

Acute Respiratory Infection

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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. That mortality due to pneumonia is ten to fifty times higher in developing countries suggests that there is ample room for improvement in addressing this important public health problem. The heterogeneity of the clinical presentations and causative organisms in ARI, however, has hampered efforts to design simple and effective interventions.

The classification and management of ARI in the industrialized world are founded on epidemiologic, radiologic, and microbiologic data, in addition to clinical history and physical examination. The syndromes of ARI, 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 4-1. As suggested by this table, ARI includes the minor upper respiratory infections (URIs), such as colds and sore throats, in addition to the more serious (and potentially fatal) acute lower respiratory infections (ALRIs) 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, on the argument 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 most significant reduction in years of life lost will be seen among infants and children. The data and strategies outlined in this chapter therefore focus primarily on children under five.

Table 4-1. Clinical Summary of Acute Respiratory Infections in Infants and Young Children

Type	Diagnosis	Most common etiology	Age at peak incidence (months)	Mortality
Upper respiratory infections	Nasopharyngitis (coryza, colds)	Viral (various)	—	No
	Otitis media (middle ear infection)	Bacterial (pneumococcus, <i>Hemophilus influenzae</i>)	6-7	No
	Pharyngo-tonsillitis	Viral (various) and bacterial (<i>Streptococcus pyogenes</i> , <i>Corynebacterium diphtheriae</i>)	—	No (except diphtheria)
	Epiglottitis	Bacterial (<i>Hemophilus influenzae</i>)	24-47	Yes
Lower respiratory infections	Laryngitis (croup)	Viral (especially parainfluenza and measles)	12-23	Rare
	Tracheobronchitis	Viral and bacterial (various)	Constant	No
	Bronchiolitis	Viral (RSV, parainfluenza 3)	0-11	Yes
	Pneumonia	Bacterial (pneumococcus, <i>Hemophilus influenzae</i>) and viral (RSV, influenza, parainfluenza, measles, adenovirus)	24-35	Yes

— Not available.

Source: Authors' data.

Risk Factors for ARI

Treatment of pneumonia clearly reduces ARI mortality, but the definitive solution to the problem of high numbers of ARI deaths in developing countries 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 ways to reduce ARI mortality through reducing the risk of pneumonia. Table 4-2 summarizes the following discussion of some of the known and suspected risks for pneumonia incidence and mortality.

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 two to three per year for adults (Datta Banik, Krishna, and Mane 1969; Kamath and others 1969; Monto and Ullman 1974; Friej and Wall 1977; Spika and others 1989). The frequency of pneumonia and the case-fatality ratio, however, are highest among both the very young and the very old (Bulla 1978; Berman and others 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 four years of age (Berman and McIntosh 1985). There is a slightly increased incidence of both overall ARI and pneumonia among male children (Bulla 1978; Berman and others 1983; Narain and Sharma 1987; Selwyn 1990), although female children have been observed to have a higher case-fatality ratio in some countries, probably as a result of poorer access and quality of care during illness episodes (Tupasi and others 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 and Menon 1981; Stansfield 1987; Tupasi and others 1988; Borrero and others 1990; Vathanophas and others 1990) have also demonstrated an increased frequency of pneumonia re-

quiring 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 pneumonia. Existing evidence suggests, however, that infants with restricted respiratory excursion of the chest wall due to obesity (Tracey, De, and Harper 1971) or swaddling (Yurdakok, Yavuz, and Taylor 1990) may have increased risk of pneumonia. Family stress also increases the risk of infections such as pneumonia among both children and adults (Foulke and others 1988; Graham and others 1990; Cohen, Tyrell and Smith 1991), probably because of interference with immune competence (Kiecolt-Glaser and Glaser 1986). Although chilling is frequently cited as a risk factor for URI or pneumonia, most studies have provided no evidence of this association (Jackson and others 1963; Douglas, Lindgram, and Cough 1968).

Nutritional Status and Practices

Poor nutrition lowers both systemic and local defenses against ARI, including 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 (Kielmann and McCord 1978; Pio, Leowski, and Luelmo 1982; Berman 1983; Sommer 1983; Sommer, Katz, and Tarwotjo 1984; Berman and others 1991). Investigators have documented an incidence of pneumonia twelve to twenty times greater in undernourished children than in children of normal weight-for-age (James 1971; Berman and others 1983; Tupasi and others 1988). Mortality due to each of these already more frequent episodes of pneumonia increases two- to thirteenfold for each decile below 80 percent weight-for-age (Escobar, Dover, and Duenas 1976; Kielmann and McCord 1978; Tupasi 1985).

While nutritional deficiency diseases augment the chances of ARI episodes, so episodes of ARI contribute to nutritional

Table 4-2. Risk Factors for Pneumonia

<i>Increased incidence</i>	<i>Increased case fatality</i>
Age less than two years or more than sixty-five	Age less than two years or more than sixty-five
Male	Low socioeconomic status
Poor nutritional status	Poor nutritional status
Low birth weight	Low birth weight
Lack of breastfeeding (in infants)	Lack of breastfeeding (in infants)
Smoking, air pollution	Lack of maternal education
Crowding	Reduced access to health care
Incomplete immunization	Crowding
Swaddling	Underlying chronic disease
Vitamin A deficiency	

Source: Authors' data.

deficiency, thus further increasing the risk of subsequent infection and death. A prospective study in the Gambia (Rowland, Rowland, and Cole 1988) showed that pneumonia reduced weight gain in young children by 14.7 grams for each 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, seen in 20–40 percent of infants in many developing countries, also increases the risk and case-fatality ratio of pneumonia. Studies (Datta 1987; WHO 1988) have shown relative risks of mortality due to pneumonia which are 2.5- to 8-fold greater among infants of low birth weight. Other than malaria and tobacco chewing, the only factors associated with low birth weight for which cause-and-effect relationships have been established in developing countries (and which are modifiable over the short term) are low prepregnancy weight, low gestational weight gain, and low caloric intake (WHO/EPI 1987). Short birth intervals, teenage pregnancy, certain genital infections, and arduous work after mid-pregnancy are other potentially modifiable factors associated with low birth weight. Although reduction of the incidence of low birth weight 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 and others (1984) failed to document any protective effect of breastfeeding, others have found a two- to fivefold decreased incidence of pneumonia (Chandra 1979; Singhi and Singhi 1987) and decreased case-fatality ratio due to pneumonia (LePage, Munyakazi, and Hennart 1981). A more rigorous study in southern Brazil (Victors and others 1987) demonstrated that infants who were completely weaned had a risk of death due to pneumonia 3.6 times higher than breastfed infants.

Vitamin A deficiency, which often accompanies protein-calorie malnutrition, results in keratinization of the respiratory epithelium and depression of the immune response, thus presumably decreasing both local and systemic resistance to bacterial colonization and infection. Still, the literature on vitamin A deficiency and its association with ARI morbidity and mortality is sparse and controversial. Two studies (Sommer, Katz, and Tarwotjo 1984; Bloem and others 1990) have suggested a two- to fourfold 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.

