). On the other hand, 95% of healthy children were found to be pneumococcal carriers in Papua New Guinea, and over 90% were culture-positive for *H. influenzae* (18). Half of the infants studied in Papua New Guinea had acquired *S. pneumoniae* at age three weeks, while in North America the mean age at acquisition was six months (13).

III. EPIDEMIOLOGY

A. Incidence

Incidence data for ARI in the LDCs are sparse. Comparison and compilation of results from investigations on ARI in different countries is all but prevented by wide variations in study design, case definitions and culture techniques. The few community-based prospective studies performed suggest that ARI is very common. The incidence observed in urban areas in LDCs is 4-8 episodes per child per year (19-22). This is comparable to the incidence documented in longitudinal studies in the U.S. (23-24) among both middle class and lower class urban children under age five. The rate is inversely related to age, peaking at 8 to 9 infections in the first two years of life and dropping to 3 to 4 per year by school age. ARI accounts for between 20 and 60 percent of all outpatient pediatric consultations (25-26), and 12-45 percent of admissions of children to hospitals in LDCs (7, 25, 27-28).

B. Mortality

ARI causes more than a third of all deaths among children under five in many countries (2, 5, 7, 27), frequently surpassing
diarrhea as the leading cause of death (1), especially in Africa where nearly one-half of deaths among children under five are due to ARI (2). In the Santa Maria Cauque study in Guatemala, 50% of neonatal and 52% (30 of 58) of post-neonatal deaths were ascribed to pneumonia during the period from 1964-1972 (29). It has been estimated that two to five million deaths each year are due to ARI (1, 30-32).

Although the incidence is comparable to that in the developed world, the greater public health import of ARI in LDCs is manifest in the mortality rates, which are 10 to 50 times greater (25-26). Prospective studies in Matlab, Bangladesh, for example, have documented acute lower respiratory infection mortality to be 10.4 per 1,000 infants and 1.6 per thousand for children one to four years of age (33). A cohort of 10,000 people living in Tari, Papua New Guinea were prospectively followed to reveal a mortality due to acute lower respiratory infection of 30 per 1,000 infants and 4 per 1,000 among children aged one to four (18). In some areas of Bolivia and Brazil, respiratory diseases (primarily infectious) are listed as the cause of death for 40-44 per 1,000 infants (25).

C. Risk Factors

The wide variations in both the incidence rates and case-fatality ratios for ARI are often linked with varying risk factors which may suggest strategies for prevention or control of these infections. Risk factors associated with either increased susceptibility or increased risk of mortality due to an episode of ARI are summarized in table 3.

The inverse relationship between ARI mortality and age is explained by both the increased incidence of infections as well
as higher case-fatality ratios among infants (after 3-4 weeks) and young children (2, 4, 34-35). The incidence of ARI among males has been observed to be approximately 1.5 times that among females (4), although case-fatality ratios are comparable. Poor nutritional status also adversely affects both the incidence and case-fatality ratios for ARI (4, 36-39). Studies in Costa Rica document a twelve-fold greater incidence of pneumonia in undernourished children (457.8 per 1000) when compared with children of normal weight for age (37.0 per 1,000) (36). At Narangwal, India, a doubling of mortality, including that due to ARI, was observed for each decile below 80% weight-for-age (37). Vitamin A deficiency, which often accompanies protein-calorie malnutrition, results in keratinization of the respiratory epithelium, thus presumably decreasing local resistance and increasing the risk of bacterial colonization and infection (38-39). Low birth weight, seen in from 20% to 40% of infants in many LDCs, also increases the risk of ARI morbidity and mortality (40).

Although there is good evidence for a protective effect of breast-feeding in the prevention of diarrhea, data on infant feeding practices and the incidence of respiratory infections are somewhat contradictory. Although several studies summarized in a recent review (41) have failed to document any protective effect of breastfeeding, others have found both a decreased incidence (42) and decreased case-fatality ratio (43) for respiratory infections among breast-fed infants and children.

Low socioeconomic status and crowding have been well documented as risk factors for respiratory infections in the developed world. Studies in India (28) and Haiti (author, unpublished data) have also demonstrated an increased incidence of ARI among children in lower socioeconomic groups and in more crowded
households. Both poverty and crowding, however, may be proximate measures for other known or as yet unrecognized risk factors.

There are conflicting data on the incidence of ARI among persons with nematode or trematode infections which are characterized by pulmonary migration of larvae or flukes. It has been suggested that the associated local inflammation and damage to lung parenchyma might predispose to bacterial superinfection. An Indonesian study of 85 Ascaris-infected children compared to 100 uninfected children matched for age and sex documented no significant difference in the prevalence of respiratory tract infection (44). Blumenthal and Schultz (45), on the other hand, reported a point prevalence of respiratory infections of 46.7% in Ascaris-infected patients compared with 13.3% in uninfected controls (p 0.05). Interpretation of these studies is complicated by the fact that parasitic pneumonia itself may cause a picture clinically and radiographically indistinguishable from bacterial pneumonia (46). In addition, no attempt was made to control for other variables such as undernutrition or poverty which are associated with intestinal nematode infections and clearly predisposing factors for ARI.

Increasing concern has developed about the effects of indoor air pollution due to combustion of biomass fuels in cookfires. There is an expanding literature from the industrialized world on the effects of maternal smoking on low birthweight and passive smoking on the respiratory health of children. Although more data are needed from LDCs, there is reason to suspect that indoor cookfires may increase infant and child mortality via an increased incidence of low birth weight through maternal exposure and/or through an increased incidence of ARI (47).
IV. DIAGNOSIS

Accurate identification of the organisms causing ARI provides information which is important for patient management and public health planning, including the selection of strategies for prevention and control and the expenditure of resources in areas such as vaccine development. The paucity of epidemiologic data regarding etiologies of ARI in the developing world stems, in part, from the lack of rapid and simple diagnostic technologies which are inexpensive and robust enough for use under sometimes adverse conditions. The cost and difficulties of logistical support of the classical culture techniques for both bacteria and viruses makes these approaches to diagnosis inappropriate for individual patient care in most LDCs at present.

Clinicians often select a "best guess" diagnosis from an assumed spectrum of regional disease problems. Diagnoses and management decisions must often be guided by the recognition that it is perhaps safer to treat with antibiotics in the absence of diagnostic data. PHC workers have understandably overused antibiotics when they fear that an undiagnosed bacterial pneumonia may go untreated.

