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Acute respiratory infections in the developing world: strategies for prevention, treatment and control

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Substantial reduction of the still unacceptable infant and child mortality rates in the developing world will be difficult to achieve without a strategy to avert deaths due to acute respiratory infections (ARI). An estimated 2 to 5 million infant and childhood deaths each year are due to ARI; up to 98% might be prevented if case-fatality ratios could be reduced to those observed in the industrialized world. However, the heterogeneity of clinical presentations and causative organisms has hampered efforts to address this leading cause of death among children.¹

The classification and management of ARI in the industrialized world is founded upon radiologic and microbiologic data, in addition to the clinical history and physical examination. ARI syndromes, which are complex clinical conditions of varying etiology and severity, have been categorized primarily on the basis of anatomical location. Common diagnostic categories for uncomplicated ARI with etiologic and clinical correlates are detailed in Table 1. Although acute upper respiratory infections, such as the common cold, are of great public health importance due to their high incidence, only the acute lower respiratory infections such as pneumonia and bronchiolitis are major causes of mortality. Although little is known about the incidence and etiologies of respiratory illnesses in developing countries, the available data suggest that more than 75% of ARI deaths are caused by pneumonia, both bacterial and viral.²

Bacterial pneumonias, which account for the majority of deaths due to ARI in the developing world, remain the most treatable of causes of severe ARI.

They may also become, with emerging vaccine technologies, preventable. This review focuses primarily on the prevention and treatment of the bacterial pneumonias in less developed countries.

INCIDENCE

Comparison and compilation of results from investigations on ARI in different countries is all but prevented by wide variations in study design, case definitions and culture techniques. The few community-based prospective studies performed suggest that ARI is very common. The incidence observed in urban areas is four to eight episodes per child per year.³⁻⁶ This is comparable to the incidence documented in longitudinal studies in the United States^{7,8} among both middle class and lower class urban children under age 5. The rate is inversely related to age, peaking at eight to nine infections in the first 2 years of life and dropping to three to four per year by school age. ARI accounts for between 20 and 60% of all outpatient pediatric consultations,^{9,10} and 12 to 45% of admissions of children to hospitals in less developed countries.^{9,11-13}

ARI causes more than one-third of all deaths among children under 5 years of age in many countries,^{2,11,12,14} frequently surpassing diarrhea as the leading cause of death,¹ especially in Africa where nearly one-half of deaths among children younger than 5 years are due to ARI.² In the Santa Maria Cauque study in Guatemala, 50% of neonatal and 52% (30 of 58) of postneonatal deaths were ascribed to pneumonia during the period from 1964 to 1972.¹⁵

Although the incidence is comparable to that in the developed world, the greater public health importance of ARI in less developed countries is manifest in the mortality rates, which are 10 to 50 times greater.^{9,10} Prospective studies in Matlab, Bangladesh, for example, have documented acute lower respiratory infection mortality to be 10.4/1000 infants and 1.6/1000

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TABLE 1. Acute respiratory infections: clinical characterization in the developed world

	Diagnosis	Common Etiology	Age of Peak Incidence (Months)	Mortality
Upper respiratory infections	Nasopharyngitis (coryza)	Viral (various agents)		No
Lower respiratory infections	Pharyngotonsillitis	Viral, bacterial (various, <i>Streptococcus</i>)		No
	Laryngitis (croup)	Viral (parainfluenza 1)	12-24	Rare
	Tracheobronchitis	Viral (various agents)	Constant	No
	Broncholitis	Viral (respiratory syncytial virus)	0-12	Yes
	Pneumonia	Bacterial, viral (pneumococcus <i>Haemophilus influenzae</i>)	24-36	Yes

for children 1 to 4 years of age.¹⁶ A cohort of 10 000 people living in Tari, Papua New Guinea were prospectively followed to reveal a mortality due to acute lower respiratory infection of 30/1000 infants and 4/1000 among children ages 1 to 4 years.¹⁷ In some areas of Bolivia and Brazil, respiratory diseases are listed as the cause of death for 40 to 44/1000 infants.⁹

ETIOLOGY

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

Cultures. Cultures of blood, pleural fluid or pulmonary exudate obtained by lung puncture yield the most reliable bacteriologic diagnoses. However, blood cultures are positive in only 10 to 30% of cases of bacterial pneumonia,¹⁸ pleural fluid is most often absent and clinicians are justifiably reticent to consider lung puncture for routine diagnosis because of the risk of serious complications of the procedure. Therefore most epidemiologic studies of pneumonia in children have relied primarily on cultures of the upper respiratory tract. Such culture data may be unrevealing or frankly misleading due to high rates of upper respiratory carriage of bacterial pathogens.

