12 Acute Respiratory Infections

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CONTENTS

KEY POINTS

- Acute respiratory infections (ARI) cause more than 25% of all deaths in children under the age of 5 worldwide. Two-thirds of these deaths are as a result from pneumonia.
- Severe disease is an outcome of frequent exposure to pathogenic organisms, virulence, and host susceptibility.
- High acquisition rates of *Streptococcus pneumoniae* and *Haemophilus influenzae* by the upper respiratory tract predispose to pulmonary invasion.
- *S. pneumoniae* and *H. influenzae* capsular polysaccharide determines invasiveness and immunogenicity of these organisms. Polysaccharide is a weak immunogen in infants.

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- The lungs are protected by an integrated set of biologic, mechanical, phagocytic, and immunologic defenses with built-in redundancies.
- The major risk factors for severe ARI are poor nutrition, indoor smoke pollution, and substandard living conditions.
- Undernourished children, very young infants, and HIV-infected children are susceptible to invasion by many different opportunistic pathogens. Nevertheless, *S. pneumoniae* and *H. influenzae* are the most important pathogens.
- Conjugate polysaccharide vaccines are effective in preventing pneumonia from *S. pneumoniae* and *H. influenzae*, but are too expensive for use in developing countries.
- Reduction of mortality from ARI depends on an integrated approach including promoting good nutrition, immunizing infants, controlling HIV transmission, and standardizing case management with selective treatment of pneumonia with antibiotics.

Introduction *(1)*

Acute respiratory infections (ARI) are the leading cause of death in children worldwide. Most ARI deaths are caused by pneumonia. The most recent data relate to 1998 when ARI caused 1.9 million child deaths, but a further 1.1 million ARI deaths were caused by specific diseases including 67% of all measles deaths, 83% of all pertussis deaths, and 25% of AIDS deaths in children. A further 10% of perinatal deaths were a result of pneumonia. All told, 28% of the estimated 10.8 million deaths in children under the age of 5 yr were caused by ARI and almost all of them occurred in developing countries.

ARI range in severity from the common cold to life-threatening pneumonia and are the most common cause for attendance at health services. Children in both developing and developed countries experience four to eight "coughs and colds" each year, but the incidence of severe ARI is 10–30 times higher in developing countries. Two bacteria–*Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*—are responsible for two-thirds of all severe ARI cases.

A public health approach to ARI was slow to develop. In the early 1980s, the World Health Organization (WHO) sponsored research that defined the causative agents of severe disease in developing countries to standardize case management. The results showed that selective antibiotic treatment of severe ARI could reduce population mortality by 20–35%. A systematic review of risk factors identified interventions most likely to reduce severe disease and death. New vaccines were evaluated. In the early 1990s, ARI, along with diarrhea, malaria, measles, and undernutrition, were included in the WHO strategy

for the integrated management of childhood illness (IMCI) that shifted the emphasis of case management from specific diseases to the sick child.

This chapter describes the interventions to control ARI as well as the reasons for the high morbidity and mortality rates found in developing countries. Severe ARI is the outcome of three sets of interacting factors. First, the frequency of exposure to pathogenic organisms. Second, virulence, which is the relative ability of organisms to cause severe disease. Third, host susceptibility.

Anatomical Classification and Pathology *(2–4)*

Official reports of morbidity and mortality are based on the International Classification of Disease. ARI are grouped into three categories, namely, acute upper respiratory infections, influenza and pneumonia, and other acute lower respiratory infections. Specific infections are grouped separately as are perinatal conditions.

It is standard clinical practice to classify ARI first by the anatomical site of maximum inflammation and second by causative agent (*see* Table 1). Inflammation of the respiratory system is a threat to life at three levels: at or about the larynx or glottis, in the bronchioles, and within the alveoli. Inflammation of the first two leads to obstruction of the airways, and of the third to diminished capacity to exchange gases. The work of respiration is increased either because of obstruction or of increased stiffness of the lungs.

In infancy, the airways are most narrow just below the larynx. Inflammatory swelling, typically from a viral laryngo-tracheo-bronchitis (croup) causes stridor—a harsh inspiratory sound. The effort of respiration brings accessory muscles of respiration into play and the child is seen to be in extreme distress. The whoop, heard in about one-third of cases of pertussis, is the sound of inhalation through an obstructed glottis following a paroxysm of coughing.

Bronchiolitis, commonly associated with respiratory syncytial virus (RSV) infection, leads to trapping of air, hyperinflation, and an expiratory noise or wheeze: respiratory effort is directed at the act of expiration.