Although hospital-based surveillance of important respiratory pathogens and periodic epidemiologic studies may be conducted with the extensive support necessary to perform bacterial and viral cultures, there remains a need for reliable rapid diagnostic techniques which can be used for both surveillance and clinical care.
Bacterial polysaccharide antigens of *H. influenzae* type b in the serum or urine of patients with pneumonia can be detected by tests including counterimmunoelectrophoresis, latex agglutination or coagglutination. These tests have also appeared promising for the detection of capsular polysaccharide of *S. pneumoniae* in patients with invasive pneumococcal disease. Further work needs to be completed to adapt these and other diagnostic methods, such as the enzyme-linked immunosorbent assay (ELISA), for use as rapid, simple "dipstick" tests for these pneumonias. To guide the choice of antibiotics, the development of a similar diagnostic technology for staphylococcus would also be of great assistance.

In addition to the immunodiagnostics, recombinant DNA technologies are being used to develop specific nucleic acid probes for both bacterial and viral pathogens. These methodologies, although promising for the future of rapid diagnosis of ARI, require resolution of problems of specimen preparation and adaptation to non-radioactive indicator systems before they show hope of being practical for use in the primary health care setting.

Adaptation of these emerging technologies will be required to provide simple, reliable and inexpensive methods for diagnosis of the major pathogens of ARI. Such technologies will improve diagnostic capabilities in peripheral areas, however classical microbiologic techniques must also be available in reference centers for quality control. These rapid diagnostic technologies will provide hope of rationalizing the clinical care of patients with pneumonia and the use of antibiotics, will offer important data for surveillance, and provide the needed measurements of efficacy for trials of vaccines.
The purpose of discriminating among cases of ARI is not to make a diagnosis, but to decide upon management. Management decisions for the care of patients with ARI are based not on anatomic diagnosis, but on the severity of illness. WHO recommends that primary health care workers in LDCs classify ARI by the signs and symptoms pertinent to two "binary" management decisions: 1) whether to treat with antibiotics or not, and 2) whether to treat as an outpatient or refer for inpatient care.

Cough and fever are very common symptoms among children. Clearly, not all of these patients require antibiotic treatment. There have been few prospective studies to determine the best clinical predictors of the presence of bacterial pneumonia and the need for antibiotics. Among patients with (48) and without (49) chest radiographs, tachypnea (ie, rapid breathing) noted by either the mother or the health worker appears to be the best predictor of the need for antibiotic therapy in a child with a cough. Although more studies are needed, the subjective assessment of the health worker appears to be almost as accurate as measuring respiratory rate (49).

The limited available evidence suggests that among patients who are treated with antibiotics for presumed pneumonia, chest indrawing (ie, intercostal or subcostal retractions) is the best clinical predictor of a high risk for mortality and the need for inpatient care (49). The inclusion of cyanosis, inability to feed and changes in consciousness as indications for admission probably ensures that most children at high risk of mortality will be admitted for more intensive therapy.
WHO has developed an algorithm for the diagnosis and treatment of ARI (50), and their Technical Advisory Group on ARI has proposed a management-oriented classification of ARI into three categories for use by community health workers or other outpatient health service providers (51). That classification system, adapted for health workers with less than six months training, is summarized in table 4. The supportive treatment recommended for all cases of ARI includes fluids, continued feeding as tolerated, neutral environmental temperature, antipyretics, and clearing any nasal or ear discharge. Steam humidification, bronchodilators and oxygen may also be used in supportive care at referral facilities. Although the prevalence of bronchospastic pulmonary disorders varies widely geographically, management algorithms may be adjusted accordingly if wheezing is a frequent presenting finding.

Acute upper respiratory infections may be complicated by sinusitis, otitis media or bacterial tonsillitis. Acute lower respiratory infections may be complicated by seizures, changes in consciousness, severe dehydration, cardiac failure or shock. The presence of these complications may require alteration of the management of the primary ARI syndrome, as noted in table 4.

When a moderate or severe episode of ARI is diagnosed by these criteria, the indication for antibiotics has been established. Reports of reduced susceptibility to penicillin among the agents of bacterial pneumonia are frequent from the developed countries. However these antibiotic resistances are often relative and are less frequent in the developing countries. Respiratory infections caused by pneumococci or H. influenzae in LDCs can be considered susceptible to adequate doses of parenteral penicillin, oral ampicillin or
trimethoprim-sulfamethoxazole (51). Parenteral penicillin is generally the first drug of choice for initial treatment because of its effectiveness and low cost. At the first referral level, however, at least one second-line antimicrobial is recommended to be available for cases which fail to respond to the first-line antibiotics.

A summary of the efficacy, toxicity and administration of antimicrobials for bacterial pneumonias has been prepared by WHO's Technical Advisory Group on Acute Respiratory Infections and is adapted in table 5. The choice of antimicrobials for routine clinical management of pneumonia will vary from country to country depending on regional drug supplies and the existing data regarding antibiotic sensitivities of the prevailing bacterial pathogens. Additional major factors affecting the choice of antibiotics include the assessed expectation of patient compliance, cultural acceptability of routes of administration, and the level of training of primary health care workers.

Monitoring and supervision of antibiotic usage to reduce indiscriminate or inadequate use as well as surveillance for antimicrobial resistance is a component of any program for adequate case-management of ARI (52). The adequacy and consistency of supplies of antibiotics is a recognized concern in order to maintain community confidence in ARI treatment programs.

WHO's Programme on ARI has produced guidelines for a prototype ARI program (25) as well as principles for implementation and evaluation of such programs. A network of WHO ARI Programme investigators provide data on the benefits of selected
interventions, which serve as a guide for the design and implementation of other LDC ARI Control Programs.

There is limited but growing evidence that such ARI control programs can reduce mortality. Access to appropriate antimicrobial therapy at a health center or hospital was associated with an 84% reduction in the case-fatality ratios for untreated moderate and severe acute lower respiratory infection in Goroka, Papua New Guinea (5). McCord and Kielmann prospectively documented that implementation of an in-service training program for Family Health Workers in the management of ARI resulted in a 45% reduction in the mortality due to pneumonia (53). Preliminary reports from an ARI control program in Chandigarh, India, demonstrated a 65% reduction in the case-fatality ratio for acute lower respiratory infections (54). Similar ARI interventions integrated into PHC systems using community or village health workers have been initiated in the Bagamoyo district in Tanzania (40) and in Bohol in the Philippines (55), as well as in several Latin American countries.