Several prospective studies have noted a reduction in overall mortality among children whose diets were supplemented with vitamin A. Vitamin A supplements given to children with severe pneumonia or measles has improved clinical outcome and reduced mortality (Barclay, Foster, and Sommer 1987; Hussey and Klein 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 subclinically deficient) have not, however, demonstrated an effect on ARI-specific morbidity or mortality (Rahmathullah and others 1990; Vijayaraghavan and others 1990; Rahmathullah and others 1991). 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 increase in risk of pneumonia from active and passive smoking. Investigators in both industrialized and developing countries have demonstrated a 1.5- to 4-fold increased incidence of pneumonia among smokers and among children whose parents smoke (Harlap and Davies 1974; Leeder and others 1976; Ekwo, 1983; Weiss and others 1983; Ware and others 1984; Pedreira and others 1985; Chen, Wanxian, and Shunzhang 1986; Burchfiel and others 1986; Lipsky and others 1986; Samet, Marbury, and Spengler 1987; USDHHS 1989). Maternal smoking also predisposes to low birth weight (Martin and Bracken 1986; Ruben and others 1986), thus increasing the risk of pneumonia 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. The recent alarming increases in the numbers of persons who smoke in developing countries, however, 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 and others 1980; WHO/UNEP 1988; Chen and others 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 million to 400 million people, mostly in the rural areas of developing countries, are adversely affected by these organic fuel emissions (de Koning, Smith, and Last 1985). Although there is a clear relation between exposure to such emissions and chronic obstructive pulmonary disease (WHO/EPP 1984; Chen and others 1990), the relation to pneumonia in the developing world is less well documented.

Indoor particulate concentrations, probably the best single indicator of toxic (noncarcinogenic) effects, are twenty times higher in the villages of developing countries than in households where two packs of cigarettes are smoked per day (Pandey, Boleij, Smith, and Wafula 1989). Several studies in developing countries have suggested that an increased incidence of pneumonia is associated with exposure to organic fuel emissions (Sofoluwe 1968; Kossove 1982; Honicky 1985; Campbell, Armstrong, and Byass 1989; Penna and Duchicade 1991), although several studies have had problems with con-

founding variables such as socioeconomic status and crowding. One study in Nepal (Pandey, Neupane, Gautam, and Shrestha 1989) has demonstrated that the number of episodes of life-threatening pneumonia 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 the mother's back during cooking may predispose children to pneumonia (Armstrong and Campbell 1991). Prospective trials are required to assess the effectiveness of interventions such as improvements in stove design, improved ventilation, and behavioral change to reduce exposure.

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 pneumonia mortality among the very young, the very old, and those immunocompromised by acquired immunodeficiency syndrome (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); 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 more than 75 percent of ARI deaths are caused by pneumonia, both bacterial and viral (Bulla and Hitze 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 *Hemophilus influenzae* (Berman and others 1983; Denny and Clyde 1983; Shann and others 1984; Selwyn 1990; WHO/ARI 1991b). Viral agents which cause fatal 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 and others 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 (laryngotracheobronchitis), 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 two-year cycles with secondary attack rates exceeding 90 percent among susceptible household contacts (Keja and others 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 six to eight months, presumably because of placentally transmitted maternal antibodies. In parts of Africa, however, 20 to 45 percent of children are infected with measles before they attain the recommended age for immunization 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 million 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."

Partly because of such variations in methods of ascertaining deaths due to or associated with measles, the reported case-fatality ratios vary widely. Williams and Hull (1983) documented a 5 percent case-fatality ratio during the acute phase of the disease, and a cumulative rate of 15 percent during the nine months following the rash. The case-fatality ratios obtained from prospective population-based studies range from 2 percent in Bangladesh to 34 percent in Guinea Bissau (WHO/EPI 1987). Rates of 50 percent 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 caused by *Bordetella pertussis*. The paroxysms of coughing, often associated with a characteristic inspiratory gasp (the whoop), may persist for four to ten weeks. Pertussis is often associated with dehydration and weight loss; and encephalitis is an occasional complication. Pneumonia, resulting either from the organism itself or from secondary bacterial infection, is the proximal cause of death in over 90 percent of cases.

Although pertussis occurs endemically, it tends to produce epidemics every three to four years, with up to 90 percent of exposed susceptibles developing the disease (Broome 1981;

Muller, Leeuwenburg, and Pratt 1986). Incidence is higher among girls than boys. Population-based studies have suggested an annual incidence of 1 to 5 percent among children under fifteen, although infants have a 16 percent chance of infection in Kenya (Voorhoeve and others 1977). The case-fatality ratio averages about 1 percent, although up to 15 percent 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 1 million infant deaths annually due to pertussis (Muller, Leeuwenburg, and Pratt 1986; Keja and others 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 percent of unvaccinated adults are immune (Ikejani 1961; Muyembe and others 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 percent of the population (Ikejani 1961; Muyembe and others 1972).

There are no community-based studies, but data from hospitals suggest diphtheria may be an important cause of pharyngitis and croup. Of 180 children hospitalized with respiratory infections in Colombia (Escobar, Dover, and Duenas 1976), seven of the nine cases of croup were caused by diphtheria. Investigators in the Gambia found evidence to suggest an annual incidence of 6 per 1,000 children under five. Salih and others (1985) have reported epidemic diphtheria and suggest 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 when 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*). Acute rheumatic fever has been reported at rates of 27 to 100 cases per 100,000 per year (WHO 1988), 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 owing 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 in developing countries a strategy for management of pharyngitis which will effectively prevent poststreptococcal 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 1988).

Other Causes of ARI Mortality

Additional causes of ARI mortality include viral bronchiolitis and epiglottitis. Bronchiolitis, especially that resulting from 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 and others 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, which is usually caused by *Hemophilus influenzae* type b, is an occasional cause of death when the infected epiglottis obstructs respiration. Additional epidemiologic investigations are 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; these more chronic infections are often distinguished clinically by their failure to respond to the usual antibiotic therapy.

Public Health Significance

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, whereas others focus only on the more severe ARI that comes to the attention of health care workers.

Current Levels and Trends in the Developing World

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.

MORBIDITY AND MORTALITY LEVELS, CIRCA 1985. Prevalence figures show that children spend from 22 to 40 percent of observed weeks with ARI, and from 1 to 14 percent of observed

weeks with ALRI, such as pneumonia or bronchiolitis. Acute respiratory infections account for 20 to 40 percent of adult outpatient consultations and 20 to 60 percent among children. Of all pediatric admissions to hospitals, 12 to 45 percent are for ARI, whereas 20 to 30 percent of adult inpatients have been admitted for ARI treatment (Bulla and Hitze 1978; PAHO 1980; Leowski 1986).

