HSPR-30

HEALTH SECTOR PRIORITIES REVIEW

ACUTE RESPIRATORY INFECTIONS

by

Sally K. Stansfield
International Development Research Center

and

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Heller School, Brandeis University, and
Harvard School of Public Health

October, 1991

Population, Health and Nutrition Division
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FOREWORD

Over the past two years the World Bank has been undertaking, with a number of collaborators, a "Health Sector Priorities Review". The core of the Review is a series of papers on the public health significance of major clusters of diseases in the developing world and on the cost and effectiveness of currently available technologies for their prevention and case management. In addition, as part of the Review, a number of cross-cutting papers provide demographic background, discuss issues involved in setting priorities, and review illustrative areas of intervention.

The Review undertakes two tasks simultaneously: (i) it shows, by extended example, that cost-effectiveness measures (of a rough-and-ready sort) can be potent tools for guiding resource allocation in the health sector; and (ii) it considers a much broader range of diseases (and associated interventions) than the communicable childhood diseases that have dominated analytical concern in public health in developing countries. By undertaking these tasks it provides a first systematic analysis of the disease control priorities appropriate to the increasingly diverse epidemiological conditions that developing countries face as a result of declining fertility and child mortality rates. While the Review does, we feel, provide valuable guidance on disease control priorities, including related priorities for international aid, it does not deal with equally important policy issues concerning infrastructure development or finance.

This paper consists of one of the 37 papers resulting from the Health Sector Priorities Review. A complete list of the papers resulting from the Review may be found at the end of this document, and copies of the papers may be obtained by contacting the authors or writing to me at the address below.

It is expected that many of the papers resulting from the Review will ultimately be published in a volume to be edited by Dean T. Jamison and W. Henry Mosley, but, until such a volume becomes available, the individual papers will constitute the Review's findings. In Paper HSPR-13 Jamison and Mosley summarize and draw conclusions from the Review as a whole.

The Review's conclusions, and those of the individual papers in it, do not, of course, necessarily reflect those of the World Bank.

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ACUTE RESPIRATORY INFECTION

by

Sally K. Stansfield and Donald S. Shepard

1. Introduction to Acute Respiratory Infection

1.1 Background

Acute respiratory infection (ARI) is the most frequent illness globally and a leading cause of death in the developing world. Among children under five alone, four million deaths annually are ascribed to ARI, most of which are due to pneumonia. The 10 to 50-fold excess mortality due to pneumonia in developing countries suggests that there is ample room for improvement in addressing this important public health problem. However, the heterogeneity of the clinical presentations and causative organisms in ARI has hampered efforts to design simple and effective interventions.

The classification and management of ARI in the industrialized world is founded on epidemiologic, radiologic and microbiologic data, in addition to clinical history and physical examination. ARI syndromes, which are complex clinical conditions of varying etiology and severity, are most frequently categorized on the basis of anatomical location. Common diagnostic categories for uncomplicated ARI with etiologic and clinical correlates are detailed in table 3.1. As suggested by this table, ARI includes the minor upper respiratory infections (URI) such as colds and sore throats in addition to the more serious (and potentially fatal) acute lower respiratory infections (ALRI) of pneumonia and bronchiolitis.

Most of the studies of ARI from developing countries have been conducted among infants and children. Programs which have been developed to prevent or treat ARI have often focused exclusively on children, arguing that the principal opportunities to reduce ARI mortality are among children under five. Although adults, particularly the elderly, may benefit from preventive and therapeutic interventions, the major impact in reducing years of life lost (YLL) will be seen among infants and children. The data and strategies outlined in this chapter therefore focus primarily on children under five.

1.2 Risk Factors for ARI

Treatment of pneumonia clearly reduces ARI mortality, but the definitive solution to the problem of excess ARI deaths in less developed countries (LDCs) will ultimately be found in prevention of pneumonia. Although the epidemiologic data from the developing world are limited, a review of the available information suggests possible approaches to the reduction of ARI mortality through reducing the risk of pneumonia. Table 3.2 summarizes the following discussion of some of the known and suspected risks for pneumonia incidence and mortality.

Table 3.1

Acute Respiratory Infections:
Anatomic Classification and Clinical Correlates

	Diagnosis	Most Common Etiologies	Age of Peak Incidence (months)	Mortality
Upper Respiratory Infections	Nasopharyngitis (coryza, colds)	Viral (various)	--	No
	Otitis media (middle ear infection)	Bacterial (pneumococcus, H. influenzae)	6-17	No
	Phayngo-tonsillitis	Viral (various) & Bacterial (S. pyogenes C. diphtheriae)	--	No (except diphtheria)
	Epiglottitis	Bacterial (H. influenzae)	24-47	Yes
Lower Respiratory Infections	Laryngitis (croup)	Viral (especially parainfluenza1 and measles)	12-23	Rare
	Tracheo-bronchitis	Viral & Bacterial (various)	Constant	No
	Bronchiolitis	Viral (RSV para-influenza 3)	0-11	Yes
	Pneumonia	Bacterial (pneumococcus, H. influenzae) & Viral (RSV, influenza, parainfluenza, measles, adenovirus)	24-35	Yes

Table 3.2

RISK FACTORS FOR PNEUMONIA

Increased Incidence	Increased Case-Fatality
Age <2 years or >65 years	Age <2 years or >65 years
Males	Low socioeconomic status
Poor nutritional status	Poor nutritional status
Low birth weight	Low birth weight
Lack of breastfeeding	Lack of breastfeeding
Smoking, air pollution	Lack of maternal education
Crowding	Reduced health care access
Incomplete immunization	Crowding
Swaddling	Underlying chronic disease
Vitamin A deficiency	

Age and Sex. The incidence of ARI (most of which is URI) is inversely related to age, peaking at four to nine infections in each of the first two years of life, dropping to three to four by school age, and remaining at 2-3 per year for adults (Datta Banik, 1969; Kamath, 1969; Monto, 1974; Friej, 1977; Spika, 1989). However, the frequency of pneumonia and the case-fatality ratio are highest among both the very young and the very old (Bulla, 1978; Berman, 1983; Ngalikpima, 1983). Studies in several developing countries have demonstrated that pneumonia occurred 1.5 to 1.8 times as frequently among infants as among children two to fours years of age (Berman, 1985). There is a slightly increased incidence of both overall ARI and pneumonia among males (Bulla, 1978; Berman, 1983; Narain, 1987; Selwyn, 1990), although female children have been observed to have a higher case-fatality ratio in some countries, probably due to poorer access and quality of care during illness episodes (Tupasi, 1990).

Socioeconomic Status and Child-Rearing Practice. Low socioeconomic status and crowding have been well documented as risk factors for mild respiratory infections in the industrialized world. Studies in developing countries (Verma, 1981; Stansfield, 1987; Tupasi, 1988; Vathanophas, 1990; Borrero, 1990) have also demonstrated an increased frequency of pneumonia requiring hospitalization among persons from lower socioeconomic groups and in more crowded households. Aaby (1988) has suggested that crowding is a predictor of an increased case-fatality ratio due to measles, in addition to an increased risk of infection.

Both poverty and crowding may, however, be proximate measures for other known or as yet unrecognized risk factors. For example, the frequent association of these factors with lower educational levels, poor nutrition, and certain child-care practices further confounds analysis of risks for ARI. Existing evidence suggests, however, that infants with restricted respiratory excursion of the chest wall due to obesity (Tracey, 1971) or swaddling (Yurdakok, 1990) may have increased risk of pneumonia. Family stress also increases the risk of infections such as pneumonia among both children and adults (Graham, 1990; Foulke, 1988), probably due to interference with immune competence (Kiecolt-Glaser, 1986). Although chilling is frequently cited as a risk factor for URI or pneumonia, most studies have have provided no evidence of this association (Jackson, 1963; Douglas, 1968).

Nutritional Status and Practices. Poor nutrition lowers both systemic and local defenses against ARI, including through reduction of the effectiveness of epithelial barriers, systemic immune responses and cough reflexes. Nutritional status is inversely related to both the incidence and the case-fatality ratio for pneumonia (Berman, 1983, 1991; Pio, 1982; Kielmann, 1978; Sommer, 1983, 1984). Investigators have documented a 12- to over 20-fold greater incidence of pneumonia in undernourished children when compared with children of normal weight for age (James, 1972; Herrero, 1983; Berman,

1983; Tupasi, 1988). Mortality due to each of these already more frequent episodes of pneumonia increases two to 13-fold for each decile below 80% weight for age (Escobar, 1976; Kielmann, 1978; Tupasi, 1985).

While nutritional deficiency diseases augment the chances of ARI episodes, so episodes of ARI contribute to nutritional deficiency, thus further increasing the risk of subsequent infection and death. A prospective study in The Gambia (Rowland, 1988) showed that pneumonia reduced weight gain in young children by 14.7 g/day of infection. Recurrent ARI episodes, as a principal cause of the weight shortfall during infancy, therefore progressively increase the risk of death due to other childhood diseases.

Low birth weight (LBW), seen in 20-40% of infants in many developing countries, also increases the risk and case-fatality ratio of pneumonia. Recent studies (Datta, 1987; WHO, 1988a) have shown relative risks of mortality due to pneumonia which are 2.5 to eight-fold greater among LBW infants. Other than malaria and tobacco chewing, the only factors associated with LBW for which cause/effect relationships have been established in LDCs (and which are "modifiable over the short term") are pre-pregnancy weight, gestational weight gain, and caloric intake (WHO, 1987a). Short birth intervals, teenage pregnancy, certain genital infections, and arduous work after mid-pregnancy are other potentially modifiable factors associated with LBW. Although reduction of the incidence of LBW would be expected to reduce ARI mortality, no prospective studies have demonstrated the feasibility and effectiveness of interventions to address this important problem.

The few well-conducted studies on infant feeding practices and the incidence of pneumonia demonstrate a protective effect of breastfeeding. The literature has suffered from wide variations in definitions, both of specific feeding practice and of ARI. Although several studies summarized in a review by Jason (1984) failed to document any protective effect of breastfeeding, others have found a two- to five-fold decreased incidence of (Chandra, 1979; Singhi, 1987) and decreased case-fatality ratio due to pneumonia (LePage, 1981). A more rigorous study in southern Brazil (Victora, 1987) demonstrated that infants who were completely weaned had 3.6 times the risk of death due to pneumonia when compared to breastfed infants.

Vitamin A deficiency, which often accompanies protein-calorie malnutrition, results in keratinization of the respiratory epithelium and depression of immune response, thus presumably decreasing both local and systemic resistance to bacterial colonization and infection. However, the literature on vitamin A deficiency and its association with ARI morbidity and mortality is sparse and controversial. Two studies (Sommer 1983; 1984; Bloem, 1990) have suggested a two- to four-fold increase in the relative risk of ARI associated with serologic or ophthalmic signs of vitamin A deficiency. In the Sommer

study (1983), mortality in the clinically vitamin A deficient group was 8.6 times that in non-xerophthalmic children.