In view of our limited preventive tools for reduction of ARI-specific mortality, some portion of our resources for ARI control will have to be focused on improved case management. Attention is being devoted to assuring that mothers' knowledge is adequate to assure appropriate symptomatic management and continued feeding during mild ARI, and accurate identification of moderate to severe ARI which should be brought to the attention of the PHC system. As suggested by the Bagamoyo data (40), families' failure to recognize life-threatening episodes of ARI was a major obstacle to improved treatment of these episodes. The importance of maternal education as a sine qua non of improved case management and reduction of ARI mortality cannot be overemphasized.
VI. PREVENTION

Preventive approaches to reducing ARI mortality remain the most practical. However, the limitations of our knowledge of the epidemiology of ARI in developing countries interfere with the selection of preventive strategies. Relatively little is known about the cost-effectiveness of such interventions as improved nutrition, environmental factors, health education or specific treatment regimens in prevention of ARI mortality.

Immunization, on the other hand, represents a simple technology of proven effectiveness in the prevention and control of many infectious diseases. Vaccine delivery, although not straightforward in LDCs, is accomplished at the convenience of the health delivery system. Improved case management of ARI, on the other hand, requires a primary health care infrastructure to respond at each time and place "selected" by omnipresent pathogens.

Measles, diphtheria, BCG and pertussis vaccines are clearly effective preventive measures for these infections of the respiratory tract. It has been estimated that deaths due to these four diseases account for up to 25% of the total mortality associated with ARI (52). Although these vaccines have been recommended for universal delivery in national immunization programs, it is estimated that less than 40% of children are fully protected. The technologies for vaccination against the other bacterial and viral agents of ARI have generally been slower to develop. Although chemoprophylaxis is sometimes suggested as a preventive strategy for the respiratory infections of viral etiology (56), the serious questions about
the feasibility and benefits of this strategy in the developed world only loom larger in LDCs. Antiviral agents will not soon be cost-effective interventions for the prevention or even treatment of viral diseases in developing countries, except perhaps for severe infections such as the viral hemorrhagic fevers in tertiary care centers.

A. Current EPI Vaccines

1. Measles

The primary strategy of choice for reducing the mortality of respiratory infections due to measles is clearly immunization. Despite the existence of an effective vaccine, there are still 1.5 million annual deaths among children under five which are "associated" with measles (57). As with other AEs, there is some suggestion that measles may often simply represent the final "fatal blow" to a child who is already "earmarked" for early death by undernutrition or other chronic disease. Investigators differ in their conclusions about the relationship between premeasles nutritional status and measles mortality, although it appears that severe undernutrition is associated with an increased measles mortality (58).

In addition to the fatalities due to acute measles infections, the intercurrent bacterial, herpesvirus and adenoviral pulmonary infections which occur within 28 days of the onset of measles are an important cause of morbidity and mortality among these undernourished children (59). Prolonged diarrhea is also a complication of measles which is associated with increased mortality but not reported as ascribable to measles (60). These sources of error in underestimation of measles-associated late mortality suggest that the impact on overall mortality of measles immunization may be larger than reported.
The interference of maternal antibody with the response to measles vaccine has influenced the selection of nine months as the optimal age for vaccination. Measles control is hampered by the fact that an estimated 20-30% of cases occur prior to that age in some areas of developing countries (61). The increasing likelihood of natural measles infection as maternal antibodies wane and the higher likelihood of vaccine failures while those antibodies are still present leave a narrow window for the optimal age of vaccination. Efficacy trials are underway with a human diploid attenuated measles vaccine which has demonstrated the ability to stimulate antibodies as early as four months of age in the presence of maternal antibodies (62).

The expense and logistical difficulties in establishing an effective cold chain for the delivery of the current chick embryo measles vaccine represent a strain on the limited health budgets and infrastructure for many developing countries. A more heat-stable dried live-attenuated measles vaccine has been prepared for administration in inexpensive single dose syringe/vial (Ezeject R) which may ease vaccine distribution outside the cold chain. (63). More information is needed regarding the safety, cost and logistical problems incurred with these alternative vaccine preparations and their routes or schedules of administration.

Through these short-term research activities and stepped-up vaccination programs, measles may be controlled or even eradicated. More basic investigations must continue, however, in order to improve the stability and decrease the cost of delivery of measles vaccine. Efforts should also continue to define and clone the genome for the protective epitopes of the measles virus, perhaps permitting the eventual production of
subunit vaccines which will have fewer adverse effects and obviate the need for a cold chain.

2. Diphtheria

The virtual elimination of diphtheria in developed countries is a testimonial to the effectiveness of immunization. There is no controversy about the selection of immunization as the primary strategy to reduce mortality due to diphtheria. Although there remains some discussion about the minimal number of doses of diphtheria toxoid to achieve protective immunity, its delivery with tetanus and pertussis vaccines will likely continue to determine immunization schedules.

3. Pertussis

Pertussis is perhaps the least well understood of the vaccine-preventable diseases of childhood. Studies of its epidemiology and pathophysiology as well as investigations of vaccine efficacy are hampered by the difficulty of clinical and laboratory diagnosis. In Europe and Japan, where acceptance of DTP recently decreased due to fear of vaccine-related adverse neurologic effects, a resurgence of epidemic disease was observed. Vaccine efficacy for fully immunized children has been estimated at 75-90% in the industrialized nations (64). In endemic areas in the developing world, however, transmission rates are such that many children are infected and many deaths occur prior to the usual age of complete immunization. These infants and younger children also fail to manifest the characteristic whoop, making clinical diagnosis and vaccine efficacy difficult to establish.
Infant and child mortality preventable by pertussis vaccination is also difficult to estimate due to the frequently prolonged nature of the illness. The Machakos project (65) reported a case-fatality ratio of 1.26% (12 deaths of 953 cases) although 2.2% died within three months of infection. WHO, however, has estimated the case fatality ratio at between 4% and 15% for infants (66). In a study of 203 pertussis cases in Nigeria, (67) cough was often prolonged (over 5 wks in 43%) with associated anorexia and vomiting resulting in weight loss of 5% or greater in 22% of the children. Prevention of pertussis-associated undernutrition may, therefore, additionally prevent later deaths among these children by reducing their susceptibility to death by other causes.

Immunization is clearly the intervention strategy of choice. Resistance to completion of the immunization series in LDCs relates to mothers' observation of local adverse effects and fever rather than the fears of adverse neurologic effects often voiced in the industrialized world. Despite the limitations of the existing vaccine, the benefits clearly outweigh the side effects in areas of higher transmission. To protect younger infants who are at greater risk of mortality, WHO recommends initiation of the DTP series at six weeks (68). Such a schedule would leave a child fully protected by age 3.5 months.