The reported incidence of ALRI varies widely, from country to country as well as with age and nutritional status. Whereas the annual incidence of pneumonia is 3 to 4 percent in children under five 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 low birth weight. In Papua New Guinea in 1973, for example, there were 72 episodes per 1,000 children of one to four years of age and 1,074 episodes per 1,000 infants (Riley and Douglas 1981). In Costa Rica an annual incidence of pneumonia of 37 per 1,000 children was observed among those of normal nutritional status, while the rate was 457.8 per 1,000 among malnourished children (Pio, Leowski, and ten Dam 1985). 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 developing countries is manifest, however, in the increased frequency of lower respiratory tract infections and in the disease-specific mortality rates that are ten to fifty times higher than in industrialized countries (WHO 1984; Mohs 1985; Camargos, Guimaraes, and Drummond 1989). Most vulnerable to death due to pneumonia are the very young and the very old.

Of the estimated 15 million deaths occurring each year among children under five, 25 to 30 percent 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 and Hitze 1978; Balint and Anand 1979; Shann and others 1984; Pio, Leowski, and ten Dam 1985; Spika and others 1989). Pneumonia causes from 2 to 8 percent of adult deaths in countries for which data are available (Hayes and others 1989), ranking from second to tenth as a cause of death among those age fifteen through sixty-four.

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 fifteen to twenty years, just as they have in the industrialized countries. Reductions in incidence of ARI as a result of improved immunization coverage (with measles, diphtheria, and pertussis vaccines) would have little effect on the overall incidence of ARI, because the frequency of viral upper respiratory infections would remain largely unchanged.

Pneumonia mortality, however, has been reduced significantly over the past fifteen to twenty years in the United States 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, Rahman, and Sarder 1980; Zimicki 1988). Mortality from ARI has increased in relative importance even in settings where high coverage with measles immunization has been achieved (Greenwood and others 1988; Zimicki 1988).

Data from industrialized countries suggest that changes in immunization policy may increase the incidence of disease. With intensive control efforts, for example, the incidence of measles in the United States had fallen to the lowest level ever recorded in 1983. When expenditure for immunization was reduced in 1984, however, increased outbreaks were observed. A similar resurgence of pertussis has been noted in countries in which changes in public opinion or immunization policy have led to a reduction in immunization coverage.

Possible Morbidity and Mortality Patterns: 2000 and 2015

As viral upper respiratory infections, which account for the bulk of ARI morbidity, are unlikely to be eradicated in the foreseeable future, the overall incidence of ARI is likely to be substantially unchanged for the next twenty-five 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 birth spacing and consequent improvements in nutritional status would be expected to substantially reduce mortality due to pneumonia during the next twenty-five 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 interventions. Although the development of newer antimicrobials has, to date, kept pace with the evolution of resistance to them, the cost 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 the number of deaths from ARI. In addition, improved vaccine technology will likely alter the currently observed patterns of mortality due to ARI during the next twenty-five years. New vaccines, too, increase hopes of reducing childhood ARI mortality due to measles and bacterial pneumonias caused by *S. pneumoniae* and *H. influenzae*.

Economic Costs of ARI

Acute respiratory infections account for an average of 35 percent of all outpatient visits globally (Bulla and Hitze 1978) and generally similar proportions of all hospitalizations among children.

DIRECT COSTS. The minimal direct cost of ALRI for children in the first two years of life in the United States has been estimated at \$35.14 per child, 56 percent of which is attributable to hospitalization (McConnochie, Hall, and Barker 1988).¹

In many developing countries, 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 and others 1991). Frequently, more than half of antibiotic use is unnecessary (Hossain, Glass, and Khan 1982; Stein and others 1984; Quick and others 1988). A study in Peru (Foreit and Lesevic 1987) showed that approximately 50 percent of the expenditure for medications to treat ARI episodes was inappropriate, at an excess cost of \$18.47 to \$21.97 per child covered. The authors of the study estimated that an 89 percent 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 and will greatly increase the future direct costs of ARI treatment as the use of more expensive antimicrobial agents becomes necessary.

INDIRECT COSTS. Acute respiratory infections account for an average of one-third of all absences from work (Bulla 1978). In Britain, one to two weeks of schooling are lost per child per year due to ARI (Crofton and Douglas 1975). Data from Ghana (Ghana Health Project Assessment Team 1981) indicate that over 94 percent of the fifty-two days of life lost per case of ARI is 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 are indirect costs due to mortality. No such estimates are available for the developing world, but ARI also likely takes a relatively greater toll in these settings in the form of growth deficits, malnutrition, and resulting learning disabilities. Although these indirect costs of ARI are difficult to quantify, it is probable that they greatly reduce the potential productivity of those affected.

Lowering the Incidence of ARI

Possible preventive approaches to reduce ARI morbidity and mortality include immunization and alteration of other risk factors which predispose children and adults to pneumonia.

Elements of the Preventive Strategy

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. 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 percent of the total mortality among children under five in the developing world.

Although the immunization programs must be part of any strategy to prevent ARI, available data do not yet justify the design and implementation of programs to reduce environmental and nutritional risk factors for ARI control. The evidence does suggest, however, that such programs may be effective. Several potential preventive interventions that might be considered for inclusion in ARI control programs have been included in the following discussion. Those for which evidence of feasibility and effectiveness are strongest are included in a comparative model of cost-effectiveness, which is summarized in table 4-3. It is important to recognize, however, that the actual benefits from these interventions would be broader than those calculated, since each would reduce morbidity and mortality resulting from many health problems beyond ARI alone. Sources for the data used and the methods for calculating the cost-effectiveness estimates are specified in the appendix to this chapter.

MEASLES IMMUNIZATION. Operational problems in maintaining the necessary cool temperatures for handling the measles vaccine are a frequent barrier to maintaining vaccine viability and efficacy. The World Health Organization has estimated the efficacy of the vaccine to be 90 percent when maintained at appropriately cool temperatures (Keja and others 1988). Because of variability in study design and alterations in vaccine viability as a result of handling, the measured efficacy of the vaccine may vary broadly, although Hull, Pap, and Oldfield (1983) achieved an efficacy of 89 percent 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 effectiveness of the vaccine in the first few months of life. Available data regarding age-specific seroconversion and measles incidence rates suggest that immunization at nine months of age will prevent the maximal number of cases (WHO/EPI 1982). These data were the basis for the WHO recommendation of one dose of measles vaccine to be given between nine and twelve months of age.

Yet, in many countries, 20 to 45 percent 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 and others 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 (Dabis and others 1988; Taylor and others 1988). Particularly in the urban areas of Africa, the increased transmission rates may lower the optimal age for immunization (McLean and Anderson 1988; Taylor and others 1988).