S. pneumoniae and *H. influenzae* stimulate an outpouring of exudate into the alveoli, in which it is spread throughout the lungs. This results in a segmental or lobar pneumonia. At autopsy, pneumonic lung is solid and airless, and is described as being consolidated. Bronchopneumonia is caused by invasion of alveoli from the airways by bacteria frequently less virulent than those causing lobar pneumonia. Bacterial pneumonias cause dense opacities in chest radiographs. Infection with staphylococcus and Gram-negative bacteria may cause abscesses or empyema (pus in the pleural cavity).

Viral pneumonia causes lymphocytic infiltration of the interstitium and has a cytopathic effect in alveolar and bronchial cells. Typically, viral pneumonias

Table 1
Anatomical Classification of ARI by Site of Maximum Inflammation

Acute upper respiratory infections
• Nasopharyngitis (common cold, coryza)
• Otitis media
• Pharyngitis (sore throat)
• Tonsillitis
• Sinusitis (especially of the faciomaxillary sinuses)
Acute lower respiratory infections
• Epiglottitis
• Laryngitis
• Bronchitis
• Bronchiolitis
• Pneumonia

cause nodular or reticular opacities in chest radiographs. The radiographic appearances of bacterial and viral pneumonia overlap, however, and neither pattern is absolutely diagnostic.

WHO Clinical Classification *(2)*

Clinical Decision-Making

The WHO clinical classification is a severity-based classification that was developed for health workers untrained in auscultation and without access to radiography or laboratory support. It is used to make decisions about whether a child requires antibiotics and whether a child should be admitted to the hospital. It sets the criteria for referral between different level health facilities.

A history of cough or difficult breathing suggests that a child may be suffering from pneumonia. Fast breathing is the single most specific sign of pneumonia. Cut-off points are 60 breaths/min in infants under 2 mo old, 50 breaths/min in infants 2–11 mo old, and 40 breaths/min in children 1–4 yr old. Chest indrawing indicates severe pneumonia. It is a paradoxical movement of the lower part of the chest wall, flexible in infancy, which is drawn inward during inspiration. It is caused by increased work of respiration resulting in increased negative intrapleural pressure. It is to be distinguished from, but often associated with, indrawing of supracostal and intercostal soft tissues. The presence of these signs increases the specificity of the diagnosis.

Stridor in the calm child and central cyanosis are indications for immediate admission. A neonate with fast breathing or chest indrawing requires admission. A child over 2 mo old with chest indrawing also requires admission. A

Table 2
Summary of the Clinical Classification and Management
at the Periphery of the Child 2–59 mo With a History of Cough or Difficult Breathing

Clinical Signs	Classification	Management
Danger signs:		
• Convulsions this illness	Very severe disease	Admit to hospital for treatment and investigation
• Lethargic or unconscious		
• Unable to drink or breastfeed		
• Vomits everything		
Respiratory signs:		
• Chest indrawing	Severe pneumonia	Admit to hospital for antibiotics
• Cyanosis		
• Stridor in the calm child		
Fast breathing	Pneumonia	Treat with antibiotics at home
None of the above	Cough or Cold	Symptomatic treatment

child over 2 mo old with fast breathing, but not chest indrawing, has pneumonia and can be treated with antibiotics at home. Children with a history of cough or difficult breathing, but with none of these signs, have a "cough or cold" and should be treated symptomatically.

The IMCI also identifies certain danger signs that may be associated with pneumonia or with a nonrespiratory bacterial infection. Classification and management of children 2–59 mo old and of infants under 2 mo old are summarized in Tables 2 and 3.

Epidemiological Studies

The clinical classification is used increasingly as an outcome measure for epidemiological studies. In this classification, pneumonia refers to a mix of conditions including laryngeal obstruction, bronchitis, bronchiolitis, and pneumonia. Many such cases will not have radiographic signs of pneumonia. Acute lower respiratory tract infection (ALRI) is a more appropriate term.

The global estimates of mortality referred to at the beginning of the chapter depend heavily on the use of verbal autopsies *(3)*. In general, the higher the mortality rate in a country, the more likely it is that a child will die without making contact with the health services. Verbal autopsy diagnoses are based

Table 3
Summary of the Clinical Classification and Management of Severe Bacterial Infection and ARI at the Periphery for the Infant Under 2 mo of Age

Clinical Signs	Classification	Management
Danger signs:		
• Convulsions this illness	Possible severe bacterial infection	Admit to hospital for treatment and investigation
• Lethargic or unconscious		
• Less than normal movement		
• Unable to feed		
• Bulging fontanelle		
• Pus draining from ear		
• Fever or hypothermia		
Respiratory signs:		
• Severe chest indrawing	Severe pneumonia	Admit to hospital for antibiotics
• Nasal flaring		
• Grunting		
• Fast breathing		
• Stridor in the calm child		
Local signs:		
• Red umbilicus or draining pus	Local bacterial infection	Admit to hospital for antibiotics
• Skin pustules		
No fast breathing; no signs of pneumonia	Cough or cold	Symptomatic treatment

on field surveys and retrospective histories taken from mothers. Essentially, the diagnosis of ALRI depends on a history of cough and difficult breathing. The coexistence of malaria and measles reduces the specificity of the diagnosis. The tendency is to over diagnose if a study focuses on ALRI to the exclusion of other conditions.