Improvements in the present vaccine aim to reduce adverse effects. Single component (pertussis toxin or LPF) and two-component (LPF with filamentous hemagglutinin or FHA) vaccines represent second generation acellular pertussis vaccines which are now undergoing clinical trials in Sweden. Initial clinical trials by a U.S. manufacturer of a Japanese acellular pertussis vaccine combined with standard diphtheria and tetanus toxoids suggest that such vaccines will be
immunogenic and cause fewer adverse effects than the current vaccines. Studies of the role of the specific proteins in the induction of protective immunity may also provide a rationale for production of vaccines with fewer adverse effects using synthetic or cloned antigens or epitopes. One research institution is currently attempting to achieve expression of a cloned library of pertussis DNA fragments. Such efforts may identify additional vaccine candidates.

4. Tuberculosis

Although pulmonary tuberculosis usually has an insidious onset in the developed world, its presentation in LDCs, particularly in children, is commonly that of acute pneumonia. BCG, or bacillus Calmette-Guerain, is the live, attenuated strain of bovine tubercle bacilli which is used in many countries to induce specific immunity against tuberculosis. Although it does not reduce the chance of natural infection, it does reduce the severity of tuberculosis infection once natural infection occurs. It is of greatest use among infants in countries with a high prevalence of infection where exposure of children is common. Although its efficacy continues to be controversial, it appears that BCG confers 60 to 80 percent protection against the development of clinical tuberculosis (69).

Chemoprophylaxis is commonly used to prevent clinically apparent tuberculosis in persons recently infected or with dormant infection. However, in developing countries where identification of clinical cases is often delayed for many months, isoniazid chemotherapy of such persons is not as effective in preventing and controlling the spread of tuberculosis. Under these circumstances, BCG vaccination of infants at birth represents an important protective measure against acute tuberculosis.
Additional work is required to improve the quality and standardization of BCG vaccines and to continue the basic research necessary to identify any specific surface antigens which induce protective immunity as candidates for subunit vaccines against tuberculosis.

B. Other Bacterial Vaccines

1. *Streptococcus pneumoniae*

The pneumococcus, along with *H. influenzae*, is a primary cause of ARI morbidity and mortality. Both of these organisms probably owe much of their virulence to their polysaccharide capsule. These capsular polysaccharides protect the organisms from opsonization and phagocytosis by masking cell wall structures which would otherwise activate the alternative complement pathway. Immunity to pneumococci therefore requires serum anticapsular polysaccharide antibody to activate opsonization.

Although 8 to 10 capsular types comprise most of the strains causing invasive infections in the developed world, eighty-four capsular polysaccharides have been identified. Data on the frequency distribution of capsular types in developing countries are sparse, such that it is difficult to predict the protective efficacy of the 23-valent vaccine which has been formulated based on primarily US data. Some capsular types, among them types 2 and 25, have been included in the vaccines based on their prevalence in Africa and the South Pacific (8). However, several types which are known to be important causes of invasive pneumococcal disease in LDCs are not included in the 23-valent vaccine formulated for use in the U.S.
A second obstacle to consideration of the use of pneumococcal vaccine to reduce ARI mortality in developing countries is the fact that the most common capsular types causing invasive disease in infants and children are poorly immunogenic in the younger age groups (70). Type 3 on the other hand, which is an infrequent cause of infection in children elicits an excellent antibody response in infants two to three months of age, demonstrating this age group is capable of producing an immune response to polysaccharide antigens. The polysaccharide of pneumococcus type 14, which, along with types 6, 19 and 23 account for 50-60% of pneumococcal infection in the first years of life, shares some structural similarities with the A, B, O blood group isoantigens (71). It has been postulated that the inability to distinguish pneumococcal from self tissue antigen at a time of immunologic immaturity may account for the frequency of these infections and the poor immunogenicity of these polysaccharide antigens in early life (72).

One hopeful approach to improving the "T-independent" immune responses elicited by polysaccharide vaccines is to covalently bind them to a protein conjugate which may alter the mechanism of the response. Avery and Goebel (73) documented in 1929 that the polysaccharide became protective against lethal challenge in laboratory animals after protein conjugation. Conjugates of both H. influenzae type b and pneumococcal type 6A polysaccharides to protein carriers have elicited protective antibody in animal models which have no response to the unconjugated polysaccharide preparations (74-76). Reinjection of these conjugates elicits a booster antibody response to the polysaccharide, suggesting that the immune response is rendered "T-independent" by the conjugation. Immunogenicity trials with H. influenzae type b and pneumococcus type 6 polysaccharides...
conjugated to diphtheria and/or tetanus toxoids in adult volunteers induce higher levels than the polysaccharides alone (77). A study in Eskimo children of H. influenzae type b vaccine given with DTP at 2, 4, and 6 months of age is underway.

Selection of a conjugate protein for a polysaccharide vaccine may be determined by the concurrent need for other immunizations and/or the adjuvant or "carriers" effect of the associated protein. The delivery of these polysaccharide vaccines in association with the DTP series or BCG vaccination is being explored. Immunization of mothers in developing countries to prevent neonatal tetanus suggests the intriguing possibility that polysaccharides delivered in conjunction with tetanus toxoid during the last trimester may provide sufficiently high titers to confer transplacental passive protection against bacterial ARI during early infancy.

A study in Papua New Guinea (78) documented a 32% reduction in the incidence of pneumonia among children immunized with the current pneumococcal vaccine who were less than 17 months of age at the time of vaccination. The effect was observed during the five months following immunization, and the overall efficacy in reducing mortality due to pneumonia was 88% (based on 9 deaths, p = 0.033). A similar protective efficacy was observed in a small trial of mothers vaccinated during pregnancy whose infants were followed for the incidence of pneumonia (78). However, no difference in overall mortality was observed. Results of a larger study in Papua New Guinea will soon be reported to support an estimated efficacy of 31% to 59% in reducing mortality due to acute lower respiratory infections (Riley, et al). Other studies being completed in Burkina Faso may lend more support to such approaches to the protection of neonates.
Although capsular polysaccharides currently appear more promising, another avenue for exploration for immunoprophylaxis against *S. pneumoniae* infections are subunit preparations which are not type-specific. More research may be warranted, for example, to explore the use of noncapsular bacterial components such as phosphocholine or pneumolysin which may confer protection against all pneumococcal disease (77).