Bacterial agents. The purulent nasal discharge so frequently seen among the children of developing countries reflects the higher carriage rate of bacterial pathogens. The undernourished and often chronically ill children of less developed countries may well be more susceptible to the descent of bacteria from the upper to the lower respiratory tract to cause pneumonia, even in the absence of antecedent viral infection. One-third of North American children younger than 5 years of age carry the pneumococcus.¹⁹ On the other hand, in Papua New Guinea, 95% of healthy children were found to carry pneumococcus in their upper respiratory tracts, and over 90% were culture-positive for *Haemophilus influenzae*.¹⁷ One-half of the infants studied in Papua New Guinea had acquired *Streptococcus pneumoniae* at age 3 weeks, while in North America the mean age at acquisition was 6 months.²⁰

In addition even minor variations in specimen collection and management will dramatically alter isolation rates and the range of organisms identified. Although a few studies in developing countries have reported culture data based on needle aspiration of lung, most have used techniques which would be expected to skew the culture results by the limited use of appropriate techniques for viral isolation or selective media which permit isolation of *H. influenzae*. Additional difficulties in establishing a single etiologic agent in a given infection arise with the frequent finding of multiple potential pathogens in a specimen of sputum, blood or even pleural fluid. Furthermore coincident viral and bacterial pulmonary infections, well-known with influenza and measles, are probably more frequent than is commonly appreciated.²¹

Despite such obstacles to obtaining etiologic data, there is consensus that the pneumococcus and *H. influenzae* are the major causes of death caused by ARI in developing countries.²²⁻²⁴ Shann et al.¹¹ point out, in their review of 1011 previously untreated children studied in 12 lung aspiration studies of pneumonia in less developed countries, that bacteria were isolated in 632 (63%). The most frequent isolates in his own study also were *H. influenzae* and *S. pneumoniae*, with *Staphylococcus aureus* often isolated only after the child had received antibiotics. Twenty-eight isolates of *S. pneumoniae* from 25 cases were serotyped. The commonest serotypes were type 6 (24%), type 4 (12%) and type 19 (12%), which is consistent with data obtained among children in the United States.²⁵ However, several serotypes; such as type 5, appear to be considerably more prevalent in less developed countries. The high proportions of nonserotypable strains and the low proportion of *H. influenzae* type b observed in this study have not been reported by other investigators. In view of the potential importance of these findings, especially for prevention of ARI with vaccines, this study will need to be corroborated in other developing countries.

Further epidemiologic investigations will also be required to define the role of *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum* and *Pneumocystis carinii*, which may be important causes of pneumonia among children in less developed countries.²⁶

Viral agents. The most frequent viral isolates from

the bulk of etiologic studies^{2,11,23,27-29} among patients hospitalized with acute lower respiratory infection are respiratory syncytial virus, parainfluenza viruses, adenovirus and influenza viruses. The role of cytomegalovirus, the isolation of which is associated with severe ARI, requires further definition as either a primary pathogen or reactivated infection in the setting of lower respiratory infection due to another organism. The isolation of viruses, particularly adenoviruses, herpes and enteroviruses, must be interpreted with caution as they are frequently found both in the absence of respiratory symptoms and in conjunction with other viral or bacterial pathogens.²⁶

RISK FACTORS

The wide variations in both the incidence rates and case-fatality ratios for ARI are often linked with varying risk factors. Risk factors associated with either increased susceptibility or increased risk of mortality due to an episode of ARI are summarized in Table 2.

Age, sex and nutritional status. The inverse relationship between ARI mortality and age is explained by both the increased incidence rate of infections as well as higher case-fatality ratios among infants (after 3 to 4 weeks of age) and young children.^{2,23,30,31} The incidence of ARI among males has been observed to be approximately 1.5 times that among females,²³ although case-fatality ratios are comparable. Poor nutritional status also adversely affects both the incidence and case-fatality ratios for ARI.^{23,32-35} Studies in Costa Rica document a 12-fold greater incidence of pneumonia in undernourished children (457.8/1000) when compared with children of normal weight for age (37.0/1000).³² At Narangwal, India, a doubling of mortality due to ARI was observed for each decile below 80% weight-for-age.³³ Vitamin A deficiency, which often accompanies protein-calorie malnutrition, results in keratinization of the respiratory epithelium, thus presumably decreasing local resistance and increasing the risk of bacterial colonization and infection.^{34,35} Low birth weight, seen in 20 to 40% of infants in many less developed countries, also increases the risk of ARI morbidity and mortality. (FTE Mtango, D Neuvians: Acute respiratory infections in children over five years: Control project in Bagamoyo district, Tanzania. Part I. Mortality reduction in first two years of intervention. World Health Organization, unpublished results.)