Etiologic Agents of Respiratory Disease

Known Etiologic Agents

An extraordinary number of organisms are capable of invading the respiratory tract (*see* Table 4). Although some pathogens are strongly associated with particular diseases, no single pathogen is known to cause only the one disease, and no disease is caused by a single pathogen.

The principal causes of population mortality are *S. pneumoniae*, *H. influenzae*, influenza A virus, measles virus, RSV, and *Bordetella pertussis (1,4,5)*. Each can cause severe disease in previously healthy persons. Recently described infective agents include the variant coronavirus that is thought to be responsible for the severe acute respiratory distress syndrome (SARS) and metapneumovirus, which appears to be responsible for a spectrum of disease similar to that of RSV *(6,7)*.

Pathways of Spread and of Transmission (8)

Organisms enter the lungs by inhalation, aspiration, invasion from the upper respiratory tract, or from the blood stream. They exit the respiratory tract in secretions. Coughing and sneezing create aerosols and droplets. Microbial aerosols can be inhaled directly into the alveoli. Droplets and other large particles settle out quickly; organisms are transmitted directly through kissing and fondling or from contaminated objects (fomites). The fetus is susceptible to vertical transmission in the birth canal. Poor management of a birth delivery exposes the fetus to organisms from the mother's bowel, or from the hands of the mother or midwife. Organisms from the skin, such as *S. aureus* and *S. pyogenes*, can invade the lungs by way of the blood stream as do *Salmonella* from bowel.

An opportunistic pathogen as distinct from a true pathogen is an organism that is not capable of invading the body and causing disease in a healthy person, but able to do so in a person with weakened immunity. Although useful conceptually, the distinction between opportunistic and true pathogens is not clear cut. Virulence and its correlate invasiveness are relative rather than absolute properties of microorganisms. Opportunistic pathogens are less virulent and less invasive than true pathogens.

Activation of latent infections, for example, *M. tuberculosis* or cytomegalovirus, is also more likely in persons with weakened immunity.

S. pneumoniae *and* H. influenzae (9–11)

S. pneumoniae and *H. influenzae* are upper respiratory commensals and extracellular pathogens. They possess a polysaccharide capsule that appears to swell in the presence of specific antibody. On the basis of this reaction, more than 80 distinct serotypes of pneumococcus and seven serotypes of *H.*

Table 4
Respiratory Pathogens
and the Diseases They Cause

Coryza (common cold)
- Rhinoviruses
- Respiratory syncytial virus (RSV)
- Influenza viruses
- Parainfluenza viruses
- Coronavirus

Pharyngitis and tonsillitis
- Respiratory viruses as above
- Adenoviruses
- Coxsackie viruses
- Herpes simplex virus
- Measles virus
- *Corynebacterium diphtheriae*
- β-haemolytic *Streptococcus pyogenes*

Acute otitis media, acute sinusitis
- Respiratory viruses
- *H. influenzae*
- *S. pneumoniae*

Acute epiglottitis
- *Haemophilus influenzae* type b

Acute laryngo-tracheo-bronchitis (croup)
- Parainfluenza virus
- RSV
- Rhinoviruses
- Measles virus
- *Corynebacterium diphtheriae*

Acute bronchitis
- Respiratory viruses as above

Whooping cough
- *Bordetella pertussis*
- Adenoviruses

Acute bronchiolitis
- RSV
- Other respiratory viruses
- *Chlamydia trachomatis*

continued

Table 4 (*Continued*)
Respiratory Pathogens
and the Diseases They Cause

Pneumonia

- Respiratory cyncitial virus
- Parainfluenza 3 virus
- Influenza virus
- Adenoviruses
- Measles virus
- Cytomegalovirus (CMV)
- *S. pneumoniae*
- *H. influenzae*
- *Staphylococcus aureus*
- Gram negative bacilli
- *Mycobacterium tuberculosis*
- *Chlamydia trachomatis*
- *Mycoplasma pneumoniae*
- *Legionella pneumophila*

influenzae have been described. The capsule enables resistance to phagocytosis and determines the organism's immunogenicity and invasiveness. There are also non capsulated strains. Virulence factors include cell wall adhesins and a toxic protein, pneumolysin, which contributes to the inflammatory response.