Although one prospective study noted a 34% reduction in mortality among vitamin A-supplemented children (Sommer, 1983), the causes of death among these children were not documented. Vitamin A supplementation of children with severe pneumonia or measles has improved clinical outcome and reduced mortality (Barclay, 1987; Hussey, 1990). Prospective studies of the effect of vitamin A supplementation in children from areas with endemic vitamin A deficiency (who are, therefore, presumed to be sub-clinically deficient) have not, however, demonstrated an impact on ARI-specific morbidity or mortality (Rahmathullah, 1990, 1991; Vijayaraghavan, 1990). The effect of vitamin A supplementation on ARI-specific morbidity and mortality among children who are not clinically xerophthalmic remains speculative.

Smoking and Air Pollution. There is a large and expanding literature from industrialized countries on the effects of active and passive smoking in increasing the risk of pneumonia. Investigators in both industrialized and developing countries have demonstated a 1.5 to four-fold increased incidence of pneumonia among smokers and among children whose parents smoke (Ekwo, 1983; Ware, 1984; Weiss, 1983; Pedreira, 1985; Yue Chen, 1986; Burchfiel, 1986; Samet, 1987; Harlap, 1974; Connochie, 1986; Leeder, 1976; Lipsky, 1986; DHHS, 1989). Maternal smoking also predisposes to low birth weight (Martin, 1986; Ruben, 1986), thus increasing the risk of ALRI mortality for the infant after birth. There are no prospective data currently available from developing countries to establish that programs to reduce smoking will reduce ARI-specific mortality. However, the recent alarming increases in the numbers of persons who smoke in developing countries argue for prompt intervention, particularly since successful reduction of smoking may be expected to yield health benefits beyond the reduction of ARI morbidity and mortality.

Exposure to both outdoor and indoor air pollution have been suspected to increase the risk of ARI in many developing countries (Kamat, 1980; UNEP, 1988; Chen, 1990). There is growing concern regarding the health effects of the products of combustion (including carbon monoxide, particulates, and sulfur and nitrogen dioxides) from cooking and heating fires. It has been estimated that 300 to 400 million people, mostly in the rural areas of developing countries, may be adversely affected by these organic fuel emissions (de Koning, 1985). Although there is a clear relationship between exposure to such emissions and chronic obstructive pulmonary disease (WHO, 1984a; Chen, 1990), the relation to pneumonia in the developing world is less well documented.

Indoor particulate concentrations, probably the best single indicator of toxic (non-carcinogenic) effects, are 20 times higher in the villages of developing countries than in

households where two packs of cigarettes are smoked per day (Pandey, 1989a). Several studies in developing countries have suggested that an increased incidence of pneumonia associated with exposure to organic fuel emissions (Kossove, 1982; Sofoluwe, 1968; Honicky, 1985; Campbell, 1989a; Penna, 1991) although several studies have had problems with confounding variables such as socioeconomic status and crowding. One study in Nepal (Pandey, 1988; 1989b) has demonstrated that the number of episodes of life-threatening ALRI among children under two is directly proportional to the reported hours per day spent near the stove. Studies in the Gambia suggest that carriage on mother's back during cooking may predispose children to ALRI (Armstrong, 1991). Prospective trials are required to assess the efficacy of interventions such as improvements in stove design, improved ventilation and/or behavioral change to reduce exposure.

1.3 Clinical Syndromes Causing ARI Mortality

The predominant known causes of ARI mortality are bacterial and viral pneumonia, measles, and pertussis. Additional epidemiologic data are needed to characterize the importance of other clinical syndromes and etiologic agents, including diphtheria, bacterial pharyngitis, and the "opportunistic" viral and bacterial infections which are likely important causes of ALRI mortality among the very young, the very old, and those immunocompromised by AIDS or malnutrition.

Pneumonia. Pneumonia is an inflammatory process of the pulmonary interstitial space or alveoli which may be diffuse or confined to lung segments or lobes. Clinically, patients with pneumonia most frequently present with cough and tachypnea (rapid breathing), while retractions (indrawing of the lower chest wall on inspiration) may also be present in more severe cases. Among neonates and younger infants, however, cough is often absent.

Available information from developing countries suggests that over 75% of ARI deaths are caused by pneumonia, both bacterial and viral (Bulla, 1978; Berman, 1991). Microbiologic data is difficult to obtain and of variable quality, yet most investigators agree that the bulk of ARI mortality among both children and adults is due to pneumonias caused by two bacteria, Streptococcus pneumoniae and Haemophilus influenzae (Denny, 1983; Berman, 1983; Shann, 1984; Selwyn, 1990; WHO, 1991a). Viral agents which cause mortality due to pneumonia include respiratory syncytial virus (RSV), measles, parainfluenza, influenza, and adenovirus. Mixed viral and bacterial infections are frequently documented (Berman, 1991). Clinical malaria has also been found to coincide frequently with the clinical and radiologic diagnosis of pneumonia (Byass, 1991).

Measles. Measles is a vaccine-preventable disease causing an acute febrile eruption which occurs naturally only in humans. The viral infection itself may result in any of several clinical syndromes, including croup, bronchitis, bronchiolitis, or even viral pneumonia, particularly in children immunocompromised by severe malnutrition. These manifestations may occur in the absence of the typical measles rash. Common complications of measles include growth faltering, chronic diarrhea, otitis media (middle ear infection), encephalitis, and pneumonia. Pneumonia, including primary measles pneumonia as well as superinfection by viruses and bacteria, is the most common complication of measles, and often represents the principal proximal cause of death.

In unimmunized populations, epidemics occur in 2-3 year cycles with secondary attack rates exceeding 90% among susceptible household contacts (Keja, 1988). Although generally a disease of childhood, measles can occur at any age in susceptible populations. Infants in industrialized countries are not usually affected under the age of 6-8 months, presumably due to placentally transmitted maternal antibodies. However, in parts of Africa, 20-45% of children are infected with measles before they attain the recommended age for immmunization at nine months.

Although improving immunization coverage progressively reduces infection rates, it was estimated in 1989 that there were 70 million annual cases of measles, and that 1.5 to 2 million of those affected would die during the month following infection. Although generally a mild disease in temperate climates, an estimated 1 to 5 percent of all affected children in developing countries will die of measles or its complications. Children who survive the acute episode have an increased risk of mortality for weeks to months following infection. Most investigators, therefore, report deaths which occur within one month of the measles rash as "measles-associated".

Due in part to such variations in methods of ascertaining deaths due to or associated with measles, the reported case-fatality ratios vary widely. Williams (1983) documented a 5% case-fatality ratio during the acute phase of the disease, and a cumulative rate of 15% during the 9 months following the rash. The case-fatality ratios obtained from prospective population-based studies range from 2% in Bangladesh to 34% in Guinea-Bissau (WHO, 1987b). Rates of 50% or more have been described in severely undernourished populations. It has been suggested, however, that deaths prevented by measles immunization will be "replaced" by deaths from other causes, such that measles immunization may prevent fewer deaths than these mortality ratios would suggest.

Pertussis. The majority of cases of "whooping cough", or the pertussis syndrome, are vaccine-preventable infections due to Bordetella pertussis. The paroxysms of coughing, often asssociated with a characteristic inspiratory gasp (the whoop), may persist for 4-10 weeks. Pertussis is often associated with dehydration and weight loss; and

encephalitis is an occasional complication. Pneumonia, due either to the organism itself or to secondary bacterial infection, is the proximal cause of death in over 90% of cases.

Although pertussis occurs endemically, it tends to produce epidemics every three to four years, with up to 90% of exposed susceptibles developing the disease (Muller, 1986; Broome, 1981). Incidence is higher among girls than boys. Population-based studies have suggested a annual incidence of 1-5% among children under 15, although infants have a 16% chance of infection in Kenya (Voorhoeve, 1977). The case-fatality ratio averages around 1%, although up to 15% of cases were fatal in studies in Uganda (Bwibo, 1971) and Santa Maria Cauque (Mata, 1978). The highest mortality is observed among females and children under two, with an estimated 500,000 to one million infant deaths annually due to pertussis (Muller, 1986; Keja, 1988).

Diphtheria. The epidemiology of diphtheria in the developing world is poorly understood. Although the causative organism, Corynebacterium diphtheriae, is widely present in Africa, and over 96% of unimmunized adults are immune (Ikejani, 1961; Muyembe, 1972), there are few reported cases of this vaccine-preventable disease. It has been suggested that immunity may result from subclinical or misdiagnosed infections, an explanation supported by the finding of carriage of the organism in 4 to 9% of the population (Ikejani, 1961; Muyembe, 1972).

There are no community-based studies, but data from hospitals suggest diphtheria may be an important cause of pharyngitis and "croup" (laryngotracheobronchitis). Of 180 children hospitalized with respiratory infections in Colombia (Escobar, 1976), seven of the nine cases of croup were due to diphtheria. Investigators in The Gambia (Heyworth, 1973) found evidence to suggest an annual incidence of 6 per 1000 children under five. Salih (1985) has reported epidemic diphtheria and suggests that it is one of the most important diseases of childhood in the Sudan.

Pharyngitis. Pharyngitis is an upper respiratory tract infection that is most commonly viral, and, therefore, self-limited. Bacterial pharyngitis, although less common, is of greater public health importance. Though acute bacterial pharyngitis (except due to diphtheria) is not a significant primary cause of mortality, acute rheumatic fever (ARF) is an occasional late complication of untreated pharyngitis caused by Group A beta-hemolytic streptococci (Streptococcus pyogenes). ARF has been reported at rates of 27 to 100 per 100,000 per year (WHO, 1988a), although it is much less frequent in industrialized countries. Microscopic cardiac damage during ARF may progress over subsequent years, frequently causing incapacitation and, ultimately, death due to changes in cardiac function.

Antibiotic therapy of bacterial pharyngitis is recommended in industrialized countries to prevent ARF and other sequelae of streptococcal pharyngitis. Management of streptococcal pharyngitis has been controversial, however, and even less is known of the epidemiology of streptococcal disease to guide its management in the developing world (Markowitz, 1981). In view of additional concerns regarding the cost and insensitivity of the laboratory tests, and the lack of criteria to distinguish streptococcal pharyngitis on clinical grounds, it is currently difficult to establish a strategy for management of pharyngitis in developing countries which will effectively prevent post-streptococcal complications. Antibiotic prophylaxis for patients with a history of rheumatic fever has, therefore, been recommended as the most feasible strategy to prevent rheumatic heart disease in developing countries (WHO, 1988a).