Table 4-3. Calculated Cost-Effectiveness of Interventions for ARI Control
(U.S. dollars)

Intervention	Expected disease-specific mortality reduction ^a (percent)	Proportion of ARI mortality addressed (percent)	Expected ARI-specific mortality reduction (percent)	Deaths averted in children under five (per million population)	Cost per person in target population	Total cost (per million population)	Cost per death averted	Cost per disability-adjusted life-year saved
Case management	60–90 (80)	38–52 (49)	23–47 (39)	351–676 (585)	\$3.61	\$220,000– \$940,000 ((\$541,877))	\$379– \$1,610 ((\$926))	\$37
Breastfeeding promotion	50–80 (72)	4	2–3.2 (2.8)	15–96 (42)	\$5.00	\$40.00	\$417– \$2,667 ((\$952))	\$38
EPI vaccines	44–80 (65)	20–25 (22.5)	8.8–20 (14.6)	66–600 (219)	\$9.08	\$122,580– \$245,160 ((\$217,920))	\$409– \$1,857 ((\$995))	\$40
Reduction of malnutrition	50–95 (80)	70–90 (80)	35–85 (64)	263–2,550 (960)	\$15.00 (malnourished) \$11.85 (all children)	\$810,000– \$1,777,500 ((\$1,500,000))	\$697– \$3,080 ((\$1,563))	\$63
Pneumococcal vaccine	0–30 (15)	30–50 (40)	0–15 (7)	0–450 (105)	\$7.28	\$98,280– \$196,560 ((\$174,720))	\$437 ((\$1,664))	\$67

Note: Most likely values in parentheses.

a. Disease is pneumonia except for EPI vaccine, where disease is pertussis and measles; for pneumococcal vaccine, disease is pneumococcal pneumonia.

Source: Authors' data.

In 1989, the World Health Organization recommended the use of the higher titer Edmonsten-Zagreb vaccine at or before six months of age in areas where measles is a major cause of infant mortality (WHO/EPI 1990). Subsequent reports of increased late mortality among children immunized with such higher titer vaccines (Garenne, Leroy, and Sene 1991) has, however, prompted a suspension of that recommendation. Alternatives to the current measles vaccines must be developed which are effective in younger infants.

Ongoing studies of the effectiveness, optimal dose, non-parenteral routes of administration (in order to overcome residual maternal antibodies), and booster response to the new vaccines will help further to 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 diphtheria-pertussis-tetanus vaccine (DPT) 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 (Wilkins and Wehrle 1979; Linnemann and others 1982; Stetler and others 1986).

PERTUSSIS IMMUNIZATION. The vaccine for pertussis is delivered together with the diphtheria and tetanus vaccines. The efficacy of pertussis vaccine for the fully immunized child (three doses) has been recently questioned but is estimated at 70 to 90 percent in the industrialized world (Church 1979; Koplan and others 1979) and 50 to 90 percent in developing countries. As 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, primarily because of concern about associated adverse neurological effects, most notably encephalopathy (Brahmans 1986), although there is also some controversy about the vaccine's effectiveness (Fine and Clarkson 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. Even with the current preparation, however, the benefit of the vaccine far outweighs the risk of adverse effects (Koplan and others 1979; Cherry 1984). Accelerated research has led to the development of acellular pertussis vaccines, which offer hope in the near future for both improved effectiveness and fewer adverse effects (Miller and others 1991).

PNEUMOCOCCAL IMMUNIZATION. The pneumococcal vaccine licensed for use in the United States is composed of the purified polysaccharide extracted from twenty-three of the eighty-four types of *Streptococcus pneumoniae*. These capsular subtypes are responsible for approximately 90 percent of invasive pneumococcal disease in the United States. Still, over 30 percent of blood culture isolates from patients with pneumonia in developing countries have been pneumococcal serotypes which are not included in the current vaccine (Ghafoor and others 1990; Mastro and others 1991). In addition, the vaccine induces little immunity in children under eighteen months of age, who are most vulnerable to mortality due to pneumococcal infections.

Studies in the United States have suggested that the currently available vaccine is 50 to 80 percent effective in preventing bacteremia and pneumonia in adults. Results of studies among the very elderly or chronically ill (Simberkoff and others 1986) and among children under eighteen months have been less encouraging. The vaccine has also been tested in Papua New Guinea, which reports that up to 50 percent of pneumonia is due to pneumococcal infection. Clinical trials there (Riley and others 1986) among children age six months through fifty-nine months have shown a 50 percent reduction in pneumonia-specific mortality rates during periods of one to five years after immunization. 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 percent lower rate of pneumonia (Riley and Douglas 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 infants and young children. The vaccine is made from *H. influenzae* type b polysaccharide, since this type accounts for virtually all invasive disease in the industrialized world. The effective protection (measured by the prevention of invasive disease, mainly meningitis and bacteremia) found in children over twenty-four months of age has ranged from 0 to 90 percent (Granoff and others 1986; Harrison and others 1987; Black and others 1988; Gilsdorf 1988). The effectiveness of the *H. influenzae* type b vaccine in reducing pneumonia morbidity and mortality cannot be estimated from U.S. 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 because of transient postvaccination reductions in antibody levels (Black and others 1988). One study (Osterholm and others 1987) actually calculated an increased risk of *H. influenzae* infection of 45 percent, 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 (Eskola and others 1990; Siber and others 1990; Ward and others 1990; Wanger and others 1991). Formulations for developing countries will need to include additional types (that is, non-b and nonserotypable *H. influenzae*) which are not a prominent cause of invasive disease in the industrialized world (Funkhouser, Steinhoff, and Ward 1991). Recent studies in Papua New Guinea (Weinberg and others 1990), Pakistan (Ghafoor and others 1990), and the Gambia have shown that approximately half of all invasive *H. influenzae* disease is due to nonserotypable or non-b strains.

The costs of the current conventional Hib vaccine is \$2.19 per dose, while the conjugate vaccine is \$14.00 per dose. Hay and Daum (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 \$64.8 million, in the setting of an anticipated social cost of \$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 4-3.

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 importance to public health of these problems and the effectiveness of immunization. Although the expected effect of diphtheria vaccine is difficult to predict because of the lack of information regarding diphtheria morbidity and mortality, marginal costs of including the vaccine with pertussis and tetanus (in DPT vaccine) are nearly negligible.

Effective vaccines against the viral causes of pneumonia and bronchiolitis would likely avert additional mortality. Attempts to develop effective vaccines against the two most important causes of mortality, RSV and parainfluenza viruses, however, have been frustrating. Still, the mechanism for the adverse hypersensitivity responses to RSV antigens has recently been identified, so that purified antigen and recombinant vaccines currently under development should offer greater hope for these important causes of respiratory mortality (Pringle 1987). Influenza vaccines have been effective in preventing infections, particularly among the elderly, but the "antigenic drift," or frequent changes in surface proteins which characterize these viruses make 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 low birth weight, poor infant-feeding practice, undernutrition, and vitamin A deficiency) and exposure to smoke (including smoke from active and passive cigarette smoking and from organic-fuel cookfires), have been suggested as additional strategies for the prevention of ARI deaths. Although the association of some of these risk factors with disease is strong, few studies support the feasibility of programs using these interventions or their effectiveness in preventing ARI. The data show as far more feasible and effective the promotion of breastfeeding and reduction of malnutrition.

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. One of the four objectives, however, is "to reduce the incidence of acute lower respiratory infection" (WHO/ARI 1991). Although intervention to alter some of the nonspecific risk factors for ARI (table 4-2) 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 pneumonia.