Some serotypes and all non capsulated strains invade only rarely and can be regarded as opportunistic pathogens; noncapsulated strains fall into this category. Other serotypes are true pathogens. They are highly invasive, are rarely found as carriage organisms, and multiply in large numbers in the alveolar exudate that they provoke *(12)*. Immune competence against capsular polysaccharide is acquired serotype by serotype as a child grows older *(13)*. It is generally poor in children less than 2 yr of age, but competence against some serotypes is not attained until after the age of 5 yr.

Children in developing countries encounter these organisms at a much younger age and have much higher carriage rates than do children in developed countries. A study of neonates in the Papuan New Guinean highlands showed the mean age of acquisition of *S. pneumoniae* to be 17 d and of *H. influenzae* to be 31 d *(14)*. In contrast, the mean age of acquisition in a US series was 6 mo *(15)*. In the US series, acquisition was associated with subsequent disease in 15% of cases. Preschool children introduced pneumococcus into households. Day care has increased the prevalence of upper respiratory colonization of infants in the United States.

Case fatality rates correlate with the degree of invasion. In the preantibiotic era, case fatality in adults was shown to increase with the extent of pulmonary involvement, and again with bacteraemia. In the 1920s, less than 20% of adult patients with bacteremic pneumococcal pneumonia survived *(16)*. Today, in developing countries, bacteremia occurs in between 5 and 20% of children who have not received prior antibiotics. Case fatality is increased fivefold in these cases.

Respiratory Viruses

Coinfection with bacteria and viruses is common. Viral nasopharyngitis spreads bacteria through sneezing and coughing. Viruses damage respiratory epithelium and upregulate epithelial receptors for bacterial attachment. Only three respiratory viruses—influenza A, measles, and RSV—are independently associated with high mortality. These are enveloped RNA viruses that attach to respiratory epithelial cell membranes.

Influenza A Virus (17)

In temperate climate countries influenza A virus causes winter epidemics associated with high mortality in the very young and the old, but is not associated with a specific respiratory syndrome. It is frequently isolated from children with pneumonia in developing countries. Epidemics are associated with "drift" and pandemics with "shift" in the molecular structure of the haemagglutinin (HA) and neuraminadase (NA) glycoproteins that are required for attachment and exit from epithelial cells. Virulence is associated with the number of points on an HA precursor that can be cleaved by proteases. The more points at which this can take place, and the greater the number of host proteases that can cleave the virus, the greater the extent of its cell tropism and hence of its virulence. Bacteria, too, produce proteases that cleave the precursor and extend cell tropism.

The primary site of attachment is usually the epithelial cells of the tracheobronchus. Primary influenzal pneumonia is rare, but can be extremely severe. Secondary pneumonia due to *S. pneumoniae* or *H. influenzae* is comparatively common. Influenza vaccine is considered to be 60–90% effective providing it contains HA and NA antigens from current epidemic strains.

Measles (18)

Measles is a disease of epithelial surfaces, and is particularly severe in undernourished children. It causes immunosuppression and vitamin A depletion. Despite mass immunization and the elimination of measles from many industrialized countries, measles was still responsible for nearly 800,000 deaths

in 2000. Vaccine coverage over 95% is required to eliminate measles from a population. Even with 80% coverage, the disease remains a major public health problem. Young infants experience very severe disease probably because they are exposed to a higher infective dose when an older sibling introduces the disease into a household.

An HA glycoprotein enables measles attachment to respiratory epithelium. Subsequent spread through the lymphatic system is followed by a secondary viremia and widespread infection of epithelium. The typical rash is caused by T-cell damage to virus-infected epithelial cells. Viral pneumonia early in the infection causes high case fatality. Later in the course of illness, secondary infection with *S. pneumoniae*, *H. influenzae*, *S. aureus*, or Gram-negative bacteria may develop. Coinfection with other respiratory viruses is also common.

Respiratory Syncytial Virus (RSV) (19)

RSV causes seasonal epidemics that often occur during the rainy season in tropical countries. Most bronchiolitis occurs in children under 12 mo old with the peak incidence at 2–6 mo of age. Immunity is not protective and reinfection occurs throughout life. The available evidence is that it is a leading cause of mortality from ARI worldwide—certainly the most important viral pathogen after measles *(7,20)*.