Other Causes of ARI Mortality. Additional causes of ARI mortality include viral bronchiolitis and epiglottitis. Bronchiolitis, especially that due to RSV and parainfluenza 3, may be responsible for up to one third of ALRI among children under five, most of which occurs in infants (Cherian, 1990). The virology of these infections is apparently similar to that observed in industrialized countries (Selwyn, 1990). The difficulty of the laboratory techniques and lack of cost-effective measures for prevention and treatment of these infections have hampered efforts to address these important causes of mortality.

Epiglottitis, primarily due to Haemophilus influenzae type b, is an occasional cause of death due to respiratory obstruction. Additional epidemiologic investigations are also needed to define the role of other organisms as causes of mortality due to pneumonia, including group B streptococcus, Chlamydia trachomatis and C. pneumoniae, Mycoplasma pneumoniae, Ureaplasma urealyticum and Pneumocystis carinii. These bacterial and parasitic pneumonias may be important causes of mortality, especially among neonates or persons immunocompromised, such as by malnutrition or AIDS. Tuberculosis and some helminthic infections may also present as pneumonia, and these more chronic infections are often distinguished clinically by their failure to respond to the usual antibiotic therapy.

2. The Public Health Significance of Acute Respiratory Infection

Compilation and comparison of results from investigations on the public health significance of ARI in different countries is all but prevented by wide variations in study design, case definitions and culture techniques. Meaningful comparison of study results is difficult, for example, when some investigators have used sensitive case definitions which include all coughs and colds, while others focus only on more severe ARI which comes to the attention of health care workers.

2.1 Current Levels and Trends in the Developing World

Morbidity and Mortality Levels, circa 1985. The few well-conducted community-based prospective studies performed suggest that overall incidence of ARI in the developing world is similar to that observed in the industrialized world. Prevalence figures show that children spend from 22% to 40% of observed weeks with ARI, and from 1% to 14% of observed weeks with ALRI, such as pneumonia or bronchiolitis. ARI accounts for 20 to 40% of adult outpatient consultations and 20 to 60% among the pediatric populations. Twelve to 45% of pediatric admissions to hospitals are for ARI, while 20 to 30% of adult inpatients have been admitted for ARI treatment (Bulla, 1978; PAHO, 1980; Leowski, 1986).

The reported incidence of ALRI varies widely, from country to country as well as with age and nutritional status. While the annual incidence of pneumonia is 3 to 4 percent in children under 5 in the industrialized countries, it ranges from 10 to 20 percent in most developing countries, reaching as high as 80 percent in populations with a high prevalence of malnutrition and LBW. In Papua New Guinea in 1972-1973, for example, there were 72 episodes per thousand children one to four years of age, and 1,074 episodes per thousand infants (Riley, 1981). While an annual incidence of ALRI of 37 per thousand children was observed among those of normal nutritional status in Costa Rica, the rate was 457.8 per thousand among malnourished children (Pio, 1982). The overall incidence of ARI, most of which is coughs and colds, is comparable to that in the industrialized world. The greater public health importance of ARI in less developed countries is manifest, however, in the increased frequency of lower tract infections, and the 10- to 50-fold increased disease-specific mortality rates (WHO, 1984b; Mohs, 1985; Camargos, 1989). Most vulnerable to death due to ARI are the very young and the very old.

Of the estimated 15 million deaths occurring each year among children under five, 25 to 30% are due to ARI. As the cause of approximately 4 million deaths annually among this age group alone, ARI often surpasses diarrhea in importance as a cause of mortality (Bulla, 1978; Balint, 1979; Shann, 1984; Pio, 1985; Spika, 1989). Pneumonia causes from 2% to 8% of adult deaths in countries for which data are available (Hayes, 1989), ranking from second to tenth as a cause of death among the 15-64 year age group.

Trends in the Period 1970 to 1985. Although surveillance data for overall ARI morbidity in the developing world are limited, it is likely that these rates have remained unchanged in the past 15-20 years, just as they have in the industrialized countries. Reductions in incidence of ARI due to improved immunization coverage (with measles, diphtheria, and pertussis vaccines) would have little impact on overall ARI incidence, as the frequency of viral upper respiratory infections would remain largely unchanged.

Pneumonia mortality, on the other hand, has been reduced significantly over the past 15 to 20 years in the U.S. for all age groups except the elderly. Similar reductions in mortality would be expected in developing countries where the risk factors such as nutritional or socioeconomic status, immunization coverage and access to health care have improved. In many countries, however, ARI has increased in relative importance, frequently emerging as the first cause of childhood death where diarrheal disease mortality rates have been successfully reduced (Chen, 1980; Zimicki, 1988). ARI mortality has increased in relative importance even in settings where high coverage with measles immunization has been achieved (Zimicki, 1988; Greenwood, 1988).

Data from industrialized countries suggests that changes in immunization policy may adversely affect disease incidence. With intensive control efforts, for example, the incidence of measles in the U.S. had fallen to the lowest level ever recorded in 1983. However, increasing outbreaks have been observed since 1984 when expenditures for immunization were reduced. A similar resurgence of pertussis incidence has been noted in countries where changes in public opinion or immunization policy have led to a reduction in immunization coverage.

2.2 Possible Patterns of Morbidity and Mortality in 2000 and 2015

As viral upper resiratory infections, which account for the bulk of ARI morbidity, are unlikely to be eradicated in the foreseeable future, overall incidence of ARI is likely to be substantially unchanged over the next 25 years. Considerable opportunity exists, however, to reduce the incidence of vaccine-preventable ARI and to reduce the case-fatality ratio for pneumonia, thereby reducing ARI mortality.

Changing demographic patterns, such as through improved birth spacing and consequent improvements in nutritional status, would be expected to substantially reduce mortality due to pneumonia over the next 25 years. Increased life expectancies may later create larger populations of the elderly, among whom pneumonia will likely remain a significant cause of mortality. Progress in improving the access to and quality of care will be instrumental in controlling mortality among both the young and the elderly.

Of potential future concern, however, is the evolution of antimicrobial resistance among the pathogens causing bacterial pneumonia, which may interfere with the effectiveness of case management interventions. Although the development of newer antimicrobials has, to date, kept pace with the evolution of resistance, costs of later generation antibiotics will not be so easily borne in developing countries. And there is evidence to suggest that inappropriate use of antimicrobials, so frequent throughout the world, speeds the evolution of resistance.

Coverage with the vaccines currently included in WHO's Expanded Programme on Immunization (EPI) may be expected to continue to increase, also leading to reduction in ARI mortality. Improved vaccine technology will also likely alter the currently observed patterns of mortality due to ARI over these next 25 years. New vaccines may further improve hopes of reducing childhood ARI mortality due to measles and bacterial pneumonias caused by S. pneumoniae and H. influenzae.

2.3 Economic Costs of ARI

Direct Costs. ARI accounts for an average of 35% of all outpatient visits globally (Bulla, 1978), and generally similar proportions of all hospitalizations among children. The minimal direct cost of ALRI for children in the first two years of life in the US has been estimated at US$35.14 per child, fifty-six percent of which is attributable to hospitalization (McConnochie, 1988).

In many developing coutries, the economic burden of treatment of ARI already exceeds the expected cost of ARI case management with improved effectiveness and broader coverage. More appropriate use of existing health personnel and pharmaceutical resources might be expected, in many countries, to avert mortality with little or no additional expenditure. For example, the prevalence of the inappropriate use of pharmaceuticals for the management of ARI suggests that a net cost savings might be achieved by improving use patterns (Stansfield, 1990; Foreit, 1991). Frequently, over half of antibiotic use is unnecessary (Quick, 1988; Stein, 1984; Hossain, 1982). A study in Peru (Foreit, 1987) showed that approximately 50% of the expenditures for medications to treat ARI episodes were inappropriate, at an excess cost of US$18.47 to $21.97 per child covered. They estimated that an 89% reduction in treatment costs would be achieved through altering outpatient treatment of ARI to conform to WHO guidelines. Both inappropriate prescription of antibiotics and poor compliance probably also contribute to the development of antimicrobial resistance, which will greatly increase the future direct costs of ARI treatment as the use of more expensive antimicrobial agents becomes necessary.

Indrect Costs. ARI accounts for an average of one third of all absences from work (Bulla, 1978). In Britain, 1-2 weeks of schooling are lost per child per year due to ARI (Crofton, 1975). Data from Ghana (Ghana Health Project Assessment Team, 1981) indicate that over 94% of the 52 days lost per case of ARI are due to mortality rather than disability. Particularly in the setting of developing countries, where case fatality ratios are high and access to services limited, the bulk of costs attributable to ARI will be indirect costs due to mortality. Although no such estimates are available for the developing world, there is also likely a relatively greater toll due to ARI in these settings

where children experience growth deficits, malnutition, and resulting learning disabilities due to recurrent ARI episodes. Although these indirect costs of ARI are difficult to quantitate, they likely greatly reduce the potential productivity of those affected.

3. Lowering the Incidence of ARI

3.1 Elements of the Preventive Strategy

Possible preventive approaches to reduce ARI morbidity and mortality include: 1) immunization and 2) alteration of other risk factors which predispose to ALRI. It has been estimated that deaths due to the four vaccine preventable respiratory diseases (measles, diphtheria, pertussis and tuberculosis) may account for up to 25% of the total mortality among children under five in the developing world. Although the data are adequate to support the use of immunization in the control of ARI, the limitations of current knowledge regarding the feasibility and effectiveness of other preventive strategies are, for the moment, a barrier to their use in programs to reduce ARI morbidity and mortality.

The available data do not yet justify the design and implementation of programs to reduce environmental and nutritional risk factors for ARI control. However, the evidence does suggest that such approaches may be effective. Several of those which might be considered for inclusion in ARI control programs have been included in the following discussion of potential preventive interventions. Those for which evidence of feasibility and effectiveness are strongest are included in a comparative model of cost-effectiveness, which is summarised in table 3.3. It is important to recognize, however, that the actual benefits for these interventions would be broader than those calculated, since each would reduce morbidity and mortality due to many health problems beyond ARI alone. Sources for the data used and the methods for calculating the cost-effectiveness estimates are specified in appendix A.

Measles Immunization. Operational problems in maintaining the "cold chain" for handling the measles vaccine are a frequent barrier to maintaining vaccine viability and efficacy. WHO has estimated the efficacy of the vaccine to be 90% in the absence of any breaks in the cold chain (Keja, 1988). Because of variability in study design and alterations in vaccine viability due to handling, measured vaccine efficacies may vary broadly, although Hull (1983) achieved an 89% efficacy in The Gambia.