2. *Hemophilus influenzae*

Like the pneumococcus, *H. influenzae* cell wall proteins are shielded from complement activation and opsonization by capsular polysaccharides. The most common respiratory infection in the industrialized world caused by *H. influenzae* is otitis media, from which the unencapsulated strains of the organism are most frequently isolated (79). However, virtually all the isolates from infected tissues or blood of patients in the developed world with invasive infections such as epiglottitis, pneumonia or meningitis are of capsular type b (Hib). The type b polysaccharide, or polyribose ribosyl phosphate (PRP), was thus selected as the best candidate for the *H. influenzae* vaccine which has recently been licensed in the U.S. for use in children over two years of age.

There are two major causes for the widespread doubt about the potential efficacy of the PRP vaccine in preventing ARI mortality in the developing world. First, only a fraction of the isolates from patients with pneumonia in Papua New Guinea were found to be capsular type b strains (7). Although of concern, these results require corroboration in other developing country settings. The importance of these nonserotypable or other non-b strains of *H. influenzae* may be further questioned.
in view of the fact that they were often isolated in conjunction with Hib, and that they are relatively rarely isolated from blood cultures.

The second major obstacle to the use of polysaccharide vaccines for the prevention of ARI mortality is their poor immunogenicity in the younger age groups which are most vulnerable to such infections. Placentally transmitted Hib antibody wanes over the first 2 to 3 months of life (79), although the antibody in infants whose mothers were boosted at 34 to 36 weeks gestation persisted at a protective level for 12 months (80). Among infants and children aged two to eighteen months, who have the highest attack rate for Hib diseases, those who respond with protective levels of antibodies are found to lose their protective titers over a period of one and a half years. In addition, there is no evidence of either immunologic memory or impairment of immunologic response on revaccination (81). Children over three years of age have a higher percentage of responders, develop a higher geometric mean titer, and have a longer duration of seropositivity (81-83).

To develop an Hib vaccine which is protective in infants, research efforts have been directed toward linking the T-cell independent polysaccharide antigens to protein or oligosaccharide conjugates to elicit a T-cell response. Encouraging preliminary results have been obtained with PRP-diphtheria toxoid conjugate preparations, and efficacy studies of these conjugate vaccines are in progress in Alaska and in Finland.

In view of the apparently higher incidence of Hib and pneumococcal infections among the very young in LDCs, passive immunization as an alternative to conjugated preparations for
this high risk group by vaccination of pregnant women deserves investigation. Studies in pregnant rhesus monkeys with two conjugate vaccines have have already been encouraging. It is probable that even with the second generation (i.e., conjugated) vaccines, active immunization of infants may not be feasible during this crucial period, particularly if multiple doses are required. The possibility that high levels of placentally transmitted antibody may inhibit active antibody formation to subsequently administered vaccines requires careful exploration, although no inhibition of response to subsequent vaccination has been observed (80).

Some researchers have been working on the development of an enteric-coated vaccine, which, in view of the apparent potential for IgA response at a very young age, offers hope that induction of mucosal immunity may provide an avenue to the protection of infants. Other candidate antigens, cross-reacting bacteria and \textit{H. influenzae} outer membrane proteins and pili are also under study as vaccine candidates (79). Investigations are required to further identify the epidemiology and molecular biology of the non-b and nonserotypable \textit{H. influenzae} infections in LDCs in order to refine vaccine development strategies.

3. \textbf{Group B Streptococcus}

\textit{Group B streptococcus} (GBS) has long been recognized as a cause of neonatal septicemia, pneumonia and meningitis in the developed world (84). Several studies have suggested an association between maternal genital tract carriage of GBS and preterm delivery, premature rupture of membranes, and low birth weight (85-87), all of which are known to earmark infants at high risk of mortality. These studies, as well as the preliminary results of a trial of the use of prophylactic
antibiotics in the last trimester to reduce neonatal and infant mortality, suggest that GBS should be studied for its role in the pathogenesis of low birth weight.

A vaccine against the polysaccharide antigen of GBS has been developed and although trial in mothers have been encouraging (88), type-specific and lot-specific immunogenicity remain to be evaluated before efficacy trials will begin. Suggestions that chorioamnionitis and/or premature rupture of membranes due to GBS may underlie low birth weight have been intriguing, however data to support such a causative for GBS will be difficult to obtain in LDCs. Once the vaccine has undergone U.S. trials, GBS polysaccharide might be included in polysaccharide vaccine trials among pregnant women to assess its impact in the reduction of both low birth weight and mortality due to neonatal infections.

4. **Staphylococcus aureus**

*Staphylococcus aureus*, probably the third most common cause of bacterial pneumonia in developing countries (89), is a less attractive candidate for prevention by immunization. Staphylococcal pneumonia is most often seen in the first six months of life, in partially treated cases, and as a complication of measles in older children (89). Its lesser incidence overall as well as its more frequent occurrence as a complication of other illnesses make vaccines against *S. aureus* less likely to be among the cost-effective interventions for ARI.

Two of the eleven known *S. aureus* polysaccharides, comprise about 70% of isolates from the blood of hospitalized patients (77). In vitro studies suggest an opsonophagocytic effect of
antibodies to type 8, the most common type. As the role of such antibody is elucidated, hope may emerge for effective vaccines against *S. aureus* infections.

5. *Mycoplasma pneumoniae*

There is little information to establish the relative importance of pneumonia due to *Mycoplasma* among children in LDCs. In the U.S., mycoplasma pneumonia is more frequently seen in children aged 5 to 9, although *M. pneumoniae* infection remains approximately twice as frequent among children 2 to 4 as among adults (90). More data are needed on the epidemiology and natural history of *M. pneumoniae* infections before immunization can be recommended. Field trials among military recruits have demonstrated a vaccine efficacy of 50-70% for an inactivated vaccine preparation, although the presence of the organism in the respiratory tract was not altered by immunization. (91) Limited evaluations of live attenuated *M. pneumoniae* vaccines in both animal models and man have seemed to provide more long-lived immunity, however theoretical and practical problems with these approaches have reduced research interest in this area.