Even this proven technology, however, has not been fully exploited to prevent ARI mortality. As of 1988, many of the 97 countries with an Expanded Programme on Immunization still had subnational coverage, often neglecting the neediest children in the most remote areas (Keja and others 1988). Vaccination efforts are most appropriately integrated with the

primary health care system, avoiding duplication of necessary management, supervision, training, and logistical resources. Immunization campaigns, although 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 percent for measles and 55 percent for the DPT series of three doses (Keja and others 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 the result of 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 and others 1988), and adverse effects of current vaccine preparations.

Increasing attention, especially in Africa, has been paid to the reuse of syringes and needles in immunizations. 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 low birth weight 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.

Table 4-4. Diagnosis and Treatment of Pneumonia in Children Aged Two Months to Five Years

<i>Disease</i>	<i>Signs</i>	<i>Treatment</i>
Very severe disease	Unable to drink Convulsions Abnormally sleepy or hard to wake Stridor in calm child Severe undernutrition	Refer urgently to hospital Give first dose of antibiotic Treat fever, if present Treat wheezing, if present If cerebral malaria possible, give antimalarial drug
Severe pneumonia	Chest indrawing	Refer urgently to hospital ^a Give first dose of antibiotic Treat fever, wheezing if present
Pneumonia	No chest indrawing Fast breathing ^b	Advise parent for home care Give antibiotic Treat fever, wheezing if present Reassess in two days; if child getting worse (unable to drink, chest indrawing, other danger signs), refer urgently to hospital; if child the same, change antibiotic or refer; if child improving (breathing slower, less fever, eating better), finish five days of antibiotic
No pneumonia: cough or cold	No chest indrawing No fast breathing	If coughing more than thirty days, refer for assessment Assess and treat ear problem or sore throat, if present Advise parent for home care Treat fever, wheezing, if present

a. If referral not feasible, treat with antibiotic and follow closely.

b. Fast breathing defined as fifty breaths per minute or more in infant age two to twelve months, forty breaths per minute or more in child age one to five years.

Source: WHO/ARI 1991b.

Table 4-5. Diagnosis and Treatment of Pneumonia in Infants Less than Two Months Old

Disease	Signs	Treatment
Very severe disease	Not feeding well Convulsions Abnormally sleepy or hard to wake Stridor in calm child Wheezing Fever or low body temperature	Refer urgently to hospital Keep infant warm Give first dose of antibiotic
Severe pneumonia	Severe chest indrawing Fast breathing ^a	Refer urgently to hospital ^b Keep infant warm Give first dose of antibiotic
No pneumonia: cough or cold	No severe chest indrawing No fast breathing	Advise parent to give following home care: Keep infant warm Breastfeed frequently Clear nose if it interferes with feeding Return quickly if breathing becomes fast or difficult, feeding becomes a problem, or infant becomes sicker

a. Fast breathing defined as sixty breaths per minute or more.

b. If referral not feasible, treat with antibiotic and follow closely.

Source: Authors' data.

Case Management

Although research must continue to improve preventive technologies for the primary causes of ARI mortality, ARI control programs for the near future will rely principally on improved case management.

Elements of the Case Management Strategy

The World Health Organization's ARI control program 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 (a) the severity and complications of acute upper respiratory tract infections, (b) the inappropriate use of antibiotics and other drugs for the treatment of ARI, and (c) the incidence of pneumonia. To improve the case management of pneumonia, WHO has developed guidelines for standard treatment at the most peripheral 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 1,000), 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, Hart, and Thomas 1982; Campbell, Byass, and Greenwood 1988; Cherian and others 1988; Campbell, Armstrong, and Byass 1989; Campbell and others 1989; Lucero and others 1990). In view of the variation of normal respiratory rates with age, WHO guidelines recommend a threshold rate of sixty or more per minute in young infants (under two months), fifty or more for older infants (two months through eleven months), and forty or more for children one through four years of age (WHO 1990).

Chest indrawing (retraction of the lower part of the chest wall on inspiration) detected in children two months to four 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 tables 4-4 and 4-5 (WHO/ARI 1991b). Any of four inexpensive antibiotics may be recommended for the home care of uncomplicated pneumonia, including co-trimoxazole (trimethoprim-sulfamethoxazole), amoxicillin, 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, Addiss, and Rizwan-Ullah 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 about whether peripheral 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/ARI 1988). Although each of the studies suffered from design flaws or confounding as a result of simultaneous introduction of other interventions, taken as a whole they present strong evidence of the effectiveness of case management by peripheral health care workers. It was found that ARI-specific mortality declined by an average of 41.6 percent (range 18–65 percent), whereas

overall mortality was reduced in the same five study areas by an average of 22.2 percent (range 11.5 to 40 percent). These studies, for which further details are presented in table 4-6, confirmed the feasibility and efficacy of providing case management of pneumonia through peripheral health workers with limited training.

These results compare favorably with earlier, more theoretical calculations of the expected effectiveness of pneumonia case management interventions. For example, Tugwell and others (1985) assumed an efficacy of co-trimoxazole in treatment of community-acquired pneumonia of 80 percent, a diagnostic accuracy of 80 percent by the health workers, a correct treatment rate of 90 percent, 80 percent patient compliance with the medication regimen, and 80 percent access to appropriate treatment, calculating an expected program effectiveness of 37 percent.

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 three and one-half days (Nils Daulaire, personal communication, 1990). Under these circumstances, active surveillance by health workers is unlikely to detect an adequate proportion of cases. Control programs for ARI 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/ARI 1988), raising the important question of the effect of antibiotic treatment on concurrent infections such as diarrhea or malaria.

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

Good Practice and Actual Practice: Are There Gaps?

By the end of 1990, fifty-four countries had prepared plans of operation for ARI control programs and forty-seven had functioning programs (WHO/ARI, 1991a). Eighteen additional countries had designated a national program manager and issued technical guidelines for case management. Therefore, a total of fifty-nine 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 intrinsic complexity 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 communication 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 ensure 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 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 pneumonia 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 ensure that adequate supplies 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 percent of cases in which inappropriate use is observed in health centers (Chaulet and Khaled 1982; Hossain, Glass, and Khan 1982; Gutierrez and others 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 labeling antibiotics in special packages (as solely for use in the treatment of pneumonia in children) is being assessed (WHO 1990), the inevitable discovery of the alternative uses of these powerful pharmaceuticals will likely render such practices ineffective.

Another obstacle to be anticipated is the resistance of physicians to empowering other health care workers with training to diagnose and treat with antibiotics. Narain and Sharma (1987), for example, have presented evidence that over 90 percent of physicians do not agree that nonphysician 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 ensure the correct selection of antibiotics (at least in reference centers), 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 resis-

Table 4-6. Case Management of ARI in Children: Summary of Intervention Studies

Location (dates)	Study design	Baseline data		Case detection		Pneumonia treatment			Mortality reduction	
		IMR ^a (per 1,000)	Measles immunization coverage (percent)	Case-finding	Maternal education	Source	First-line antimicrobial	Referral care	ALRI-specific (percent)	Overall (percent)
Haryana, India (1982–84)	Concurrent control; low birth weight only	210–275	0	Active (weekly)	Yes	Community health worker	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	Community health worker or clinic	Co-trimoxazole	Poor access	56	55
Bohol, Philippines (1984–87)	Concurrent control	49–63	58–60	Passive	No	Clinic	Co-trimoxazole	Yes	25	13
Bagamoyo, Tanzania (1985–87)	Concurrent control; subsequent intervention in control area	137	53	Passive	No	Community health worker or clinic	Co-trimoxazole	Yes	30	27
Kathmandu, Nepal (1984–87)	Before and after	162	11	Active (every 2 weeks)	Yes	Community health worker	Ampicillin	Poor utilization	62	40
Kediri, Indonesia (1986–87)	Before and after	154	1.5	Active (every 2 weeks)	Yes	Community health worker	Co-trimoxazole	Poor access	67	41

a. Infant mortality rate.