Considerable controversy surrounds the issue of immunization strategy for measles. Studies with the currently available (Schwartz) vaccine have demonstrated that residual levels of maternal antibody restrict the efficacy of the vaccine in the first few months of

Table 3.3

INTERVENTIONS FOR ARI CONTROL: SUMMARY OF CALCULATIONS* OF EXPECTED COST-EFFECTIVENESS

INTERVENTION	Expected Disease-Specific Mortality Reduction	Proportion of ARI Mortality Addressed	Expected ARI-Specific Mortality Reduction	Under-Five Deaths Averted (Per Million Population)	Cost U.S. $ Per Person In Target Population	Total Cost (U.S. $) (Per Million Population)	Cost (U.S. $) Per Death Averted	Cost per Discounted Healthy Life Years Saved
CASE MANAGEMENT	60%–90% (80%) (pneumonia)	38%–52% (49%)	23%–47% (39%)	351–676 (585)	$3.61	$220,000–$940,000 ($541,877)	$379–$1610 ($926)	$37
BREASTFEEDING PROMOTION	50%–80% (72%) (pneumonia)	4%	2%–3.2% (2.8%)	15–96 (42)	$5.00	$40,000	$417–$2667 ($952)	$38
EPI VACCINES	44%–80% (65%) (pertussis, measles)	20%–25% (22.5%)	8.8%–20% (14.6%)	66–600 (219)	$9.08	$122,580–$245,160 ($217,920)	$409–$1857 ($995)	$40
REDUCTION OF MALNUTRITION	50%-95% (80%) (pneumonia)	70%–90% (80%)	35%–85% (64%)	263–2550 (960)	$15.00 (malnourished) $11.85 (all children)	$810,000-$1,777,500 ($1,500,000)	$697–$3080 ($1563)	$63
PNEUMOCOCCAL VACCINE	0%–30% (15%) (pneumoccal pneumonia)	30%–50% (40%)	0%–15% (7%)	0–450 (105)	$7.28	$98,280–$196,560 ($174,720)	>$437 ($1664)	$67

* Most likely values in parentheses

life. Available data regarding age-specific seroconversion and measles incidence rates suggested that immunization at nine months of age would prevent the maximal number of cases (EPI, 1982). These data were the basis for the WHO recommendation of one dose of measles vaccine to be given between 9 and 12 months of age.

Yet, in many countries, 20 to 45% of measles cases occur among infants before nine months of age, when they are most vulnerable to measles mortality. It had been suggested that "herd immunity" achieved with adequate immunization coverage among older infants and children may serve to reduce the infection rate among younger infants (Black, 1982; Heymann, 1983). Recent evidence, however, suggests that in areas of high population density, there is no shift in the age distribution of cases or reduction in incidence greater than the level of vaccination coverage (Taylor, 1988; Dabis, 1988). Particularly in the urban areas of Africa, the increased transmission rates may lower the optimal age for immunization (Taylor, 1988; McLean, 1988).

In view of these and other findings, the Expanded Programme on Immunization (EPI) of WHO has endorsed the use of the newer high potency vaccines at six months of age in countries where measles is a significant problem among infants under nine months of age. The Edmonston-Zagreb (EZ) strain measles vaccine and other such high potency preparations have demonstrated more promising immunogenicity and protection in younger infants than the vaccines in current use, most of which are lower-titer derivatives of the Edmonston-Enders strain. The new EZ vaccine has demonstrated higher seroconversion rates among infants in Mexico (Sabin, 1983, 1984), The Gambia (Whittle, 1988), and Bangladesh (Khanum, 1987), as well as in several unpublished studies (WHO, 1990), without serious adverse reactions. Similar titers to those obtained with Schwartz vaccine at nine months are observed at 4-6 months with EZ vaccine in the developing country trials.

Ongoing studies of the efficacy, optimal dose, non-parenteral routes of administration (in order to overcome residual maternal antibodies), and booster response to the new vaccines will help to further refine immunization policies in the near future. More studies are needed to explore the cost-effectiveness of a two-dose schedule, such as initial measles immunization with the third DTP dose (followed by a second dose at six to twelve months of age). High drop-out rates, which are a major barrier to the success of immunization programs, also argue in favor of using earlier opportunities for immunization, even if children are less than the ideal age for achieving seroconversion or optimum protection. Some investigators, however, have raised the concern that earlier immunization may interfere with antibody response at the time of revaccination (Stetler, 1986; Wilkins, 1979; Linnemann, 1982).

Pertussis Immunization. The vaccine for pertussis is delivered together with the diphtheria and tetanus vaccines (DTP). Pertussis vaccine efficacy for the fully (i.e., 3 doses) immunized child has been recently questioned, but is estimated at 70-90% in the industrialized world (Church, 1979; Koplan, 1979) and 50-90% in developing countries (WHO/EPI, 1985). Like for measles, however, transmission rates in endemic areas are such that many children are infected and most deaths occur prior to the usual age of completed immunization.

Pertussis immunization coverage in some industrialized countries has fallen off in the last fifteen years due primarily to concern about associated adverse neurological effects, most notably encephalopathy (Brahmans, 1986), although there is also some controversy about the vaccine's effectiveness (Fine, 1987). Outbreaks of pertussis have been observed in Great Britain, Japan and Sweden, where policy changes or public opinion have led to a reduction of immunization coverage. However, even with the current preparation, the benefit of the vaccine far outweighs the risk of adverse effects (Koplan, 1979; Cherry, 1984). Accelerated research has led to the development of acellular pertussis vaccines which offer hope in the near future for both improved efficacy and fewer adverse effects (Miller, 1991).

Pneumococcal Immunization. The pneumococcal vaccine licensed for use in the U.S. is composed of the purified polysaccharide extracted from 23 of the 84 types of Streptococcus pneumoniae. These capsular subtypes are responsible for approximately 90% of invasive pneumococcal disease in the U.S. However, over 30% of blood culture isolates from patients with pneumonia in developing countries have been pneumococcal serotypes which are not included in the current vaccine (Ghafoor, 1990; Mastro, 1991). In addition, the vaccine induces little immunity in children under 18 months of age, who are most vulnerable to mortality due to pneumococcal infections.

Studies in the U.S. have suggested a 50-80% efficacy in preventing bacteremia and pneumonia among adults with the currently available vaccine. Results of studies among the very elderly or chronically ill (Simberkoff, 1986) and among children under 18 months have been less encouraging. The vaccine has also been tested in Papua New Guinea, which reports one of the highest proportions of ALRI due to pneumococcal infections at up to 50%. Clinical trials there (Riley, 1986) among children 6-59 mos of age have shown a 50% reduction in ARI-specific mortality rates during periods of one to five years after immunization. However, there appears to have been no reduction in pneumonia incidence and there is little evidence to suggest that the vaccine was immunogenic in the younger age groups. The cause of the mortality reduction is, therefore, not clear and the results need to be replicated in other developing countries. Also of potential interest was the finding that infants of mothers immunized during their last trimester had a 32%

lower rate of pneumonia (Riley, 1981). Such "passive" protection of infants while they await completion of immunization series deserves further investigation.

H. influenzae Vaccine. Like pneumococcal vaccine, which is also a polysaccharide vaccine, the current H. influenzae vaccine has limited immunogenicity in infant and young children. The vaccine is made from H. influenzae type b (Hib) polysaccharide, since this type accounts for virtually all of invasive disease in the industrialized world. Protective efficacy measured in children over 24 months of age has ranged from 0% to 90% (Granoff, 1986; Harrison, 1987; Black, 1988; Gilsdorf, 1988), based on prevention of invasive disease (mainly meningitis and bacteremia). The efficacy of the Hib vaccine in reducing pneumonia morbidity and mortality cannot be estimated from US data, since the frequency of pneumonia due to Hib is too low.

An increase in early cases after Hib immunization has been variously ascribed to unmasking of latent infection or shortening of the incubation period, perhaps due to transient post-vaccination reductions in antibody levels (Black, 1988). One study (Osterholm, 1987) actually calculated an increased risk of H. influenzae infection of 45%, leaving the protective effect of Hib vaccine in some doubt.

The newer Hib conjugate vaccines, which link Hib antigens to protein carriers, show improved immunogenicity in children under two and hold greater promise for preventing H. influenzae disease in the very young. Although experience with use of diphtheria toxoid as a conjugate has been mixed, tetanus toxoid carriers may be more effective (Ward, 1990; Siber, 1990; Eskola, 1990). Formulations for developing countries will need to include additional types (i.e., non-b and non-serotypable H. influenzae) which are not a prominent cause of invasive disease in the industrialized world (Funkhouser, 1991). Recent studies in Papua New Guinea (Weinberg, 1990), Pakistan (Ghafoor, 1990), and The Gambia have shown that approximately half of all invasive H. influenzae disease is due to non-serotypable or non-b strains.

The costs of the current conventional Hib vaccine is US$2.19 per dose, while the conjugate vaccine is $14 per dose. Hay (1987) compared the costs and benefits of rifampin prophylaxis of exposed contacts to immunization with the currently available unconjugated vaccine. Vaccination was predicted to be the most cost-effective strategy with a calculated overall net savings of US$64.8 million, in the setting of an anticipated social cost of US$1.94 billion for H. influenzae disease in the 1984 birth cohort. Because of the paucity of data on Hib vaccine effectiveness in developing countries, no estimates of cost-effectiveness have been included in table 3.3.

Other Immunizations. Vaccination to induce immunity to organisms which cause ARI mortality is clearly an effective preventive intervention. There is good evidence to

support the use of vaccines against measles and pertussis, both in the documented public health importance of these problems and the effectiveness of immunization. Although the expected impact of diphtheria vaccine is difficult to predict due to the lack of information regarding diphtheria morbidity and mortality, marginal costs of including the vaccine with pertussis and tetanus (in DTP vaccine) are nearly negligible.
Effective vaccines against the viral causes of pneumonia and bronchiolitis would likely avert additional mortality. However attempts to develop effective vaccines against the two most important causes of mortality, RSV and parainfluenza viruses, have been frustrating. Recently, however, the mechanism for the adverse hypersensitivity responses to RSV antigens has been identified, so that purified antigen and recombinant vaccines currently under development should offer greater hope for these important cause of respiratory mortality (Pringle, 1987). Influenza vaccines have been effective in preventing infections, particularly among the elderly, but the "antigenic drift" which characterizes these viruses makes vaccine production and distribution more costly. Such immunization programs for adults have also been poorly received and achieve limited coverage.

Environmental and Nutritional Risk Reduction. Alteration of other documented and suspected risk factors for ARI mortality, such as poor nutritional status (including LBW, poor infant feeding practice, undernutrition, and vitamin A deficiency) and exposure to smoke (including active and passive cigarette smoking and smoke due to organic fuel cookfires), have been suggested as additional strategies for the prevention of ARI deaths. Although for some of these risk factors the associations are strong, there are few studies which support the feasibility and effectiveness of programs using these interventions to prevent ARI. The data are strongest for promotion of breastfeeding and reduction of malnutrition.

3.2 Good Practice and Actual Practice: Are There Gaps?

Correct case management is the central strategy of WHO's Programme for the Control of Acute Respiratory Infections, however, one of the four objectives is "to reduce the incidence of acute lower respiratory infection." Although intervention to alter some of the non-specific risk factors for ARI (table 3.2) is an intriguing possibility for prevention of pneumonia, immunization remains the only strategy known to be effective in the prevention of morbidity and mortality due to ARI.