RSV infects upper respiratory mucosa. An asymptomatic period of 4–5 d is followed by nasopharyngitis with profuse discharge of secretions. Cough develops on about the seventh day and a wheeze about the eighth day. In cases of bronchiolitis, RSV infects bronchiolar epithelium producing edema and mucus secretion. The lumen contains thick plugs of necrotic debris. Virulence factors are not well understood. Trials of an inactivated virus vaccine in the 1960s did not protect against subsequent infection; 80% of the recipients were admitted to hospital and two died. These deaths appeared to be caused by a virus-induced cell-mediated immune process. Subunit vaccines are currently under development but routine immunization is thought to be 5–10 yr away.

HIV-Associated Respiratory Infection (21,22)

A vicious cycle involving HIV, tuberculosis, and undernutrition is now common in sub-Saharan Africa. Active tuberculosis hastens the onset of HIV. HIV and protein-energy deficiency suppress Th1 and macrophage functions and result in the reactivation of latent tuberculosis. HIV-1 and tuberculosis worsen nutritional status.

Bacterial pneumonia caused by the usual pathogens is common in HIV-1 infected individuals and is frequently associated with bacteremia, abscess formation, and empyema. *Pneumocystis carinii*, an airborne fungus, is an oppor-

tunistic pathogen of low virulence. It was first described as a cause of pneumonia in undernourished African children. *P. carinii* pneumonia is the most common cause of death in HIV-infected children in Africa.

Respiratory Defenses Against Bacterial Invasion of the Lungs *(23,24)*

The lungs are protected by an integrated set of biologic, mechanical, phagocytic, and immunologic defenses. Because the system contains redundancies, invasion is only likely to occur when more than one level of defense has been compromised. Commensal bacteria of the upper respiratory tract inhibit colonization by pathogenic bacteria including enteric Gram-negative bacteria. Colonization is also regulated by the availability of adherence sites, and secretory immunoglobulin (Ig) A. Undernutrition, passive smoking, abnormalities of mucociliary clearance, and antibiotics all increase colonization.

Branching of the airways and the consequent sudden alterations in the direction of airflow lead to the deposition of foreign particles onto epithelial mucosa. The mucus layer covering ciliated epithelial cells carries trapped particles upward to where they trigger the cough reflex and are expelled. Particles less than 10 mm diameter (PM_{10}) are sufficiently small not to be affected by turbulent airflow and can penetrate into alveoli where they are either deposited on alveolar walls or exhaled. Respiratory mucosa also secretes surfactant (that has antibacterial activity), immunoglobulins, and complement.

Successful eradication of bacteria depends principally on phagocytosis. Experiments on mice using a bolus of *S. aureus*, an extracellular pathogen, emphasize that inoculum size as well as bacterial virulence and the state of host defenses determine whether bacteria will be eradicated or not. At the lowest dose, 10^5 bacteria were completely cleared by alveolar macrophages. At the next level, 10^6 bacteria were cleared slowly but completely; this required a granulocyte response. 10^7 *S. aureus* evoked a marked granulocytic response, but the number of organisms remained constant. After the greatest inoculum of 10^8 *S. aureus*, the organisms proliferated; most of the mice died from pneumonia despite an even greater granulocytic response *(25)*.

Secretory IgA is the predominant immunoglobulin of the upper airways. IgA does not activate complement but neutralizes viruses and agglutinates bacteria. Mucosal immunity to bacterial polysaccharide matures much earlier than does systemic immunity. IgG enters the airways from the circulation, but is also produced in the lung. Deficiencies of immunoglobulin lead to infection by encapsulated extracellular bacteria.

Risk Factors

Poor nutrition, environmental pollution, and substandard living conditions all contribute to the high burden of disease and death from ARI. Increasingly,

population-based descriptive and intervention studies that depend on household monitoring of disease events are using the WHO clinical definition of ALRI as their principal morbidity outcome. Verbal autopsies are used to measure disease-specific mortality. A WHO systematic review of interventions for the prevention of childhood pneumonia included a meta-analysis of potential risk factors. The more important of these are described below *(26)*.

The contribution of the major risk factors to the global burden of disease has also been assessed recently *(27)*. Low weight-for-age (below −1 standard deviation [SD]) was responsible for 9.5% of the total burden; vitamin A deficiency for 1.8%; zinc deficiency for 1.9%; and indoor smoke from solid fuels for 2.6%. Principal outcomes of poor nutrition were pneumonia, measles, diarrhea, and malaria. For indoor smoke they were ALRI and chronic lung disease. The effects of these risk factors are thus substantially mediated through ARI.

Nutrition

With the exception of measles, there is little theory and less evidence relating particular nutritional deficiencies to specific respiratory infections. Interactions and confounding among nutritional and other risk factors, the extent of the deficiency, the complexities of immunological deficits, and the multiplicity of opportunistic pathogens and respiratory syndromes make prediction difficult. Variation between populations in the effectiveness of nutritional interventions can be difficult to explain.