TABLE 2. Risk factors for acute respiratory infections

Increased Incidence	Increased Mortality
Age younger than 2 years	Age younger than 2 years
Poor nutritional status (vitamin A deficiency, low birth weight)	Poor nutritional status (vitamin A deficiency, low birth weight)
Crowding	Early weaning
Low socioeconomic status	Lack of maternal education
Indoor air pollution	Reduced health care access

Breast-feeding. Although there is good evidence for a protective effect of breast-feeding in the prevention of diarrhea, data on infant feeding practices and the incidence of respiratory infections are somewhat contradictory. Although several studies summarized in a recent review³⁶ have failed to document any protective effect of breast-feeding, others have found both a decreased incidence³⁷ and decreased case-fatality ratio³⁸ for respiratory infections among breast-fed infants and children.

Socioeconomic status. Low socioeconomic status and crowding have been well-documented as risk factors for respiratory infections in the developed world. Studies in India¹³ and Haiti (SK Stansfield, unpublished data) have also demonstrated an increased incidence of ARI among children in lower socioeconomic groups and in more crowded households. Both poverty and crowding, however, may be proximate measures for other known or as yet unrecognized risk factors.

Parasitic infections. There are conflicting data on the incidence of ARI among persons with nematode or trematode infections which are characterized by pulmonary migration of larvae or flukes. It has been suggested that the associated local inflammation and damage to lung parenchyma may predispose to bacterial superinfection. An Indonesian study of 85 *Ascaris*-infected children compared to 100 uninfected children matched for age and sex documented no significant difference in the prevalence of respiratory tract infection.³⁹ Blumenthal and Schultz,⁴⁰ on the other hand, reported a point prevalence of respiratory infections of 46.7% in *Ascaris*-infected patients compared with 13.3% in uninfected controls ($P < 0.05$). Interpretation of these studies is complicated by the fact that parasitic pneumonia itself may cause a picture clinically and radiographically indistinguishable from bacterial pneumonia.⁴¹ In addition no attempt was made to control for other variables such as undernutrition or socioeconomic status.

Air pollution. Increasing concern has developed about the effects of indoor air pollution due to combustion of biomass fuels in cook fires. There is an expanding literature from the industrialized world on the effects of maternal smoking on low birth weight and passive smoking on the respiratory health of children. Although more data are needed from less developed countries, there is reason to suspect that indoor cook fires may increase infant and child mortality via such "passive smoking".⁴²

MANAGEMENT

Cases of ARI are stratified to decide on management. Management decisions for the care of patients with ARI are based not on anatomic diagnosis but on the severity of illness. WHO recommends that primary health care workers in less developed countries

classify ARI by the signs and symptoms pertinent to two "binary" management decisions: (1) whether to treat with antibiotics or not; and (2) whether to treat as an outpatient or refer for inpatient care.

Among patients with⁴³ and without⁴⁴ chest radiographs, tachypnea (i.e. rapid breathing) noted by either the mother or the health worker appears to be the best predictor of the need for antibiotic therapy in a child with a cough. Chest indrawing (i.e. intercostal or subcostal retractions) is the best clinical predictor of a high risk for mortality and the need for inpatient care.⁴⁴ The inclusion of cyanosis, inability to feed and changes in consciousness as indications for admission probably ensures that most children at high risk of mortality will be admitted for more intensive therapy.

WHO algorithm. WHO has developed an algorithm for the diagnosis and treatment of ARI,⁴⁵ and their Technical Advisory Group on ARI has proposed a management-oriented classification of ARI for use by community health workers or other outpatient health care providers.⁴⁶ That classification system, adapted for health workers with less than 6 months training, is summarized in Table 3. The supportive treatment recommended for all cases of ARI includes fluids, continued feeding as tolerated, neutral environmental temperature, antipyretics and clearing of any nasal or ear discharge. Steam humidification, bronchodilators and oxygen may also be used in supportive care at referral facilities.

When a moderate or severe episode of ARI is diagnosed by these criteria, the indication for antibiotics has been established. Respiratory infections caused by pneumococci or *H. influenzae* in less developed countries are considered susceptible to adequate doses of parenteral penicillin, oral ampicillin or trimethoprim-sulfamethoxazole.⁴⁶ Parenteral penicillin is generally the first drug of choice for initial treatment because of its effectiveness and low cost.