Even this proven technology, however, has not been fully exploited to prevent ARI mortality. As of 1988, 97 countries had an Expanded Programme on Immunization (EPI) (Keja, 1988), but many of these have subnational coverage, often neglecting the neediest children in the most remote areas. Vaccination efforts are most appropriately integrated with the primary health care system, avoiding duplication of necessary management,

supervisory, training, and logistical resources. Immunization campaigns, while they result in high short-term coverage, may compromise sustainability and divert resources from the development of the rest of the primary health care infrastructure.

Global coverage estimates for children immunized during the first year of life are 50% for measles and 55% for the DTP series of three doses (Keja, 1988), although figures are considerably lower in Africa. Barriers to achieving improved coverage with the EPI vaccines include difficulties with supply and management systems and the practical problems of maintaining the cold chain. High "drop-out" rates for immunization series are partly due to limitations of resources for social mobilization, the opportunity costs to the family in obtaining immunizations, failure of health workers to profit from clinic visits by giving immunizations (Keja, 1988), and adverse effects of current vaccine preparations.

There has been increasing attention, especially in Africa, to the frequent problem of reuse of syringes and needles. These unsafe immunization practices introduce the risk of transmission of blood-borne diseases such as hepatitis and AIDS.
Efforts to prevent ARI mortality through reduction of the prevalence of malnutrition and LBW are hampered by the obvious social, economic and political barriers to development. Promotion of appropriate infant feeding practice, including breastfeeding, represents an opportunity to reduce ARI morbidity and mortality that deserves greater emphasis. Although research must continue to improve preventive technologies for the major causes of ARI mortality, ARI control programs for the near future will rely principally on improved case management to reduce ARI mortality.

4. Case Management

4.1 Elements of the Case Management Strategy

WHO's ARI Control Programme has taken the lead in promoting intervention to address the problem of ARI in children. The primary objective of the program is the reduction of ALRI mortality through effective case management. Secondary objectives include the reduction of 1) the severity and complications of acute upper respiratory tract infections, 2) the inappropriate use of antibiotics and other drugs for the treatment of ARI, and 3) the incidence of pneumonia. To improve the case management of pneumonia, WHO has developed guidelines for standard treatment at first level and referral health facilities and at the community level.

In countries with a high incidence of bacterial pneumonia (generally those with an infant mortality rate greater than 40 per 1000), pneumonia may be relatively reliably diagnosed on the basis of simple clinical criteria alone. For any child under five with cough or

difficult breathing, tachypnea (rapid breathing) appears to be the best single predictor of pneumonia and the need for antibiotic treatment (Shann, 1982; Cherian, 1988; Campbell, 1988; 1989a; 1989b; Lucero, 1990). In view of the variation of normal respiratory rates with age, WHO guidelines recommend a threshold of 60 or more per minute in young infants (under two months), 50 or more for older infants (2 to 11 months), and 40 or more for children one to four years of age (WHO, 1990b). Chest indrawing (retraction of the lower part of the chest wall on inspiration) detected in children two months to 4 years of age, indicates the presence of severe pneumonia requiring hospitalization. The algorithms used for diagnosis and treatment of childhood pneumonia, including additional criteria for referral for hospitalization, are summarized in figures 3.1 and 3.2 (WHO, 1991a). Any of four inexpensive antibiotics may be recommended for the home care of uncomplicated pneumonia, including cotrimoxazole (trimethoprim-sulfamethoxazole), amoxycillin, ampicillin, and procaine penicillin.

Although wheezing (including asthma) is managed within this algorithm, there are separate guidelines for care of sore throats and ear infections. All cases receive general supportive care, including fluids, continued feeding, treatment of fever, and clearing of nasal or ear discharge as needed. Although these findings require further confirmation, studies in Pakistan have suggested that such supportive measures may actually reduce the likelihood of progression of uncomplicated coughs and colds to life-threatening pneumonias (Khan, 1990).

There is no doubt about the importance of bacterial pneumonia as a cause of mortality or about the effectiveness of antimicrobials in reducing case-fatality ratios. But to address concerns whether periperal health care workers with limited training could identify and treat cases appropriately, several intervention studies were conducted to test the algorithm for case-management in an operational setting in several developing countries. These and another study conducted in Jumla, Nepal, were recently reviewed (WHO, 1988a). Although each of the studies suffered from design flaws and/or confounding due to simultaneous introduction of other interventions, taken as a whole they present strong evidence of the efficacy of case management. It was found that ARI-specific mortality declined by an average of 41.6% (range 18-65%), while overall mortality was reduced in the same five study areas by an average of 22.2% (range 11.5-40%). These studies, for which further details are presented in table 3.4, confirmed the feasibility and efficacy of providing case management of ARI through peripheral health workers with limited training.

These results compare favorably with earlier more theoretical calculations of the expected effectiveness of ARI case management interventions. For example, Tugwell (1985) assumed an efficacy of cotrimoxazole in treatment of community-acquired ALRI of 80%, a diagnostic accuracy of 80% by the health workers, a correct treatment rate of

Figure 3.1

THE YOUNG INFANT (AGE LESS THAN 2 MONTHS)

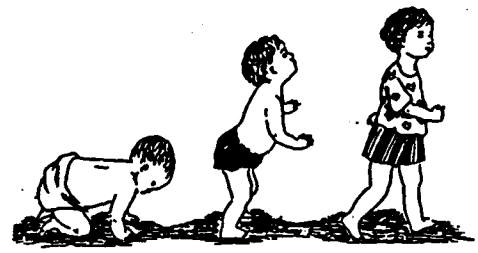
SIGNS:	• Stopped feeding well, • Convulsions, • Abnormally sleepy or difficult to wake, • Stridor in calm child, • Wheezing, or • Fever or low body temperature.
CLASSIFY AS:	VERY SEVERE DISEASE
TREATMENT:	► Refer URGENTLY to hospital. ► Keep young infant warm. ► Give first dose of an antibiotic.

SIGNS:	• Severe chest indrawing, or • Fast breathing (60 per minute or MORE).	• No severe chest indrawing, and • No fast breathing (LESS than 60 per minute).
CLASSIFY AS:	SEVERE PNEUMONIA	NO PNEUMONIA: COUGH OR COLD
TREATMENT:	► Refer URGENTLY to hospital. ► Keep young infant warm. ► Give first dose of an antibiotic. (If referral is not feasible, treat with an antibiotic and follow closely.)	► Advise mother to give the following home care: ► Keep young infant warm. ► Breast-feed frequently. ► Clear nose if it interferes with feeding. ► Return quickly if: ► Breathing becomes difficult. ► Breathing becomes fast. ► Feeding becomes a problem. ► The young infant becomes sicker.

Figure 3.2

THE CHILD
AGE 2 MONTHS UP TO 5 YEARS

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



SIGNS:	• Chest indrawing. *[If also recurrent wheezing, go directly to ▸ Treat Wheezing]*	• No chest indrawing, and • Fast breathing (50 per minute or more if child 2 months up to 12 months; 40 per minute or more if child 12 months up to 5 years).	• No chest indrawing, and • No fast breathing (Less than 50 per minute if child 2 months up to 12 months; Less than 40 per minute if child 12 months up to 5 years).
CLASSIFY AS:	SEVERE PNEUMONIA	PNEUMONIA	NO PNEUMONIA: COUGH OR COLD
TREATMENT:	▸ Refer URGENTLY to hospital. ▸ Give first dose of an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. (If referral is not feasible, treat with an antibiotic and follow closely.)	▸ Advise mother to give home care. ▸ Give an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. ▸ Advise mother to return with child in 2 days for reassessment, or earlier if the child is getting worse.	▸ If coughing more than 30 days, refer for assessment. ▸ Assess and treat ear problem or sore throat, if present (see chart). ▸ Assess and treat other problems. ▸ Advise mother to give home care. ▸ Treat fever, if present. ▸ Treat wheezing, if present.

	Reassess in 2 days a child who is taking an antibiotic for pneumonia:		
	WORSE		IMPROVING
SIGNS:	• Not able to drink. • Has chest indrawing. • Has other danger signs.	THE SAME	• Breathing slower. • Less fever. • Eating better.
TREATMENT:	> Refer URGENTLY to hospital.	> Change antibiotic or Refer.	> Finish 5 days of antibiotic.

Table 3.4

CASE MANAGEMENT OF ARI IN CHILDREN: SUMMARY OF INTERVENTION STUDIES

		BASELINE DATA		CASE DETECTION		PNEUMONIA TREATMENT			MORTALITY REDUCT.	
Location (Dates)	Study Design	IMR (Per 1000)	Measles Im. Coverage	Case-finding	Maternal Education	Source	First Line Antimicrobial	Referral Care	ALRI Specific	Overall
Haryana, India (1982-84)	Concurrent control low birth weight only	210-275	0%	Active (weekly)	Yes	CHW *	Penicillin (oral)	None	42%	24%
Abbottabad, Pakistan (1985-87)	Concurrent control, subsequent intervention in control area	90-100	5.4%	Active (every 10-14 days)	Yes	CHW or clinic	Cotrimoxazole	Poor access	56%	55%
Bohol, Philippines (1984-87)	Concurrent control	49-63	58-60%	Passive	No	Clinic	Cotrimoxazole	Yes	25%	13%
Bagamoyo, Tanzania (1985-87)	Concurrent control, subsequent intervention in control area	137	53%	Passive	Yes	Clinic or CHW	Cotrimoxazole	Yes	30%	27%
Kathmandu, Nepal (1984-87)	Before and after	162	11%	Active (every 2 wks)	Yes	CHW	Ampicillin	Poor utilization	62%	40%
Kediri, Indonesia (1986-87)	Before and after	154	1.5%	Active (every 2 wks)	Yes	CHW	Cotrimoxazole	Poor access	67%	41%

Adapted from WHO/ARI/88.2 and WHO/ARI/91.20 *Community Health Worker, **Not Significant

90%, 80% patient compliance with the medication regimen, and 80% access to appropriate treatment, calculating an expected program effectiveness of 37%.

Lessons learned from the case management intervention trials must be taken into account in program design and selection of research priorities. For example, the Jumla study documented a mean duration of fatal episodes of pneumonia of 3 1/2 days (Daulaire, personal communication, 1990). Under these circumstances, active surveillance by health workers is unlikely to detect an adequate proportion of cases. ARI control programs must rely on families to detect signs and symptoms of pneumonia and bring suspected cases to a health worker for evaluation and treatment. Reductions in deaths due to diarrhea were observed in Jumla, where only pneumonia cases were treated (WHO, 1988a), raising the important question of the impact of antibiotic treatment on concurrent infections such as diarrhea or malaria.