The association between vitamin A deficiency and measles is well established. Vitamin A deficiency causes squamous metaplasia and impairs the integrity of respiratory epithelium. Squamous metaplasia of the thymus was observed at autopsy in Filipino children who had died from pneumonia *(4)*. A meta analysis showed that the administration of massive doses of vitamin A to patients hospitalized with measles reduced case fatality by approx 60%; deaths related to respiratory infections accounted for 80% of mortality in these studies *(28)*. Furthermore, the administration of vitamin A to children older than 6 mo as part of a community-based prevention study reduced all-cause mortality by about 30%. This was associated with a reduction of diarrheal and measles mortality but not of pneumonia mortality. In community-based studies, vitamin A affected neither the incidence nor the severity of pneumonia *(29)*. No consistent effect of vitamin A supplements on the course of nonmeasles pneumonia has been shown in hospitalized children. Indeed, under certain circumstances, most notably in children who are not undernourished, vitamin A may increase the severity of respiratory infections. This may be because of a pharmacologic effect of the supplement on the inflammatory response. Vitamin A supplements are indicated for children with clinical evidence of vitamin A deficiency and for measles. They are not indicated for children with nonmeasles pneumonia *(29,30)*.

An important unifying hypothesis is that as deficiency of zinc or protein energy becomes limiting, the myeloid series of cells is maintained but lymphopoiesis is severely limited. In other words, macrophages and neutrophils are spared at the expense of humoral- and cell-mediated immunity *(31)*. Supplementation with zinc reduced the incidence of pneumonia by more than 40%. Zinc was effective whether serum levels were normal or low, whether the child was wasted or not wasted, or whether vitamins were administered concurrently *(32)*. The effect on mortality from ALRI is still not known.

The risk of dying from ALRI increases as weight-for-age decreases. The risk of dying from ALRI is four times higher in a child with a z-score below –2 SD than in a child with a z-score above 0. The incidence of pneumonia is higher in low weight-for-age children. Those with pneumonia and z-scores below –2 SD experienced case fatality rates about double those of children with normal weight-for-age *(33)*.

Breastfeeding reduces the frequency of infection with encapsulated organisms, even though breast milk has little effect on rates of upper respiratory colonization *(27)*. Breastfeeding reduces mortality from ALRI by about 50%, the effect being relatively constant during the first year of life *(34)*.

Indoor Air Pollution (35)

Because of poverty, more than 2 billion people rely on biomass fuels. Dung, crop residues, and wood are burned indoors in open fires or poorly functioning stoves. Industrial and vehicle emissions and tobacco smoke are other sources of indoor pollution.

Exposure to indoor air pollution varies greatly through the day and is greatest when a household member is closest to the fire—lighting the stove, adding fuel, stirring the cooking pot, and so forth. Women are more likely to be exposed than men. An infant may be carried on its mother's back or suspended in a cradle from the wall where the height, and hence the exposure, may vary.

The US standard for 24-h average PM_{10} is less than 150 mg/m^3. An intervention study in Kenya found PM_{10} in one house to be in excess of 7000 mg/m^3. Improvements to wood stoves reduced the incidence of ALRI by more than 50% in houses where PM_{10} was initially more than 1000 mg/m^3 *(36)*. Switching to charcoal as fuel would have been even more effective.

Upper Respiratory Carriage of Pathogenic Bacteria

Crowding and poor hygiene increase the transmission and acquisition of upper respiratory pathogens. A post-World War II longitudinal study of 1000 children in Newcastle-upon-Tyne, England, identified chronic upper respiratory infection as a significant precursor of ALRI *(37)*. A chronic nasal dis-

charge is common in children living under conditions of poverty. Little attention has been paid to this phenomenon, which must necessarily increase the size of bacterial inocula to the lungs during sleep.

Interpretation of Etiologic Studies

Proving that a particular organism isolated from a patient with pneumonia has actually caused the disease is difficult. Because respiratory secretions may contaminate the lower respiratory tract, even organisms isolated from bronchoscopic aspirate may have been derived from the upper respiratory tract and not be invasive. Isolation from lung aspirate or blood culture is regarded as definite proof of invasion. However, now that the etiology of community-acquired pneumonia in developing countries has been established as the basis for the first line of treatment, it is no longer considered ethical to take lung aspirates for research purposes only. Vaccine trials, for example, now depend on blood culture as the only specific outcome measure available. Blood culture, however, is quite insensitive. An assay such as polymerase chain reaction (PCR) is sensitive, but its specificity is low because of its propensity to detect commensals, particularly if their total mass has been increased because of upper respiratory infection.