Source: WHO/ARI/88.2 and WHO/ARI/91.20.

tance to commonly used antimicrobials in several countries (El-Mouza and others 1988; Lataorre Otin, Juncosa Morros, and Sanfeliu Sala 1988; Mastro and others 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 pneumonia case management. Reduction in pneumonia deaths by 25 percent was included among targets established for the 1990s by the World Health Organization and United Nations Children's Fund (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.

Priorities for ARI Control

The many national health plans which emphasize the priority of interventions to reduce infant and child mortality cannot long ignore pneumonia which is often a primary 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).

Priorities for Resource Allocation

In view of the effectiveness of the vaccines and of antibiotic therapy for pneumonia, it is probable that more than half of ARI deaths could be averted through use of 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 effect 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 and Becker 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 pneumonia will reduce mortality due to ARI and, possibly, overall mortality in that population. As WHO has pointed out (WHO/ARI 1988), "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." Al-

though most countries have active EPI programs, these programs must also be strengthened to ensure improved coverage (Poore 1988).

Referral care for pneumonia in persons who have responded poorly to antibiotic treatment requires adequate laboratory support to obtain bacteriologic cultures, identify organisms, and determine antibiotic sensitivities. Any national ARI control program must, therefore, allocate adequate resources to monitor antibiotic resistance competently 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 main pathogens.

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. The World Health Organization recently reviewed research priorities for ARI control (WHO/ARI 1989a, 1990), preparing a list which we have adapted and present below.

- 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 *Hemophilus 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.
- Identify the signs and symptoms which indicate the need for hospital care.
- Evaluate the performance of the treatment protocols, 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 effectiveness of co-trimoxazole in treatment of malaria.
- Define the clinical features and optimal treatment of serious bacterial infections (pneumonia, sepsis, and meningitis) in young infants (less than three months of age).
- Determine the special needs of undernourished children, including defining the clinical features and causes of pneumonia and the optimal treatment for these children.
- Examine cultural and other factors which determine the ability of families 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, including strategies for the modification of risk factors for pneumonia.

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

Additional research needs that must 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 effect of antibiotic use on the incidence of and mortality from other diseases (especially malaria and diarrhea) and the socio-cultural factors which modulate the effectiveness of programs. Vaccine research issues, in addition to those detailed in the list above, 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 five. 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 to have an effect 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 the attention of health workers and the supplies of antibiotics for children at the perceived expense of the communities' adult decisionmakers 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, and user fees, to increase the financial sustainability of national programs.

Appendix 4A. Sources of Data and Method Used to Obtain Cost-Effectiveness Estimates Summarized in Table 4-3

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 4-3 are obtained primarily from retrospective observations of relative risk. These figures, therefore, represent indirect estimates of the potential effectiveness 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 assume a standard population of 1 million persons, with 15 percent of the population being children under five (approximately 3 percent infants) and 8 percent mothers of

children under five. Estimates of cost and effectiveness for immunization interventions are made using a coverage range of 45 to 90 percent, as used by Feachem and Koblinsky (1983). "Most likely" values for immunization interventions are calculated assuming an immunization coverage of 80 percent, the target specified for UNICEF's goal of universal childhood immunization. Calculations of deaths averted are based on pre-intervention ARI-specific mortality rates of 5 to 20 per 1,000 (with a most likely value of 10 per 1,000), which yields an expected 750 to 3,000 (most likely 1,500) deaths among the 150,000 children under five in the standard population of 1 million.

The effect of implementing 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 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 1987).

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

The calculations presented below consider only the short-term effects of these interventions upon mortality. It is not known whether the long-term effect 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 4-3 are of use primarily as estimates of the relative cost-effectiveness of interventions when implemented alone to reduce ARI mortality.

Expanded Programme 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 nine months and twelve months, with an ideal effectiveness of 90 percent and a coverage of between 45 and 90 percent, can avert 44 to 64 percent of measles cases. In anticipation of the improved effectiveness 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 percent. Since pertussis vaccine has a similar ideal effectiveness, it is assumed that a similar proportion of cases would be averted at the same coverage rates of 45 to 90 percent. Therefore, for pertussis and measles, an effectiveness range of 44 to 80 percent has been

used for the model, with an intermediate most likely value of 65 percent.

It has been estimated that up to 2,596 of ARI mortality may be preventable if current EPI vaccines are used. Mortality among children under five due to measles-associated ARI accounted for approximately 20 percent of all ARI mortality (1.8 per 1,000 out of 9.1 per 1,000) in seventeen study areas during case management trials for WHO (WHO/ARI 1988). It is therefore assumed that 20 to 25 percent of ARI mortality would be addressed through use of current EPI vaccines. An expected ARI-specific mortality reduction of 8.8 to 20 percent (most likely 14.6 percent) may be calculated from these figures. These estimates are comparable to the ARI mortality reduction figures of 5 to 20 percent calculated by Singhi and Singhi (1987), although it was observed that measles vaccine provided an effective protection of 22 percent against respiratory deaths in Bangladesh. Based on the expected number of deaths of 750 to 3,000, 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 percent of the overall mortality prevented through EPI vaccines, 60 percent (\$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 to 90 percent among the 30,000 infants in the target age group) may, therefore, be calculated at \$409 to \$1,857, with a most likely value of \$995.

Pneumococcal Immunization

The effectiveness of pneumococcal vaccine, particularly among the youngest children, has not been clearly demonstrated in the developing world. The reported effective range in adults of 0 to 80 percent and the effectiveness of 69 percent noted among children in the United States suggest a range of 0 to 70 percent. Still, because the vaccine is less immunogenic among children under two (who constitute approximately 40 percent of children under five), an estimated 20 percent of invasive, pneumococcal infections in developing countries are caused by serotypes not included in the vaccine, and assuming a 45 to 90 percent coverage (as for the EPI vaccines), the expected disease-specific mortality reduction may be in the range of 0 to 30 percent. An intermediate most likely value of 15 percent has been selected.

Since pneumococcal disease accounts for less than one-third to one-half of pneumonia cases (WHO/RSD 1986), the maximal reduction in pneumonia mortality with the presently available vaccine is likely about 0 to 15 percent, with a most likely value of 7 percent. Although this range does not include the greater reductions in ARI-specific mortality observed among children six months through fifty-nine months of age in Papua New Guinea (Riley and others 1986), the epidemiology of pneumo-

coccal disease in that country is probably not typical of that in most developing countries. On the basis of the 750 to 3,000 expected deaths among children under five, 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 (\$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 (\$2.44 average), since the costs of EPI vaccines (\$0.04–\$0.15 per dose) are small in relation to the cost of the pneumococcal vaccine. The resulting estimated cost per dose delivered of \$7.28 suggests that (at coverage levels of 45 to 90 percent) the cost per death averted would be greater than \$437, with a most likely value of \$1,664.