Few operational programs for ARI case management have measured cost per case treated or death averted. The figures which are available have been obtained in research settings, where expenditures may not be representative. Costs per case treated in the Philippines have been estimated at US$5.15 and $4.37 (Brenzel, 1990). Costs per death averted have ranged from US$200 in Indonesia to $350 in Nepal (Brenzel, 1990). Using a model to estimate cost-effectiveness outlined in appendix A, we have calculated an expected cost per death averted of US$926, and a cost per discounted healthy year of life saved of US$37.

4.2 Good Practice and Actual Practice: Are There Gaps?

By the end of 1990, 54 countries had prepared plans of operation for ARI control programs and 47 had functioning programs (WHO, 1991b). Eighteen additional countries had designated a national program manager and issued technical guidelines for case management. Therefore, a total of 59 countries, most of which are in the Americas and Western Pacific, had taken some steps to establish a national ARI control program.

Yet it is clear that the "greater intrinsic complexity" (WHO, 1990b) of the management of ARI will present great challenges in the implementation of control programs. The significant operational problems encountered in immunization and diarrheal disease control programs, for example, are likely to be dwarfed by the obstacles to successful implementation of an ARI control program. Appropriate case management requires that each of many difficult conditions be met, including the design and comunication of culturally appropriate and effective health education for family recognition of suspected pneumonia, prompt presentation to an effectively trained and carefully supervised health worker, correct diagnosis and selection of treatment, development and maintenance of

reliable logistical systems to assure adequate supplies of antibiotics, family compliance with appropriate instructions for care, and access to competent referral care as required.

These prerequisites for effective case management of pneumonia are inextricably linked to the the basic infrastructure for primary health care. Although ARI control may be introduced as another "vertical" program, it is less conveniently addressed outside the context of the health care delivery system as a whole. Strengthening of systems to reduce ARI mortality therefore requires a more comprehensive approach to improving access and quality of care.

It will be important, for example, to rationalize the use of antibiotics for other health problems in order to assure adequate supplies will remain to treat cases of pneumonia. Even when basic antibiotics are unavailable in peripheral health centers, the presence of antibiotics in remote markets provides evidence of the effectiveness of informal systems of distribution. Such sales of antimicrobials in the informal sector likely leads to their inappropriate use in even more than the 50 to 95% of cases in which inappropriate use is observed in health centers (Chaulet, 1982; Hossain, 1982; Gutierrez, 1986). Reduction of the inappropriate use of these supplies may actually avert pneumonia deaths at no increased cost, both through increasing effective use and reducing adverse effects and the evolution of antimicrobial resistance (Stansfield, 1990). Although the feasibility of labelling of antibiotics in special packages (as solely for use in the treatment of pneumonia in children) is being assessed (WHO, 1990b), the inevitable discovery of the alternative uses of these powerful pharmaceuticals will likely render such devious practices ineffective.

Another obstacle to be anticipated is the resistance of physicians to empowering other health care workers with limited training to diagnose and treat with antibiotics. Narain (1987), for example, has presented evidence that over 90% of physicians do not agree that non-physician health workers should be provided with antibiotics to treat children suffering from pneumonia. Vigilance will also be required to prevent commercial drug companies from exploiting new markets by extracting inflated prices for basic pharmaceutical supplies.

Many countries will require assistance in the development of laboratory capability to assure correct selection of antibiotics (at least in tertiary care facilities), particularly for referral patients who have failed treatment with first-line antibiotics, through basic bacterial cultures and tests for antibiotic sensitivity. These capabilities are also required to maintain the necessary surveillance for the emergence of significant antibiotic resistance patterns, as is evidenced by the alarming resistance to commonly used antimicrobials in several countries (El Mouzam, 1988; Lataorre, 1988; Mastro, 1991).

Donor agencies must recognize these gaps when allocating resources for ARI control program development.

Although the historical lack of donor support in this area has also been an important obstacle to ARI control, the donor community has recently shown increased interest in strengthening ARI case management. Reduction in ARI deaths by 25% was included among targets established for the 1990s by the WHO/UNICEF Joint Committee on Health Policy. This commitment is only beginning to be reflected in increased levels of national, bilateral, and multilateral funding to ARI control programs.

5. Priorities for ARI Control

5.1 Priorities for Resource Allocation

The many national health plans which emphasize the priority of interventions to reduce infant and child mortality cannot long ignore ARI, which is often a major cause of this mortality. Global commitment to addressing this problem was reflected in the adoption, at the World Summit for Children in September 1990, of a resolution to reduce deaths due to ARI by one third during the final decade of this century (UNICEF, 1991). In view of the efficacy of the vaccines and of antibiotic therapy for pneumonia, it is probable that over half of ARI deaths could be averted using only the currently available technologies of immunization and improved case management. Breastfeeding promotion and reduction of the prevalence of malnutrition are also likely to be cost-effective in reducing mortality due to ARI. Interventions for the promotion of breastfeeding, reduction of malnutrition, and immunization with EPI vaccines will have a broader impact on child survival through their effectiveness in prevention of mortality due to diseases other than ARI. These three interventions, along with appropriate case management, should be given high priority for implementation, particularly in countries with high infant mortality. Such a combined curative-preventive approach is likely to be the most effective as a strategy to reduce mortality (Mosley, 1988).

National ARI control programs should be developed or accelerated according to the guidelines recently refined by WHO's Programme for the Control of Acute Respiratory Infections. Intervention studies have provided adequate evidence among children under five that improved case management of ARI will reduce mortality due to ARI and, possibly, overall mortality in that population. As WHO has pointed out (WHO, 1988a), "there is no technical justification in delaying any further the expansion of ARI control programmes as an essential component of child survival efforts, and with the same priority attached to the Expanded Programmes on Immunization (EPI) and the diarrheal disease control (CDD) programmes." Although most countries have active EPI

programs, these programs must also be strengthened to assure improved coverage (Poore, 1988).

Referral care of pneumonia in persons who have responded poorly to antibiotic treatment requires adequate laboratory support to perform bacteriologic cultures, organism identification, and antibiotic sensitivities. Any national ARI control program must, therefore, allocate adequate resources to competently monitor antibiotic resistance in at least one national reference center. Ability to conduct vaccine trials will also depend on laboratory capability in the identification of specific serotypes for the major pathogens.

5.2 Research Priorities

During program design and implementation, high priority should also be assigned to establishing a strong evaluation or applied research component to aid in assessing the effectiveness of operational programs, refining program priorities and addressing the many questions which remain regarding optimal strategies for prevention and case management. WHO recently reviewed research priorities for ARI control (WHO, 1989; 1990c), preparing a list which is adapted and presented in table 3.5.

Additional research needs to be addressed include the development and validation of survey techniques for detection of ARI episodes and pneumonia deaths for use in program evaluation. Studies are also needed to determine the impact of antibiotic use on the incidence and mortality of other diseases (especially malaria and diarrhea) and the sociocultural factors which modulate the effectiveness of programs. Vaccine research issues, in addition to those detailed in table 3.5, should include additional efficacy trials of the newer measles vaccines and two-dose schedules of administration.

Another issue for operational research will be the effect of current program emphasis on children under 5. Promoting the recognition of the need and increasing the demand for health services will be essential to the success of ARI control programs. Although the opportunity for impact is greatest among the program's target group, it will be important to assess the benefits and costs to national programs which attempt to reserve health workers' attentions and antibiotic supplies for children at the perceived expense of the communities' adult decision-makers and opinion leaders.

Opportunities to explore mechanisms to achieve financial sustainability may be limited for the immunization interventions designed to prevent ARI. For the curative care provided in the case management of ARI, however, it will be important to explore mechanisms for cost recovery, such as health insurance schemes, taxation, or user fees to enhance the financial sustainability of national programs.

Table 3.5
(adapted from WHO/ARI/89.4 and 90.7)
RESEARCH PRIORITIES FOR ACUTE RESPIRATORY INFECTION CONTROL

EPIDEMIOLOGIC RESEARCH

* Assess the effectiveness of interventions and programs to modify the risk of pneumonia, especially through reduction of exposure to biomass fuel emissions.
* Document the epidemiology of invasive strains of Haemophilus influenzae and Streptococcus pneumoniae, to guide the development of effective vaccines.
* Define the relative prevalence and etiologies of pneumonia, sepsis and meningitis in less immunocompetent groups such as young infants (less than three months of age) and undernourished children.

CASE MANAGEMENT (CLINICAL) RESEARCH

* Identify the signs and symptoms which indicate the need for hospital care.
* Evaluate the performance of the treatment protocol, including for wheezing, at first level referral facilities.
* Explore the most effective ways to define and teach the reliable distinction between clinical presentations of pneumonia and malaria, and to determine the efficacy of cotrimoxazole in treatment of malaria.
* Define the clinical features and optimal treatment of serious bacterial infection (pneumonia, sepsis, and meningitis) in young infants (< three months of age).
* Determine the special needs of undernourished children, including the clinical features and causes of pneumonia and the optimal treatment for these children.

SOCIAL SCIENCE RESEARCH

* Examine cultural and other factors which determine families' ability to recognize signs of pneumonia, seek appropriate care and comply with treatment regimens.
* Identify optimally effective strategies for the design of appropriate health education programs for ARI control, including for the modification of risk factors for pneumonia.

VACCINE AND DIAGNOSTICS DEVELOPMENT RESEARCH

* Develop inexpensive, simple, and reliable diagnostic technologies which will aid in counting respiratory rate and determining the etiology of pneumonias, such as by identifying viral or bacterial antigens in urine or blood.
* Perform field trials of the available polysaccharide pneumococcal vaccine and of conjugate vaccines for H. influenzae type b and for nonserotypable H. influenzae, RSV and parainfluenza viruses when available.

Appendix A

SOURCES OF DATA AND METHOD USED TO OBTAIN COST-EFFECTIVENESS ESTIMATES SUMMARISED IN TABLE 3.3

Since no prospective data are available for the effectiveness of preventive interventions in the reduction of ARI mortality among children under five, the estimates used in table 3.3 are obtained primarily from retrospective observations of relative risk. These figures, therefore, represent indirect estimates of the potential efficacy of the intervention rather than a measure of effectiveness achieved in an operational setting. Cost estimates for these preventive interventions are also obtained indirectly, through review of data for similar programs. Cost estimates for case management interventions are similarly derived from data available from other programs with similar interventions.

Estimates were made assuming a standard population of one million persons, with 15% of the population being children under five (approximately 3% infants) and 8% mothers of children under five. Estimates of cost and effectiveness for immunization interventions are made using a coverage range of 45% to 90%, as used by Feachem (1983). "Most likely" values for immunization interventions are calculated assuming an immunization coverage of 80%, the target specified for UNICEF's goal of "Universal Childhood Immunization". Calculations of deaths averted were based on pre-intervention ARI-specific mortality rates of 5 to 20 per thousand (with a "most likely" value of 10/1000), which yields an expected 750 to 3000 (most likely 1500) deaths among the 150,000 children under five in the standard population of one million.