When more than one organism has been isolated from the same site, the known virulence of these isolates is the only guide to their pathogenicity. For example, in the 1980s, an influential study from Papua New Guinea confirmed *S. pneumoniae* and *H. influenzae* as significant pathogens *(38)*. The two organisms were isolated alone or in combination from more than 50% of patients with severe pneumonia. However, in 28% of cases, commensals of lesser virulence were isolated from lung or blood. These included non typable and non b serotypes of *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Acinetobacter*. It was concluded that even though the infants were likely to have poor immunity these organisms were not pathogenic. The most likely explanation of their presence in the lungs was that the child had inhaled a bolus of secretions and opportunistic pathogens had multiplied in the exudate stimulated by true pathogens. Even so, the question of whether vaccines should be developed against non b serotypes of *H. influenzae* remains open to debate *(38)*.

S. pneumoniae and *H. influenzae* have fastidious growth requirements. Also, they are more sensitive to antibiotics administered before admission to the hospital than *S. aureus* and the Gram-negative bacteria. Because of poor laboratory techniques, early studies underestimated the significance of these organisms. This problem still affects many hospital service laboratories today.

Patterns of Disease in Developing Countries

The significance of *S. pneumoniae* and *H. influenzae* as major pathogens was established during the 1980s. First-line antibiotic treatment guidelines were based on their susceptibility and resistance patterns. It needed to be known, however, whether the guidelines were valid for special groups such as undernourished children, very young infants, and children with associated HIV infection. Recent etiologic studies have focused on these susceptible groups. It must be remembered that hospital series reflect the pattern of pulmonary invasion and the relative importance of pathogens but, without a baseline population, do not indicate the true incidence of disease.

Clinical Undernutrition and ARI

Very few studies have examined the association between clinical undernutrition and ARI. A study in The Gambia in the early 1990s compared commensal organisms and pathogens in undernourished and well-nourished children with and without radiographic pneumonia. Children were enrolled if their weight-for-age was below 70% of the United States National Center for Health Statistics median or if they were edematous. One-half of the sample were undernourished, severely undernourished, or had edematous malnutrition (*see* Chapter 4). Measles and HIV infection were uncommon *(40)*. Carriage rates of *S. pneumoniae* and *H. influenzae* were high (more than 70%) in all children. These were also the most common invasive bacteria to be isolated. Gram-negative carriage and bacteremia, *Salmonella* bacteremia, and pulmonary *M. tuberculosis* infection were all more common in undernourished children. RSV infection was more common in well-nourished children. The undernourished children were susceptible to invasion by a wide spectrum of bacteria and viruses which, overall, were less virulent than the organisms causing pneumonia in the well-nourished group. These included both extracellular and intracellular pathogens, upper respiratory commensals, and blood borne organisms suggesting impairment of defenses at all levels. That undernourished children were less able to localize infection was suggested by radiographic consolidation being less well defined. The authors saw no justification for changing recommendations for first line therapy.

Serious Infections in Young Infants

Etiologically, pneumonia, meningitis, and sepsis in the neonate are part of a single problem of exposure and susceptibility. Because of their naïve, immature immune systems, very young infants have difficulty in localizing infection; clinical signs are not well expressed. Clinically, it is difficult to distinguish between these diseases. Case management strategies, therefore, tend to refer to the seriously ill infant rather than to anatomically classified diseases. Although

the demographic definition of a neonate is an infant less than 1 mo of age, the boundary between the susceptible, very young infant and the older infant is not well demarcated.

In the 1990s, WHO coordinated a multicenter study in Ethiopia, Papua New Guinea, The Philippines, and The Gambia of serious infections in infants under 3 mo old *(41)*. Overall case fatality was 5.4%, being highest in the youngest infants: 63% of deaths occurred in children less than 1 mo of age, and 51% occurred in children less than 1 wk old. Case fatality of infants with clinical signs suggestive of serious bacterial infection and a positive blood culture was 30%. Between 4 and 11% of the children were bacteremic. Three organisms, *S. pneumoniae*, *S. aureus*, and *S. pyogenes*, accounted for nearly 60% of blood culture isolates. *S. pneumoniae* was the cause of more than 40% of cases of bacterial meningitis. Many different Gram-negative bacteria including *Acinetobacter* spp., *Klebsiella* spp., *E. coli*, and *Salmonella* spp. caused invasive disease. *Chlamydia trachomatis*, a sexually transmitted infection, was strongly associated with severe pneumonia in Papua New Guinea. These results are consistent with early and intense upper respiratory colonization by *S. pneumoniae* and *H. influenzae*. Most of the Gram-negative bacteremia was probably a consequence of poor birth delivery techniques. Guidelines for first-line antibiotics for neonatal pneumonia were revised to take into account the frequency of *Salmonella*.