6. *Chlamydia trachomatis*

*Chlamydia trachomatis* may be an important agent of subacute pneumonia in newborns in LDCs, and is probably acquired in passage through the birth canal in infected mothers (92-93). Preliminary evidence from the improved pregnancy outcomes and infant mortality reductions reported during trials of the prophylactic use of erythromycin funded by AID in Haiti suggest that prevention of infections with *Chlamydia*, mycoplasma, and/or group B streptococcus may reduce perinatal and infant mortality.
C. Other Viral Vaccines

1. Respiratory Syncytial Viruses

Respiratory syncytial viruses (RSV) infect 11-25% of infants from 2 to 12 months of age, and 27-50% by age two, with manifestations severe enough to require hospitalization in up to 20% of infected infants (94). Formerly considered to be antigenically homogenous, these important causes of acute broncholitis and pneumonia in infants and young children are now known to be a biologically as well as antigenically diverse group of viruses. Variability in the two major surface glycoproteins, the G and F proteins, confers the heterogeneity (95). Antibodies to the F protein, the fusion protein which permits the spread of virus between cells, protect against respiratory challenge (95). It is not known whether past infection with one antigenic serotype provides protection against subsequent challenge by an antigenically distinct virus, although the risk of infection appears to decrease after two RSV infections (96). The frequent multiple infections with RSV observed among infants and very young children could be due to the immunologic immaturity of the neonatal respiratory tract or infection with multiple serotypes which do not cross-protect.

Attempts to produce a vaccine against RSV have been frustrating. Severe disease develops in infants despite the presence of maternal antibody (96), and initial killed virus vaccines actually increased the severity of subsequent naturally acquired infections (97). Candidate attenuated vaccines have also failed to protect from subsequent infections (98). Local respiratory tract IgA also appears to be inadequate to prevent reinfection. IgE-mediated allergic responses and cell-mediated hypersensitivity in the pathogenesis of RSV broncholitis have
been proposed to explain the enhancement of disease severity after inactivated viral vaccines, although more research is needed to define vaccine development strategies.

Attempts to produce subunit vaccines using recombinant DNA technology and ultracentrifugation techniques are ongoing and may provide hopeful avenues for immunoprophylaxis of these infections. A vaccinia-vectored RSV vaccine using the gene coding for the major surface glycoprotein has been found to protect cotton rats against intranasal challenge with the virus. Acceleration of such work may provide the technology to prevent this important cause of infection in infants.

2. Parainfluenzae Viruses

Of the four serotypes of the genus Paramyxovirus which cause disease in humans, types 1 and 5 are the most important clinically. Type 1 is the most frequent cause of laryngitis (croup) or laryngotracheobronchitis in children. Like type 2, which causes similar but often less severe disease, this serotype tends to occur in epidemic form. Of the remaining two serotypes, which are considered endemic, type 4 causes minor illness. Parainfluenza type 3 ranks next to RSV as an important cause of bronchiolitis and pneumonia in infants (31).

Formalin-inactivated monovalent and trivalent vaccines have been shown to be immunogenic when administered parenterally, but confer no obvious protection against naturally acquired infection (99-100). The use of live attenuated virus by aerosol or installation via the respiratory tract have yielded some encouraging results in animals but have not yet been tested in humans (101). Although parainfluenza types 1 and 2 could be administered later in infancy, parainfluenza type 3 vaccines
would have to be delivered to very young infants, as placentally acquired maternal antibody does not appear to protect and type 3 infections have a peak occurrence before 6 months of age (31). Vaccination against parainfluenza type 3 may yield additional benefits in that it is frequently implicated as a cause of antecedent viral infection, at least among adult patients with pneumococcal pneumonias (15). A candidate vaccine consisting of the purified glycoproteins (HN and F) for parainfluenza type 3 has been found to induce antibody in rabbits and is awaiting tests in humans (102).

Partial immunity, such as that seen after natural infection, may be all that can be expected from vaccines against RSV and parainfluenza. One hopeful approach might be to use subunit vaccines in pregnant mothers to increase the duration of passive immunity while live attenuated vaccines are administered for active immunization of infants at age six to twelve months.

Identification of protective epitopes and antigen production through recombinant technologies offer the best hopes for vaccine development for both RSV and parainfluenza viruses. So little is known about the epidemiology of these infections in the developing world that no distinct strategy can be identified based on LDC concerns.

3. Influenza Viruses

The genus Influenzavirus contains three antigenically distinct subgroups, namely A, B and C. Differences in the antigenic characterization of the surface hemagglutinin (H) and neuraminidase (N) proteins form the basis of the "antigenic drift", so characteristic of the influenzae A viruses. Due to the adverse effects of inactivated whole virus vaccines as well
as the short efficacy due in part to the antigenic drift of the virus, influenza vaccines currently have no place in preventing ARI in children in developing countries.

4. Other Viral Diseases

It is estimated that only 5% of acute respiratory disease in children is adenoviral in etiology (31). Adenoviral respiratory infection in children, which is often asymptomatic, is caused primarily by six or seven of the 36 immunotypes (31). Because of the limited severity of adenoviral ARI, which generally presents as a common cold, as well as the oncogenicity of some adenoviral serotypes in animals, adenoviral vaccines are not regarded as candidates for development for prevention of ARI in infants and children at this time.

Enteroviruses comprise an antigenically diverse genus including the Coxsackieviruses, enteroviruses and echoviruses which cause respiratory infections in addition to having a well known etiologic role in poliomyelitis, aseptic meningitis, herpangina and conjunctivitis. Although they more frequently give rise to a common cold syndrome when they cause ARI, all three groups can induce lower respiratory infections. Because of the antigenic and clinical heterogeneity of these viruses, with the exception of poliovirus they have not been regarded as attractive candidates for vaccine development.

Rhinoviruses and coronaviruses, which cause only upper respiratory infections syndromes, have not been regarded as feasible or desirable targets for immunoprophylaxis with vaccines because of their antigenic diversity as well as mild clinical illness. The efficacy in reducing the mortality due to pneumonia through prevention of antecedent URIs has, however, not been systematically explored.
VII. CURRENT AID ACTIVITIES

AID currently has several activities to address acute respiratory infections, with both direct interventions and research now in progress. The Agency's Child Survival (CS) Strategy seeks to reduce the number of infant and child deaths through the expanded use of immunizations and ORT as the "twin engines" toward achieving this goal. The delivery of basic vaccines, with the goal of universal immunization by 1990, provides hope of averting up to 25% of the infant and child deaths due to ARI.

The Board on Science and Technology in Development (BOSTID) of the National Research Council has been conducting an AID-funded research program since 1981. ARI was unanimously selected as one of the six project areas by the Committee on Research Grants, and the program has been evolving since the initial coordination meeting in 1983. Fourteen projects have been funded in as many LDCs to investigate the epidemiology, etiology, clinical features and diagnosis of ARI. The program has promise of providing much needed information which may guide the selection of future intervention strategies.