Breastfeeding Promotion

Reductions in incidence of and case-fatality ratios for pneumonia that have been noted with breastfeeding (Chandra 1979; LePage, Munyakazi, and Hennart 1981; Victora and others 1987) suggest that a 50 to 80 percent ARI-specific mortality reduction might be realized among breastfed infants. The protective effect is observed, however, only below twelve months of age (approximately 20 percent of children under five), and actual prevalence of breastfeeding among infants is generally over 80 percent in high-mortality countries, such that only about 4 percent of children under five would benefit from a program to promote breastfeeding. Even assuming 100 percent effectiveness in changing breastfeeding practice, the reduction of ARI-specific mortality among children under five resulting from such promotion would be only 2 to 3.2 percent (with, on the basis of Victora's observation of over 70 percent reduction in relative risk, a most likely value of 2.8 percent). The end result would be an estimated fifteen to ninety-six (most likely forty-two) deaths averted through promotion of breastfeeding.

The average cost of a program to promote breastfeeding has been estimated at \$5 (Feachem and Koblinsky 1984; Feachem 1986; Phillips, Feachem, and Mills 1987) per mother. Even if targeting of services is only adequate to identify the subset of 50 percent of the mothers who are "at risk" of not breastfeeding, the population served might be reduced to half of the mothers with infants (8,000 in the standard population of 1 million). The estimated cost per ARI death averted for an educational program to promote breastfeeding may be calculated to be \$417 to \$2,667, with a most likely value of \$952.

Reduction of Malnutrition

Expected mortality reduction with improved nutritional status was estimated on the basis of mortality two to twenty times higher observed in malnourished children (Kielmann and McCord 1978; Tupasi and others 1988). Successful improvement of nutritional status might be expected to result in a 50

to 95 percent reduction in the risk of ARI-mortality among malnourished children. A most likely value of 80 percent reflects the modest estimate of a fivefold higher relative risk of pneumonia deaths among these malnourished children. Since 70 to 90 percent of all pneumonia deaths occur among the malnourished, expected ARI-specific mortality reductions of 35 to 85 percent (most likely 64 percent) 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 percent reduction (from 48 to 37 percent) in the prevalence of mild to moderate malnutrition (less than 80 percent weight-for-age) and a 60 percent reduction (from 5 to 2 percent) in the prevalence of severe malnutrition (less than 60 percent weight-for-age) were associated with a 64 percent reduction in ARI-specific mortality. The expected number of ARI deaths averted at this level of effectiveness would be 263 to 2,550, 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 expenditure of \$15.00 per year per malnourished child under five (Ashworth and Feachem 1986), although effective targeting of the malnourished children would be difficult to achieve. The Joint Nutrition Support Program 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 \$11.85 per child if the initial program start-up costs can be spread over five years. On the basis of this model, therefore, the cost per million population would likely be between \$810,000, for the targeted program for the expected 54,000 children (36 percent, on the basis of 1990 UNICEF data) (UNICEF 1991) who are malnourished, and

\$1,777,500, to serve all 150,000 children expected in the sample population. The use of the most likely value of \$1,500,000 reflects the better credibility of the figures from Tanzania. Final evaluation of the Joint Nutrition Support Program may yield costs per child as low as \$2.50 per year (UNICEF, personal communication, June 1991). On the basis of the less favorable preliminary figures, however, the cost per death averted is calculated to be \$697 to \$3,080, with a most likely value of \$1,563.

Case Management

There is little information available to date regarding the cost of operational programs for ARI case management for which 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 the costs of the following:

- Health education or sensitization regarding program interventions (E).
- Outpatient care for coughs and colds ($U \cdot C_u \cdot (V + M + Z \cdot A)$), where U = the incidence of coughs and colds (per 1,000), C_u = 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 nonantimicrobial medications, Z = the proportion of URI cases inappropriately treated with antimicrobials, and A = the average cost of a course of antimicrobials).

Table 4A-1. Range of Values for Variables in Model of Cost-Effectiveness of ARI Case Management

Symbol	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 pharmaceuticals	\$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	5,000	7,500	10,000
S	Cases of severe or complicated pneumonia	1,000	1,500	2,000
C_u	Proportion of URI cases seen and treated by health worker	0.10	0.05	0.02
Z	Proportion of URI cases seen and 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_s	Percent reduction in mortality with appropriate antibiotic treatment	0.60	0.80	0.90

Source: See text of appendix.

Table 4A-2. Derived Variables and Their Most Likely Values

Symbol	Variable	Derivation ^a	Most likely value (U.S. dollars)
C	Cost per capita of ARI care	$E + U \cdot C_u \cdot (V + M + Z \cdot A) + P \cdot C_p \cdot (M + A + N \cdot V) + S \cdot C_s \cdot (V + H)$	0.54
T _p	Number of uncomplicated pneumonia cases treated	$P \cdot C_p$	3,000
T _s	Number of complicated or severe pneumonia cases treated	$S \cdot C_s$	975
D	Number of ALRI deaths averted	$(T_p \cdot F_p + T_s \cdot F_s) \cdot R$	585
CE	Cost-effectiveness, or cost per ALRI death averted	C, D	926
CE _{DALY}	Cost per disability-adjusted life-year saved	CE/25	37

a. For symbols not defined in this table, see table 4A-1.

- Outpatient care for pneumonia ($P \cdot C_p \cdot (M + A + N \cdot V)$), where P = the incidence of pneumonia (per million), C_p = the coverage or proportion of pneumonia cases in the community which are diagnosed and treated appropriately (that is, given antimicrobials with or without other medications for supportive care), and N = the number of consultations per episode).
- Inpatient care for severe pneumonia ($S \cdot C_s \cdot (H + V)$), where S = the incidence of severe pneumonia (per million), C_s = the coverage or proportion of severe pneumonia in the community which is diagnosed and treated appropriately (that is, 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:

$$E + U \cdot C_u \cdot (V + M + Z \cdot A) + P \cdot C_p \cdot (M + A + N \cdot V) + S \cdot C_s \cdot (H + V)$$

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 "most favorable," for the effect on cost-effectiveness, "least favorable," and "most likely." The specific values used for each variable are listed in table 4A-1 and the "most likely" values for the derived variables in table 4A-2.

Sensitization costs (E) are derived from estimates by Phillips, Feachem, and Mills (1987), including a low-cost option, which used person-to-person communications at a cost of \$1 per mother (in groups of ten), and a high-cost program, which used mass media at a cost of \$10 per mother (assuming that there are 80,000 mothers of children under five). The intermediate cost program estimate of a cost of \$5 per mother equals those estimates used for breastfeeding promotion and weaning education programs (Feachem 1986; Phillips, Feachem, and Mills 1987).