The effect of implementing of multiple interventions to prevent ARI mortality is unlikely to be simply additive. Many children who die with ARI suffer from several risk factors, such as the malnourished child who dies of pneumococcal pneumonia during or within one month of an episode of measles. One possibility is that such "competing risks" of mortality (Mosley, 1986) may operate on the same children, so that prevention of one potentially mortal event may only leave children vulnerable to other causes of so-called "replacement mortality" (WHO/EPI, 1987b).

Another possibility is that prevention of ARI is actually synergistic with other preventive interventions through reducing the cumulative contributions to the "frailty" (Mosely, 1985) of the child, such as is observed in the growth faltering with recurrent infection. An example of the potential for synergism among interventions has been suggested by recent observations of a reduction of diarrheal disease mortality in a program which treats only childhood pneumonias (WHO, 1988a).

The calculations presented below consider only the short-term effects of these interventions upon mortality. It is not known whether the longer term impact of these preventive and curative interventions would be augmented by reduction in the frailty of these children, or offset by replacement mortality. Because of these theoretical problems and the many operational problems associated with predicting the effects of multiple health interventions, the figures presented in table 3.4 are of use primarily as estimates of the relative cost-efficacy of interventions when implemented alone to reduce ARI mortality. All costs are stated in US dollars.

Expanded Program on Immunization. Most of the ARI mortality prevented by the EPI vaccines is due to measles and pertussis. Feachem and Koblinsky (1983) estimate that measles immunization between the ages of 9 and 12 months, with an ideal efficacy of 90% and a coverage of between 45 and 90% can avert 44-64% of measles cases. Anticipating the improved efficacy of the higher potency vaccines and immunization before nine months of age, the upper limit of the proportion of cases averted was adjusted to 80%. Since pertussis vaccine has a similar ideal efficacy (WHO, 1985), it is assumed that a similar proportion of cases would be averted at the same coverage rates of 45% to 90% Therefore, for pertussis and measles, an efficacy range of 44% to 80% has been used for the model, with an intermediate "most likely" value of 65%.

It has been estimated that up to 25% of ARI mortality may be preventable using current EPI vaccines. Mortality among children under 5 due to measles-associated ARI accounted for approximately 20% of all ARI mortality (1.8/1000 out of 9.1/1000) in 17 study areas during case management trials for WHO (WHO, 1988a). It is therefore assumed that 20% to 25% of ARI mortality would be addressed through use of current EPI vaccines. An expected ARI-specific mortality reduction of 8.8% to 20% ("most likely" 14.6%) may be calculated using these figures. These estimates are comparable to the ARI mortality reduction figures of 5% to 20% calculated by Singhi (1987) and Steinhoff (1987), although Clemens (1988) observed a 22% protective efficacy of measles vaccine for respiratory deaths in Bangladesh. Based on the expected numbers of deaths of 750 to 3000, the number of deaths averted may be calculated to range from 66 to 600, with a "most likely" value of 219.

The cost per child served for EPI immunization interventions to prevent ARI mortality is calculated as that portion of the cost of delivering all EPI vaccines which is proportional to the benefit achieved in averting ARI deaths. Tetanus is the only non-ARI EPI disease which is a significant cause of infant and child mortality. Since tetanus accounts for up to 40% of the overall mortality prevented through EPI vaccines, 60% ($9.08) of the $15.13 average cost per fully immunized child (Brenzel, 1989) was ascribed to ARI prevention. The cost per ARI death averted (achieving

coverage levels of 45-90% among the 30,000 infants in the target age group) may, therefore be calculated at $409 to $1857, with a "most likely" value of $995.

Pneumococcal Immunization. The efficacy of pneumococcal vaccine, particularly among the youngest children, has not been clearly demonstrated in the developing world. The reported efficacy in adults of 0-80% and the efficacy of 69% noted among children in the U.S. suggest a range of 0-70%. However, since the vaccine is less immunogenic among children under two (approximately 40% of under fives), an estimated 20% of invasive pneumococcal infections in developing countries are caused by serotypes not included in the vaccine, and assuming a 45 to 90% coverage (as for the EPI vaccines), the expected disease-specific mortality reduction may be in the range of 0% to 30%. An intermediate "most likely" value of 15% was selected.

Since pneumococcal disease accounts for less than one third to one half of pneumonia (IOM, 1986), the maximal reduction in pneumonia mortality with the presently available vaccine is likely approximately 0% to 15%, with a "most likely" value of 7%. Although this range does not include the greater reductions in ARI-specific mortality observed among children 6-59 months of age in Papua New Guinea (Riley, 1986), the epidemiology of pneumococcal disease in that country is probably not typical of that in most developing countries. Based on the 750 to 3000 expected deaths among under fives, the number of deaths averted may be calculated to be from 0 to 450, with a most likely value of 105.

The estimated cost per child vaccinated is calculated by reducing the current price of the vaccine (US$9.69 per dose) by one half (assuming that the cost will be reduced for the international market in exchange for waiver of liability and once research and development costs are recovered) and adding the cost per dose delivered for the EPI vaccines (US$2.44 average), since the costs of EPI vaccines (US$0.04-US$0.15 per dose) are small relative to the cost of the pneumococcal vaccine. The resulting estimated cost per dose delivered of US$7.28 suggests that (at coverage levels of 45% to 90%) the cost per death averted would be greater than US$437, with a most likely value of $1664.

Breastfeeding Promotion. Reductions in incidence and case-fatality ratios for pneumonia noted with breastfeeding (Chandra, 1979; LePage, 1981; Victora, 1987) suggest that a 50% to 80% ARI-specific mortality reduction might be realized among breastfed infants. However, the protective effect is observed only below 12 months of age (approximately 20% of under fives), and actual prevalence of breastfeeding among infants is generally over 80% in high-mortality countries, such that only approximately 4% of under fives would benefit from a program to promote breastfeeding. Even assuming 100% effectiveness in changing breastfeeding practice, ARI-specific mortality reduction among children under five observed with breastfeeding promotion would be only 2% to 3.2%

(with a "most likely" value of 2.8% based on Victora's observation of over 70% reduction in relative risk), resulting in an estimated 15 to 96 ("most likely" 42) deaths averted through promotion of breastfeeding.

The average cost of a program to promote breastfeeding has been estimated at US$5.00 (Feachem, 1984; 1986; Phillips, 1987) per mother. Even if targeting of services is only adequate to identify the subset of 50% of the mothers who are "at risk" of not breastfeeding, the population served might be reduced to half of the mothers with infants (8000 in the standard population of one million). The estimated cost per ARI death averted for an educational program to promote breastfeeding may be calculated to be US$417 to US$2667, with a "most likely" value of $952.

Reduction of Malnutrition. Expected mortality reduction with improved nutritional status was estimated based on the two- to 20-fold higher mortality observed in malnourished children (Kielmann, 1978; Herrero, 1983; Tupasi, 1988). Successful improvement of nutritional status might be expected to result in a 50% to 95% reduction in the risk of ARI-mortality among malnourished children. A "most likely" value of 80% reflects the modest estimate of a five-fold higher relative risk of pneumonia deaths among these malnourished children. Since 70 to 90% of all pneumonia deaths occur among the malnourished, expected ARI specific mortality reductions of 35% to 85% ("most likely" value 64%) might be expected with successful improvement of nutritional status. Support for these estimates is provided by the results of a nutritional intervention program in Tanzania (UNICEF, 1988b), where a 23% reduction (from 48% to 37%) in the prevalence of mild to moderate malnutrition (<80% weight for age) and a 60% reduction (from 5% to 2%) in the prevalence of severe malnutrition (<60% weight for age) were associated with a 64% reduction in ARI-specific mortality. The expected number of ARI deaths averted at this level of effectiveness would be 263 to 2550, with a "most likely" value of 960, although these figures would be highly dependent on the initial prevalence of undernutrition.

The lower estimate for the cost of such a program to improve nutritional status is based on expenditures of US$15 per year per malnourished child under five (Ashworth, 1986), although effective targeting of the malnourished children would be difficult to achieve. The Joint Nutrition Support Program (JNSP) in Tanzania (UNICEF, 1988b) estimated its costs at $10.05 per child per year (from both national and donor sources), with the addition of $9.00 per child for "start-up" costs. Annual costs may be estimated at US$11.85 per child if the initial program "start-up" costs can be spread over five years. The cost, therefore, per million population would likely be between $810,000, for the targeted program for the expected 54,000 (36%, based on 1990 UNICEF data) children who are malnourished, and $1,777,500, to serve all of the 150,000 using the model of the Tanzania program. The use of the "most likely" value of $1,500,000 reflects the better

credibility of the figures from Tanzania. Final evaluation of the JNSP Program may, however, yield costs per child as low as $2.50 per year (UNICEF, personal communication, 1991). The cost per death averted is calculated, however, with the less favorable preliminary figures to be $697 to $3080, with a "most likely" value of $1563.

Case Management. There is little information available to date regarding the costs of operational programs for ARI case management where effectiveness has also been assessed. Cost per child treated and death averted may, however, be estimated from drug costs and costs for implementing other programs with similar interventions. The following model was constructed to provide an estimate of the cost of case management for cost-effectiveness calculations:

The cost per million population of appropriate case management for ARI is equal to the sum of: 1) the cost of health education or sensitization regarding program interventions (**E**), 2) the cost of outpatient care for coughs and colds (**U*Cu*(V+M+Z*A)**), where **U** = the incidence of coughs and colds (per 1000), **Cu** = the coverage or proportion of coughs and colds in the community which come to the attention of the health care system, **V** = the average cost of an ambulatory care visit or consultation, **M** = the cost of non-antimicrobial medications, **Z** = the proportion of URI cases inappropriately treated with antimicrobials, and **A** = the average cost of a course of antimicrobials), 3) the cost of outpatient care for pneumonia (**P*Cp*(M+A+N*V)**), where **P** = the incidence of pneumonia (per million), **Cp** = the coverage or proportion of pneumonia cases in the community which are diagnosed and treated appropriately (i.e., given antimicrobials with or without other medications for supportive care), and **N** = the number of consultations per episode), and 4) the cost of inpatient care for severe pneumonia (**S*Cs*(H+V)**), where **S** = the incidence of severe pneumonia (per million), **Cs** = the coverage or proportion of severe pneumonia in the community which is diagnosed and treated appropriately (i.e., given antimicrobials and referred for more specialized care), and **H** = the cost of referral, generally including inpatient hospital care). Therefore, the total cost of case management per million population is:

$$\mathbf{E + U*Cu*(V+M+Z*A) + P*Cp*(M+A+N*V) + S*Cs*(H+V)}$$

Clearly, each of the variables in the model has a range of values. Calculations of cost and effectiveness were made using a range of values, including a "most favorable" (in terms of impact on cost-effectiveness), "least favorable", and "most likely". The specific values used for each variable are listed in table 3.6 and the "most likely" values for the derived variables in table 3.7.