Vaccine research, as an element of the CS strategy, is also in progress with Agency support. Funding was provided for the work by the Institute of Medicine in developing a model to establish priorities for vaccine development among the diseases of importance in the developing world. The Committee on Issues and Priorities for New Vaccine Development is currently finishing this second volume of its report which has been released only in draft form. Their work will assist in guiding the selection of
vaccine research areas for acceleration with AID investments. Three respiratory pathogens were listed among the top five as highest priority for vaccine development for diseases of domestic importance. Those included RSV, H. influenzae type b and influenza. Pneumococcal infections ranked first on the IOM's list for diseases of importance in LDCs.

AID's Vaccine Development and Health Research PASA with the Public Health Service is funding important trials of the new human diploid cell measles vaccine and an efficacy trial of an acellular pertussis vaccine. Meetings of experts in research on pneumococcal and group B streptococcal infections have been held to explore the need and opportunity for vaccine development and field testing for these important infections. Additional studies are planned to identify approaches to improving the heat stability of vaccines, including those to prevent ARI.

AID/Delhi is conducting studies of genital carriage of pathogens, including mycoplasma, chlamydiae and group B streptococcus, and the impact upon perinatal and infant mortality. ARI due to these organisms, in addition to intrauterine infections and neonatal septicemia, are possible mechanisms of perinatal deaths due to these infections. These investigations may also provide important information to guide future program planning and AID investment in reducing the ARI death toll among infants and children.

Child survival projects in Egypt and Nepal have incorporated ARI interventions into their activities. AID/Cairo points out that ARI, which has been second to diarrhea as a cause of death among children under five, is emerging as the major cause of mortality as diarrhea deaths are decreased due to ORT interventions. Their project is working to train health care providers in the
diagnosis and treatment of ARI, to improve the diagnostic and treatment capabilities of the health centers, and develop public education programs to encourage early treatment of ARI episodes.

A child survival project in Nepal is field testing methods to identify and treat serious ARI. A pilot study in the Jumla district has been undertaken to improve current treatment regimens, measure changes in the mortality and determine the cost per death averted. These projects and the evaluation of their impact will provide important guidance in refining strategies for the design of ARI control programs.

VIII. RECOMMENDATIONS

Given our current limited knowledge of the pathogenesis, prevention and treatment of ARI, we have an opportunity to use the available technologies to reduce infant and child mortality due to these infections and provide resources for the needed research. The interventions which are known to reduce ARI mortality include preventive measures, such as immunizations, and improved case management. Directed research efforts should be escalated and should select those areas which will improve and continually refine existing strategies for the prevention and treatment of these infections.

1) Epidemiology

- Sustain and strengthen efforts such as that of the AID-funded BOSTID program's ARI activity, which are designed to advance our knowledge of the epidemiology of ARI in LDCs.
Consider support for the formation of an international center for clinical and epidemiologic research in ARI in an LDC setting, encouraging research which will assist in improving strategies for ARI prevention and management.

Encourage research to systematically assess the distribution of serotypes of the major pathogens of bacterial pneumonias, especially the pneumococcus and H. influenzae, in order to rapidly refine immunization strategies.

Support further investigations of the role of such bacteria as mycoplasma, chlamydia and the group B streptococcus in the pathogenesis of intrauterine infections, low birth weight, neonatal sepsis and pneumonias in LDCs.

Initiate studies to assess the burden of disease in LDCs due to the major viral pathogens, including RSV and the parainfluenza viruses, to determine whether disproportionate disease burden in the LDCs warrants special AID investment in vaccine development research for these viruses.

Explore the importance of risk factors for ARI, such as by characterizing possible alterations in the immune status of LDC children, which may explain the increased mortality due to these infections.

2) Diagnosis

Accelerate work to develop rapid, simple diagnostic technologies for the major causes of ARI mortality, especially pneumococcal and F. influenzae pneumonias, through AID's DiaTech project.
Support, through DiaTech, the incorporation of newer diagnostic technologies into ARI control programs to improve the identification and treatment of bacterial pneumonias.

- Develop or improve diagnostic technologies which will aid in efficacy trials of emerging vaccines.
- Emphasize efforts to develop rapid simple diagnostics for tuberculosis which may aid in early identification of persons requiring treatment, thus reducing disease transmission.

3) Case Management
- Consider support to WHO's ARI Programme, especially to assess the magnitude of the problem in the member nations and to assist in the development of national ARI control strategies.
- Consider implementation of ARI control programs through existing primary health care activities such as CCCD and the bilateral PHC projects.
- Encourage the integration of ARI case management interventions into pilot Child Survival activities funded by AID where the infrastructure is adequate to implement and sustain those programs.
- Support, through applied research in an LDC setting, efforts to further refine existing algorithms for the clinical diagnosis and treatment of severe ARI.
- Provide technical assistance, through AID's Communications for Child Survival (HEALTHCOM) project, to ARI control programs for community education in the prevention, identification and management of severe ARI.
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4) Prevention

- Sustain and strengthen ongoing efforts to deliver the basic EPI vaccines, including measles, diphtheria pertussis, and BCG for the prevention of up to 25% of ARI mortality.

- Direct and accelerate vaccine research, especially to address the ARI problems of LDCs which will not be the subject of research funded by other agencies, through projects such as AID's Vaccine Development and Health Research PASA with the Public Health Service:
  
  To immediately carry out a vaccine trial with the currently licensed 23-valent pneumococcal vaccine to confirm its efficacy in infants and children.

  To explore approaches to improving the immunogenicity of the polysaccharide vaccines, especially for H. influenzae and the pneumococcus, among infants and young children through techniques such as protein conjugation and their delivery with EPI vaccines.

  To promptly assess the efficacy of transplacental passive protection of infants through immunization of pregnant mothers with polysaccharide vaccines (including pneumococcus, H. influenzae, meningococcus and group B streptococcus) in the reduction of infant mortality.
To identify more heat-stable preparations of vaccines to reduce the cost and logistical problems of delivery.

To establish optimal schedules and routes of administration to improve cost-effectiveness of existing and emerging vaccines.

To support efforts, in conjunction with domestically oriented vaccine research programs, to produce cloned, synthesized or subunit vaccines in hopes of reducing adverse effects, heat-instability and cost of existing vaccines.

To continue trials, in the interim, of such improved vaccines as the acellular pertussis vaccine.

To improve the production and standardization of the BCG vaccines against tuberculosis.

To improve the production and standardization of the BCG vaccines against tuberculosis.

Support, possibly through the proposed international center for ARI research, the basic and operational research necessary to refine preventive strategies for ARI control, such as through defining the effectiveness of such interventions as improved nutrition, environmental factors, health education or specific treatment regimens in prevention of ARI mortality.