HIV and Respiratory Infections (42,43)

The number of HIV-infected children, particularly in sub-Saharan Africa is continuing to increase. The countries that had contributed most to the disease burden from ARI in childhood are the same as those where HIV infection is now endemic. The clinical features of tuberculosis, bacterial sepsis, and *P. carinii* pneumonia overlap, but treatment guidelines have been slow to reflect this.

The prevalence of HIV in children in a South African population was below 5%, but HIV-infected children comprised 45% of hospital admissions for pneumonia and 85% of those who died. An HIV-infected child in the community was more than 40 times more likely to develop pneumococcal bacteremia, 20 times more likely to develop *H. influenzae* bacteremia, and 20 times more likely to develop tuberculosis than were non-HIV-infected children. HIV-infected children who were undernourished experienced even higher rates of bacteremia. *P. carinii* pneumonia was extremely common. These observations suggest global immune defects.

Conjugate Polysaccharide Vaccines

Conjugation of the polysaccharide to a carrier protein alters the immune response that becomes T-cell dependent. A conjugated polysaccharide vaccine

is effective in young infants and stimulates immune memory. Hib conjugate vaccines, which were introduced into industrialized countries in the late 1980s, have been shown to prevent more than 90% of cases of invasive disease, principally meningitis. They prevent *H. influenzae* type b carriage so that in addition to a direct effect they have an indirect effect through "herd immunity." In randomized, controlled trials, Hib vaccines were shown to prevent more than 20% of radiographic pneumonia in Chile and The Gambia *(44,45)*.

Because of the larger number of potentially invasive serotypes, pneumococcal conjugate vaccines are more complex and more expensive to produce than the Hib vaccine. In the United States, a 7-valent vaccine was shown to prevent nearly 90% of invasive pneumococcal disease in children and more than 20% of radiographic pneumonia *(46)*. This vaccine was licensed in the United States in 2000. Since then, the incidence of invasive pneumococcal disease has not only declined by nearly 70% in children under 5 yr old, it has also declined markedly in adults *(47)*. In the absence of other causes, this suggests a herd effect. Currently, vaccine trials are underway in The Gambia and the Philippines. A South African trial should be reported shortly.

Although conjugate vaccines could be expected to have major impact on the burden of ARI, the Hib conjugate has not been introduced into a national immunization program in any country in Africa or Asia. The problem is one of cost. Even if the price were reduced to $US 1.50 per dose, vaccine cost per child for routine immunization in the poorer countries of Asia, including India and China, would rise from $4.50 to $6 *(48)*. This increase would represent between 1 and 3% of GNP in those countries where treatment costs are low. Paradoxically, high income countries with a lesser burden of disease have far greater financial incentive to introduce Hib conjugate vaccine because of comparatively high treatment costs. Pneumococcal conjugate vaccines are expected to be even more expensive.

Management of ARI by Peripheral Health Services in Developing Countries

International research and program development focus on cost-effective interventions. Peripheral health services are concerned with cost-efficiency, that is, with providing the highest possible levels of population coverage of interventions within the limits of a restricted health budget. Devolution of health services gives greater responsibility to local government and greater budgetary control to local politicians. Advocacy is needed to get the right mix of resources allocated to curative and outreach services, staff training, health promotion, transport, and logistics. Prepackaging of interventions, as with IMCI, should make advocacy and planning easier *(49)*.

A program based on case management raises questions about the equitable distribution of health resources. The health manager may need to advocate cost-effective treatment to both public and private sector physicians. In the event of life-threatening disease, families deserve the right of access to potentially life-saving drugs for their children at a cost that will not cripple them economically. Far too often, physicians prescribe a cocktail of drugs of which only one or two are likely to be effective. Drug costs, especially when drugs are purchased retail, tend to reflect international and not domestic cost structures. It is not unusual for a family to have to draw on their capital by selling farm animals, for example, because of a child's illness.

The incidence of severe ARI will reflect the socioeconomic status of the population as well as the adequacy of immunization, nutrition, and HIV control programs. Diagnosis and treatment require community health workers to have high levels of skill. High quality supervision is necessary. Drug supplies must be maintained. Management practices need to be integrated in primary, secondary, and tertiary facilities so that referral systems function efficiently.

The effectiveness of case management depends on the mother accessing services as soon as possible after the onset of fast breathing. Her decisions will depend on traditional beliefs, the severity of the infection, and her expectation of cost. Reduction of mortality from ARI still depends on selective treatment with highly effective antimicrobial agents.

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