There is limited but growing evidence that such ARI control programs can reduce mortality. Access to appropriate antimicrobial therapy at a health center or hospital was associated with an 84% reduction in the

case-fatality ratios for untreated moderate and severe acute lower respiratory infection in Goroka, Papua New Guinea.¹⁴ McCord and Kielmann⁴⁷ prospectively documented that implementation of an in-service training program for Family Health Workers in the management of ARI resulted in a 45% reduction in the infant and childhood mortality caused by pneumonia. Preliminary reports from an ARI control program in Chandigarh, India, demonstrated a 65% reduction in the case-fatality ratio for acute lower respiratory infections.⁴⁸ Similar ARI projects have been integrated into primary health care systems using community or village health workers in the Bagamoyo district in Tanzania (FTE Mtango, D Neuvians: Unpublished World Health Organization report previously cited) and in Bohol in the Philippines,⁴⁹ as well as in several Latin American countries.

PREVENTION

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

Chemoprophylaxis. Although chemoprophylaxis is sometimes suggested as a preventive strategy for the respiratory infections of viral etiology, the serious questions about the feasibility, costs and benefits of this strategy in the developed world loom only larger in less developed countries. Immunization with available vaccines, on the other hand, represents a simple, inexpensive technology of proved effectiveness in the prevention and control of several important acute respiratory infections.

Vaccines. Measles, tuberculosis (*Bacillus Calmette-Guérin*) (BCG) and pertussis vaccines and diphtheria toxoid are clearly effective preventive measures for those infections of the respiratory tract. It has been estimated that deaths due to those four diseases

TABLE 3. Acute respiratory infections: classification and case management for health workers with <6 months of training^{46 a}

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

^a Supportive measures include fluids, continued feeding as tolerated, neutral environmental temperature, antipyretics and clearing of any nasal or ear discharge. Steam humidification, bronchodilators and oxygen may also be used in supportive care at referral facilities.

account for up to 25% of the total mortality associated with ARI.⁵⁰ Although these vaccines have been recommended for universal delivery in national immunization programs, it is estimated that less than 40% of children are fully protected. The first priority for the prevention of ARI is to work toward the goal of universal immunization.

Measles vaccine. Although the current measles vaccine is quite effective, measles control is hampered by the fact that an estimated 20 to 30% of cases occur prior to the recommended age of vaccination of 9 months.⁵¹ Efficacy trials are under way with a human diploid attenuated measles vaccine which has demonstrated the ability to stimulate antibodies in infants as young as 4 months of age in the presence of maternal antibodies.⁵²

Pertussis vaccines. There is no concern regarding the efficacy or adverse effects of the current diphtheria vaccine. However, efforts are under way to improve the current pertussis vaccine through reducing its adverse effects. Single component (pertussis toxin or lymphocytosis-promoting factor) and two-component (lymphocytosis-promoting factor with filamentous hemagglutinin) vaccines represent second generation acellular pertussis vaccines which are now undergoing clinical trials in Sweden and elsewhere.

BCG. Although pulmonary tuberculosis usually has an insidious onset in the developed world, its presentation in less developed countries, particularly in children, is commonly that of acute pneumonia. BCG, the live, attenuated strain of bovine tubercle bacilli which is used in many countries to induce specific immunity against tuberculosis, is of greatest use among infants in countries with a high prevalence of infection where exposure of children is common. Although its efficacy continues to be controversial, it appears that BCG confers 60 to 80% protection against the development of clinical tuberculosis (O Tidjani, A Amedome, HG ten Dam: The protective effect of BCG vaccination of the newborn against childhood tuberculosis in an African community, submitted for publication.)

***H. influenzae* and pneumococcal polysaccharide vaccines.** Reduction of mortality due to the primary causes of ARI-related deaths, the pneumococcus and *H. influenzae*, must rely primarily on improved case management for the near future. The poor immunogenicity of the unconjugated polysaccharides which comprise the currently available vaccines against those two organisms in the younger age groups and the paucity of epidemiologic information about the distribution of disease due to specific capsular types in less developed countries prevent their routine use in children.

Although 8 to 10 capsular types comprise most of the strains of pneumococcus causing invasive infections in the developed world, 84 capsular polysaccha-

rides have been identified.²⁷ Several types which are known to be important causes of invasive pneumococcal disease in less developed countries are not included in the 23-valent vaccine formulated for use in the United States, such that it is difficult to predict the potential efficacy.