Of the estimated two to five million deaths each year due to ARI, 90 to 98% might be prevented if case-fatality ratios could be reduced to those observed in the industrialized world. Even limited interventions in LDCs have resulted in ARI-specific mortality reductions of 36 to 84% (40, 53-54), suggesting that simple, readily transferable technologies may save literally millions of lives each year. ARI represents the next major challenge and hope of reducing the still appalling infant and child mortality rates in LDCs.
Table 1

Acute Respiratory Infections
Clinical Characterization in the Developed World

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Common Etiology</th>
<th>Age of Peak Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis (coryza)</td>
<td>Viral (various agents)</td>
<td>--</td>
<td>No</td>
</tr>
<tr>
<td>Pharyngotonsillitis</td>
<td>Viral, bacterial</td>
<td>--</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(various, streptococcus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngitis (croup)</td>
<td>Viral (parainfluenza 1)</td>
<td>12-24 mos.</td>
<td>Rare</td>
</tr>
<tr>
<td>Lower Respiratory Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheobronchitis</td>
<td>Viral (various agents)</td>
<td>constant</td>
<td>No</td>
</tr>
<tr>
<td>Broncholitis</td>
<td>Viral (Respiratory Syncytial Virus)</td>
<td>0-12 mos.</td>
<td>Yes</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Bacterial, viral</td>
<td>24-36 mos.</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(pneumococcus H. influenzae)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2*

**Annual Deaths from Acute Respiratory Infections Other than Influenza**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Proportions of Deaths&lt;sup&gt;a&lt;/sup&gt; (percent)</th>
<th>Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Under 5</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>11.5</td>
<td>244,260</td>
</tr>
<tr>
<td>Parainfluenza viruses</td>
<td>5.5</td>
<td>116,820</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>7.0</td>
<td>148,680</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>22.5</td>
<td>477,900</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>2,124,000</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> These proportions are based on a very limited number of reports and assume that the distribution of deaths parallels the isolation of pathogens from individuals with lower respiratory tract infection.

<sup>b</sup> The total includes deaths caused by other pathogens for which vaccine prospects are considered poor, or for which an etiologic agent is not yet identified.

* *DRAFT, from New Vaccine Development: Establishing Priorities, Volume II, Diseases of Importance in Developing Countries, Appendix B, "The Burden of Disease Resulting from Acute Respiratory Illness."*
### Table 3

**Risk Factors for Acute Respiratory Infections**

<table>
<thead>
<tr>
<th>Increased Incidence</th>
<th>Increased Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than two</td>
<td>Age less than two</td>
</tr>
<tr>
<td>Poor nutritional status</td>
<td>Poor nutritional status</td>
</tr>
<tr>
<td>(Vitamin A deficiency, low birth weight)</td>
<td>(Vitamin A deficiency, low birth weight)</td>
</tr>
<tr>
<td>Crowding</td>
<td>Early weaning</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>Lack of maternal education</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>Reduced health care access</td>
</tr>
</tbody>
</table>


Table 4*

Acute Respiratory Infections
Classification and Case Management for Health Workers with 6 months Training (55)

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe</td>
<td>Cough or wheeze, plus unable to drink cough without wheeze, plus chest indrawing. Cough with wheeze, plus respirations 70/per minute or complicated by cyanosis, seizures, apnea change in consciousness, severe dehydration or stridor at rest.</td>
<td>Referral + Antimicrobials (plus supportive measures)</td>
</tr>
<tr>
<td>2. Moderate</td>
<td>Respirations 50-70/minute with cough, wheeze or fever but no chest indrawing</td>
<td>Antimicrobials at home (plus supportive measure)</td>
</tr>
<tr>
<td>3. Mild</td>
<td>Cough, hoarseness, wheeze or fever with respiration 50/per minute. Stridor relieved at rest. Red throat with or without exudate. Blocked or runny nose. Earache or ear discharge (can be referred for treatment)</td>
<td>No Antimicrobials (supportive measures only)</td>
</tr>
</tbody>
</table>

*Supportive measures include fluids, continued feeding as tolerated, neutral environmental temperature, antipyretics, and clearing of any nasal or ear discharge. Steam humidification, bronchodilators and oxygen may also be used in supportive care at referral facilities.
Table 5
Efficacy, Toxicity and Administration of Antimicrobials for Outpatient and Inpatient Treatment of Bacterial Pneumonias
(Adapted from WHO/IMI/ARI. TAC. II/85-11)

<table>
<thead>
<tr>
<th>OUTPATIENT ANTIMICROBIALS</th>
<th>INPATIENT ANTIMICROBIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Sensitivities</td>
<td>Sensitivities</td>
</tr>
<tr>
<td>B. influenzae</td>
<td>Good (0-25% resistance)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Very good</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Poor</td>
</tr>
<tr>
<td>Group A streptococcus</td>
<td>Very good</td>
</tr>
<tr>
<td>Chlamydia, pneumonia</td>
<td>NIL</td>
</tr>
</tbody>
</table>

Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Cost (5 days, 10 kg child)</th>
<th>Toxicity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>$0.20</td>
<td>$0.40</td>
<td>$0.08</td>
<td>$0.18</td>
</tr>
<tr>
<td>$1.00</td>
<td>$6.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toxicity

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Cefuroxime</th>
<th>Erythromycin</th>
<th>Chloramphenicol</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal anaphylaxis in 1/250,000</td>
<td>Diarrhea, rash, fatal anaphylaxis less than 1/250,000</td>
<td>Dose-related megaloblastic anemia, rare fatal complications</td>
<td>Fetal anaphylaxis in 1/250,000</td>
<td>Irreversible fatal anaphylaxis in 1/250,000</td>
<td></td>
</tr>
</tbody>
</table>

Comment

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Cefuroxime</th>
<th>Erythromycin</th>
<th>Chloramphenicol</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually effective, long acting, but IM administration not always feasible</td>
<td>Usually effective, but short acting, mild side effects common. Amoxicillin preferable if cost is acceptable</td>
<td>Effective, cheap, and long acting, but rare serious toxicity. Use in cylindrical areas may induce Fanuslar resistance</td>
<td>Usually effective, cheap</td>
<td>Effective, side effects rare but serious toxicity. Use in cylindrical areas may induce Fanuslar resistance</td>
<td>Expensive, reserved for staphylococcal pneumonia</td>
</tr>
</tbody>
</table>
REFERENCES


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68. World Health Organization: Indications and contraindications for vaccines used in EPI. Weekly Epidemiological Record 59:15, 1984

69. Tidjani O, Amedome A, ten Dam HG: The protective effect of BCG vaccination of the newborn against childhood tuberculosis in an African community. (submitted for publication)