The cost of one outpatient consultation (v) has been derived from figures for diarrheal disease and immunization consultations (Phillips, Feachem, and Mills 1987), under the assumption 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 expenditure on nonantimicrobial pharmaceuticals in many developing countries (Quick and others 1988).

The values selected for the cost per episode of antimicrobials (A) were based on UNICEF prices in 1988 for a five-day course for a child weighing ten kilograms. 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 co-trimoxazole for a ten-kilogram child, \$0.40 for the intermediate figure (Bates and others 1987; Quick and others 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, an intermediate figure of \$45 (three days at \$15 per day) from Rwanda (Shepard 1989), and a low-cost figure of \$6 (three days at \$2 per day). The ideal number of visits per episode (N) is 2, although a lower average value of 1 is used, because some programs require no follow-up visit (WHO 1988). 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, Krishna, and Mane 1969; Kamath and others 1969; Friej and Wall 1977; Foreit and Lesevic 1987), yielding the numbers of episodes specified in table 4A-1 among the 150,000 children under five in the standard population. For pneumonia incidence (P), the figures selected were 100, 50, and 25 per 1,000 (Riley and Douglas 1981; Pio, Leowski, and Luelmo 1982; WHO/ARI 1989b), suggesting a range of 5,000 to 10,000 cases of uncomplicated pneumonia. For severe pneumonia (S), the figures are 25, 10, and 5 per 1,000 (Chen and others 1980; Riley and others 1983; WHO 1984), implying a range of 1,000 to 2,000 cases of severe pneumonia, with a most likely value of 1,500.

Although ideally fewer than 2 percent of coughs and colds will be brought to the attention of and diagnosed by the health worker (C_u), a likelier figure is 5 percent, and more than 10

percent has been observed in some programs (Foreit and Lesevic 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 percentage 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 percent should be achievable with careful training and supervision of health workers. A study in Lesotho (Redd, Moteetee, and Waldman 1990) found that 6 to 15 percent of practitioners (before being retrained under 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 (C_p), the figures selected for the model are 70 percent, 40 percent, and 10 percent. The World Health Organization estimates that 12 percent of all childhood pneumonias were treated with antibiotics in 1990, and it projects increases to 40 percent in 1995 and 60 percent by 2000 (WHO/ARI 1991a). Although there are no good data from operational setting, it has been estimated that from 40 to 90 percent (with a most likely value of 65) of severe pneumonias may be seen and diagnosed by a health care worker (C_s). Incidence and coverage figures selected for URI and pneumonias suggest that 4 percent (least favorable) to 50 percent ("most favorable")—with a most likely value of 17 percent—of all cases of ARI presenting to health facilities would be diagnosed as pneumonia. These figures reflect such measurements made in operational settings (WHO/ARI 1990; Foreit and Lesevic 1987; Quick and others 1988). The incidence (P and S) and case-fatality

ratios (F_p and F_s) specified in table 4-6 yield ARI-specific mortality values of 5 per 1,000, 10 per 1,000, and 20 per 1,000, reflecting probable levels of ARI mortality (UNICEF 1991; WHO/ARI 1991b) among children under five in middle-mortality, high-mortality, and very high mortality countries. Numbers of deaths averted were, therefore, calculated on the basis of expected numbers of deaths of 750 (5 per 1,000), 1,500 (10 per 1,000), and 3,000 (50 per 1,000) for moderate-, high-, and very high mortality countries, respectively. The range of assumptions for effectiveness of treatment (R) includes 90 percent for a highly efficacious program (Berman and McIntosh 1985), 80 percent for the intermediate level of effectiveness (Institute of Medicine 1986), and 60 percent for the lower level of effectiveness, such as may be seen in settings where compliance is poor.

The additional variables defined in table 4A-2 were derived from the values for each variable specified in table 4A-1. Calculation of the cost per capita of ARI care (C) using these figures yields a most likely per capita value of \$0.54, or \$541,877 for the sample population of 1 million. The ranges for total cost (of \$220,000 to \$940,000) and for the cost-effectiveness figures used in table 4-3 reflect values obtained from the sensitivity analysis, which is summarized in table 4A-3, 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 (as measured by deaths averted) is most sensitive to the proportion of uncomplicated pneumonia cases appropriately diagnosed and treated.

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

Table 4A-3. Least and Most Favorable Costs, Effectiveness, and Cost-Effectiveness for Each Variable in Case Management Model for ARI

Variable ^a	Cost per capita (U.S. dollars)		Deaths averted		Cost-effectiveness (cost per death averted, U.S. dollars)	
	Least favorable	Most favorable	Least favorable	Most favorable	Least favorable	Most favorable
E	0.94	0.22	585	585	1,610	379
V	0.57	0.51	585	585	976	877
M	0.72	0.54	585	585	1,222	919
A	0.59	0.54	585	585	1,014	917
H	0.63	0.50	585	585	1,076	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	1,120	791
S	0.53	0.56	494	676	1,066	824
C_u	0.63	0.49	585	585	1,075	837
Z	0.56	0.54	585	585	955	919
C_p	0.53	0.55	351	819	1,524	670
C_s	0.52	0.56	480	690	1,093	811
F_p	0.54	0.54	513	753	1,056	720
F_s	0.54	0.54	585	702	926	772
R	0.54	0.54	439	658	1,235	823

Note: Figures enclosed in boxes represent the minimum and maximum values for cost, effectiveness, and cost-effectiveness.

a. For definition of symbols, see table 4A-1.

Source: Authors' data.

Table 4A-4. Cost-Effectiveness of ARI Case Management for Low- and High-Mortality Countries

Mortality	Low-mortality country	High-mortality country
Cost per capita of ARI care	\$0.52	\$0.56
Cost per target population	\$3.49	\$3.61
Deaths averted	338	1,160
Cost per death averted	\$1,152	\$483
Cost per disability-adjusted life-year saved	\$46	\$19

Source: See text of appendix.

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 4A-4. 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 (John Snow International, unpublished data).

Calculations of cost per discounted healthy year of life saved are made using a life expectancy of fifty years, an average age at death of two years, and a discount rate of 3 percent per annum. Ranges for the intermediate variables and a summary of the cost-effectiveness calculation are presented in table 4-3, in a format for comparison with the analogous figures for the other ARI interventions.

Notes

The authors would like to express their gratitude for the invaluable contributions of the many colleagues and friends who reviewed and commented on drafts of this chapter, with special recognition of assistance provided by C. J. Clements, Nils M. P. Daulaire, Floyd W. Denny, Don de Savigny, Ralph R. Frerichs, Y. Ghendon, Sandy Gove, Davidson Gwatkin, Dean Jamison, Joel A. Lamounier, Nancy Pielemeier, Antonio Pio, Mark C. Steinhoff, Tessa L. Tan-Torres, and James Tulloch.

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Source: Dean T. Jamison, W. Henry Mosley, Anthony R. Measham, and Jose Luis Bobadilla (eds.). *Disease Control Priorities in Developing Countries*. New York: Oxford University Press for the World Bank. 1993.