The existing pneumococcal vaccine may be more effective in young children of less developed countries than has been expected. Riley et al.⁵³ in Papua New Guinea estimated a vaccine efficacy of 59% (19 to 79%, 95% confidence interval) of the currently available 23-valent preparation in reducing mortality caused by acute lower respiratory infections and 19% (-10% to 40%, 95% confidence interval) in reducing overall mortality among children younger than 5 years of age. Children 6 months to 5 years of age were vaccinated and similar protective efficacies were observed even in the younger age group. Analogous studies have not been done for the *H. influenzae* vaccine.

The existing *H. influenzae* vaccine has raised similar doubts of its potential efficacy in reducing ARI mortality in less developed countries. Virtually all the isolates from infected tissues or blood of patients in the developed world with invasive *H. influenzae* infections such as epiglottitis, pneumonia or meningitis are of capsular type b. The type b polysaccharide polyribose ribosylphosphate was thus selected as the best candidate for the *H. influenzae* vaccine recently licensed in the United States for use in children older than 2 years of age. However, only a fraction of the isolates from patients with pneumonia in Papua New Guinea were found to be capsular type b strains.⁷ These results require corroboration in other developing countries. The importance of these nonserotypable or other non-b strains of *H. influenzae* may need further study since they were often isolated in conjunction with *H. influenzae* type b and are relatively rarely isolated from blood cultures.

An approach to improving the immune responses elicited in younger children by polysaccharide vaccines has been to bind them covalently to a protein conjugate, rendering the mechanism of the response "T-dependent".⁵⁴⁻⁵⁸ The delivery of polysaccharide vaccines in association with the diphtheria-tetanus toxoids-pertussis series or BCG vaccination is currently being studied.

Transplacental protection. Immunization of mothers in developing countries to prevent neonatal tetanus suggests the intriguing possibility that polysaccharides, possibly delivered in conjunction with tetanus toxoid during the last trimester, may provide sufficiently high titers to confer transplacental passive protection against bacterial ARI during early infancy.⁵⁹ Subunit preparations of nonpolysaccharide antigens which are not type-specific are another ave-

nue for exploration in immunoprophylaxis against both *S. pneumoniae* and *H. influenzae* infections.^{58,60}

Other agents. There is little information to establish the relative importance of pneumonia caused by such agents as *M. pneumoniae*, *C. trachomatis* and Group B *Streptococcus* among children of less developed countries. More data are needed on the epidemiology and natural history of infection before immunization can be recommended. Data to support the hypothesized association between maternal genital tract carriage of these bacteria and preterm delivery, premature rupture of membranes, and low birth weight,⁶¹⁻⁶⁶ all of which are known to earmark infants at high risk of mortality, are difficult to obtain in less developed countries. Preventive measures against these infections, including prophylactic antibiotics as well as vaccines, require further study for their efficacy in the prevention of low birth weight and mortality due to neonatal infections.

The lesser incidence overall of staphylococcal pneumonia as well as its more frequent occurrence as a complication of other illnesses⁶⁷ make vaccines against *Staph. aureus* less likely to be among the cost-effective interventions for ARI.

Respiratory syncytial viruses and parainfluenza viruses are important causes of acute bronchiolitis and pneumonia in infants and young children; however, attempts to provide protective immunity using classic vaccine technologies have been frustrating.⁶⁸⁻⁷⁰ So little is known about the epidemiology of these infections in the developing world that no distinct strategy can be identified based on less developed countries' concerns.

Because of the adverse effects of inactivated whole virus vaccines as well as the short efficacy caused in part by the antigenic drift of the virus, influenza vaccines currently have no place in preventing ARI in children in developing countries. Because of the limited severity of adenoviral ARI, which generally presents as a common cold, as well as the oncogenicity of some adenoviral serotypes in animals, adenoviral vaccines are not regarded as candidates for development for prevention of ARI in infants and children at this time.

Enteroviruses (coxsackieviruses, enteroviruses and echoviruses) more frequently give rise to a common cold syndrome when they cause ARI; however, all three groups can induce lower respiratory infections. Because of the antigenic and clinical heterogeneity of these viruses, with the exception of poliovirus they have not been regarded as attractive candidates for vaccine development.

Rhinoviruses and coronaviruses, which cause only upper respiratory infection syndromes, have not been regarded as feasible or desirable targets for immunoprophylaxis with vaccines because of their antigenic

diversity as well as mild clinical illness. The efficacy in reducing the mortality due to pneumonia through prevention of antecedent upper respiratory infections has, however, not been systematically explored.

Directed research efforts will improve and continually refine existing strategies for the reduction of mortality due to ARI. Available technologies now known to be effective include immunizations and improved case management. The use of these interventions to avert deaths due to ARI represents the next major challenge and hope of reducing the unacceptable infant and child mortality rates in developing countries.

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