Sensitization costs (**E**) are derived from estimates by Phillips (1987), including a low cost option using person to person communications at $1 per mother (in groups of 10), and a

Table 3.6

SUMMARY OF VARIABLES AND RANGE OF VALUES FOR MODEL OF COST-EFFECTIVENESS OF ARI CASE MANAGEMENT

Name	Variable	Least Favorable	Most Likely	Most Favorable
E	Sensitization cost	$800,000	$400,000	$80,000
V	Cost of one outpatient consultation	$2.00	$1.50	$1.00
M	Cost per episode of non-antimicrobial pharmeceuticals	$3.20	$0.08	0
A	Cost per episode of antimicrobials	$7.00	$0.80	$0.16
H	Cost of inpatient or referral care	$135	$45	$6
N	Average number of visits per episode	2	1.5	1
U	Cases of coughs and colds	1,500,000	1,050,000	600,000
P	Cases of uncomplicated pneumonia	5000	7500	10,000
S	Cases of severe or complicated pneumonia	1000	1500	2000
C_U	Proportion of URI cases seen and treated by health worker	0.10	0.05	0.02
Z	Proportion of URI cases inappropriately treated with antibiotics	0.50	0.10	0
C_P	Proportion of uncomplicated pneumonia cases appropriately diagnosed and treated	0.10	0.40	0.70
C_S	Proportion of severe pneumonia cases appropriately diagnosed and treated	0.40	0.65	0.90
F_P	Case fatality ratio for untreated uncomplicated pneumonia	0.10	0.13	0.20
F_S	Case fatality ratio for untreated severe or complicated pneumonia	0.25	0.35	0.50
R	Percent reduction in mortality with appropriate antibiotic treatment	0.60	0.80	0.90

Table 3.7

SUMMARY OF DERIVED VARIABLES AND THEIR MOST LIKELY VALUES

NAME	VARIABLE	DERIVATION	MOST LIKELY VALUE
C	Cost (per capita) of ARI care	$E + U \times C_U \times (V + M + Z \times A) + P \times C_P \times (M + A + N \times V) + S \times C_S \times (V + H)$	$ 0.54
T	Number of uncomplicated pneumonia cases treated	$P \times C_P$	3000
T_S	Number of complicated or severe pneumonia cases treated	$S \times C_S$	975
D	Number of ALRI deaths averted	$(T \times F + T_S \times F_S) \times R$	585
CE	Cost-effectiveness, or cost per ALRI death averted	$\frac{C}{D}$	$926
CE_{DHLY}	Cost per discounted healthy life year saved	CE/25	$37

high cost program including use of mass media at $10 per mother (assuming that there are 80,000 mothers of children under five). The intermediate cost program estimate of $5 per mother equals those estimates used for breastfeeding promotion and weaning education programs (Feachem 1986; Phillips, 1987).

The cost of one outpatient consultation (**V**) has been derived from figures for diarrheal disease and immunization consultations (Phillips, 1987), assuming that the time spent by the health worker is comparable. A high cost figure of $2.00 reflects average costs per visit in many Latin American countries, the intermediate cost of $1.50 and low cost of $1.00 are more typical of costs per outpatient consultation in Asia and Africa. Costs for non-antimicrobial pharmaceuticals (**M**), which are optional in the management of ARI, are estimated at zero for the low cost figure, $0.08 for intermediate costs typical of five days supply of a locally made cough syrup, and $3.20 to reflect the often larger expenditures on non-antimicrobial pharmaceuticals in many developing countries (Quick, 1988).

The values selected for the cost per episode of antimicrobials (**A**) were based on UNICEF (1988) prices for a five day course for a 10 kg child. These figures were doubled to include costs for transport, packaging and dispensing these medications. Basic prices included a low cost figure of $0.08 for five days of cotrimoxazole for a 10 kg child, $0.40 for the intermediate figure (Bates, 1987; Quick, 1988), and $3.50 for intramuscular penicillin and chloramphenicol for the high cost program. Costs for referral care with hospitalization (**H**) used in the model include a high cost figure of $135 (three days at $45 per day) from Brazil (Shepard, unpublished data, 1989), an intermediate figure of $45 (three days at $15 per day) from Rwanda (Shepard, unpublished data, 1989), and a low cost figure of $6 (three days at $2 per day). The number of visits per episode (**N**) will ideally be two, although a lower value of one is used, as some programs require no follow-up visit (WHO, 1988a). The intermediate figure of 1.5 reflects probable level of compliance with the recommended follow-up visit.

The values used for high, intermediate and low incidence of coughs and colds among children under five (**U**) are ten, seven and four per child per year (Datta Banik, 1969; Kamath, 1969; Friej, 1977; Foreit, 1987), yielding the numbers of episodes specified in table 3.6 among the 150,000 children under five in the standard population. For pneumonia incidence (**P**), the figures selected were 100, 50, and 25 per 1000 (Riley, 1981; Pio, 1982; WHO, 1989b). For severe pneumonia (**S**), the figures are 25, 10, and 5 per 1000 (Chen, 1980; Riley, 1983; WHO, 1984b).

Although ideally fewer than 2% of coughs and colds will be brought to the attention of and diagnosed by the health worker (**Cu**), a likelier figure is 5%, while over 10% has been observed in some programs (Foreit, 1987). The cost of inappropriate treatment of

coughs and colds with antibiotics is included in the model, since this may be a source of excess costs and of potential savings in improving case management practices (Stansfield, 1990). The percent of coughs and colds seen by a health worker and treated inappropriately with antibiotics (**Z**) will ideally be zero, although in many programs up to half of such cases receive antimicrobials. A "most likely" value of 10% should be achieveable with careful training and supervision of health workers. A study in Lesotho (Redd, 1990) found that 6% to 15% of practitioners (before retraining using WHO guidelines) reported that they would treat a cough or cold with antimicrobials, so it is likely that observed rates of inappropriate use of antimicrobials would exceed these reported rates.

For pneumonia coverage (**Cp**), the figures selected for the model are 70%, 40%, and 10%. WHO estimates that 12% of all childhood pneumonias were treated with antibiotics in 1990, and projects increases to 40% in 1995 and 60% by 2000 (WHO, 1991b). Although there are no good data from operational settings, it has been estimated that from 40% to 90% (with a "most likely" value of 65%) of severe pneumonias may be seen and diagnosed by a health care worker (**Cs**). Incidence and coverage figures selected for URI and pneumonias yield proportions which are pneumonia (among all ARI cases presenting in health facilities) of 4% ("least favorable") to 50% ("most favorable"), with a "most likely" value of 17%. These figures reflect such measurements made in operational settings (WHO, 1990c; Foreit, 1987; Quick, 1988).

The incidence (**P** and **S**) and case-fatality ratios (**F** and **Fs**) specified in table 3.4 yield ARI-specific mortality values of 5/1000, 10/1000, and 20/1000, reflecting probable levels of ARI mortality (UNICEF, 1990; WHO, 1991a) among under fives in middle mortality, high mortality, and very high mortality countries. Numbers of deaths averted were, therefore, calculated based on expected numbers of deaths of 750 (5/1000), 1500 (10/1000), and 3000 (50/1000) for moderate, high, and very high mortality countries, respectively. The range of assumptions for treatment efficacy (**R**) includes 90% for a highly efficacious program (Berman, 1985), 80% for the intermediate level of efficacy (IOM, 1986), and 60% for the lower level of efficacy, such as may be seen in settings where compliance is poor.

Using the values for each variable specified in table 3.6, the additional variables defined in table 3.7 were derived. Calculation of the cost per capita of ARI case management (**C**) using these figures yields a most likely value of $0.54, or $541,877 for the sample poulation of one million. The ranges for total cost (of $220,000 to $940,000) and for the cost-effectiveness figures used in table 3.3 reflect values obtained from the sensitivity analysis, which is summarized in table 3.8, obtained by varying one parameter at a time. The sensitivity analysis data indicate that program costs and cost effectiveness are most sensitive to the costs for health education or "sensitization". The program effectiveness

Table 3.8

SUMMARY OF SENSITIVITY ANALYSIS FOR ARI CASE MANAGEMENT MODEL: LEAST AND MOST FAVORABLE COSTS, EFFECTIVENESS AND COST-EFFECTIVENESS FOR EACH VARIABLE RANGE

Variable Name	Cost (per Capita) of ARI Care		Deaths Averted		Cost-Effectiveness (Cost per Death Averted)	
	Least Favorable	Most Favorable	Least Favorable	Most Favorable	Least Favorable	Most Favorable
E	$0.94	$0.22	585	585	1610	379
V	$0.57	$0.51	585	585	976	877
M	$0.72	$0.54	585	585	1222	919
A	$0.59	$0.54	585	585	1014	917
H	$0.63	$0.50	585	585	1076	861
N	$0.54	$0.54	585	585	930	922
U	$0.58	$0.50	585	585	990	862
P	$0.54	$0.55	481	689	1120	791
S	$0.53	$0.56	494	676	1066	824
C_U	$0.63	$0.49	585	585	1075	837
Z	$0.56	$0.54	585	585	955	919
C_P	$0.53	$0.55	351	819	1524	670
C_S	$0.52	$0.56	480	690	1093	811
F_P	$0.54	$0.54	513	753	1056	720
F_S	$0.54	$0.54	585	702	926	772
R	$0.54	$0.54	439	658	1235	823

(as measured by deaths averted) is lowest with low values for coverage of uncomplicated pneumonia, and highest when the incidence of severe pneumonia is high.

A "most likely" value for cost-effectiveness for ARI case management of $926 (per death averted) was calculated. Use of the extreme figures for incidence and case-fatality ratios (rather than varying one parameter at a time, as in the sensitivity analysis), such as may be observed in high and low mortality countries, yields cost and effectiveness figures specified in table 3.9. These figures underline the fact that interventions to improve ARI case management are of highest priority in the countries with high overall and ARI-specific infant and child mortality rates. These estimates are higher than the estimates of $350 per death averted obtained in a field study in Nepal and $131 per death averted obtained in the Philippines (JSI, unpublished data).

Calculations of cost per discounted healthy year of life saved are made using a life expectancy of 50 years, an average age at death of two years, and a discount rate of 3% per annum. Ranges for the intermediate variables and a summary of the cost-effectiveness calculation are presented in table 3.3, in a format for comparison with the analogous figures for the other ARI interventions.

Table 3.9

COST-EFFECTIVENESS OF ARI CASE MANAGEMENT FOR LOW AND HIGH MORTALITY COUNTRIES

MORTALITY	LOW MORTALITY	HIGH
Cost per Capita of ARI Care	$0.52	$0.56
Cost per Target Population	$3.49	$3.61
Deaths Averted	338	1160
Cost per Death Averted	$1152	$483
Cost per Discounted Healthy Year of Life Saved	$46	$19

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