7 Acute Lower Respiratory Infections

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7.1 INTRODUCTION

Acute respiratory infections are the leading cause of morbidity and mortality among infants and children in developing countries. It is estimated that pneumonia causes up to 2 million deaths per year in children under 5 years of age, and neonatal pneumonia or sepsis causes an additional 1 million deaths per year [1]; an important contributing factor to these deaths is malnutrition [2]. Acute respiratory infections include both acute upper-respiratory infections and acute lower-respiratory infections. Acute lower-respiratory infections consist primarily of pneumonia, but also include croup, tracheobronchitis, and bronchiolitis. The specific aims of this chapter are to present current knowledge regarding the epidemiology, pathophysiology, diagnosis, and treatment of acute lower-respiratory infections and the potential role of nutrition in treatment and prevention.

7.2 PUBLIC HEALTH IMPORTANCE

The recently published report of the Disease Control Priorities Project (DCPP) has estimated that lower-respiratory infections in general caused 3.7 million deaths in the world in 2001, representing 6.7% of all causes of deaths in all ages and 5.6% of all disability-adjusted life years (DALYs) lost in the world [3]. The number of deaths caused by lower-respiratory infections in children under 5 years of age was estimated to be 1.9 million in the year 2001, representing 18.3% of all child deaths, higher than for diarrheal diseases, which explained only 15.1% of all child deaths [4] (Fig. 7.1).

7.3 HISTORICAL BACKGROUND

Among the acute respiratory infections, influenza epidemics are well described in historical accounts from at least the 12th century [5]. Epidemics have been especially well documented in Great Britain [6]. Influenza is known to have occurred in many pandemics, with involvement of all areas of the globe and a characteristic geographical spread along the routes of human travel. The great influenza pandemic in 1918–1919 is considered to have accounted for the most deaths from an epidemic disease since the Black Death of the 14th century, killing an estimated 21 million people worldwide [7, 8]. The threat of the avian influenza virus H5N1 to mutate and be able to spread among humans has alerted the world of the current risk of a similar deadly pandemic [9, 10].

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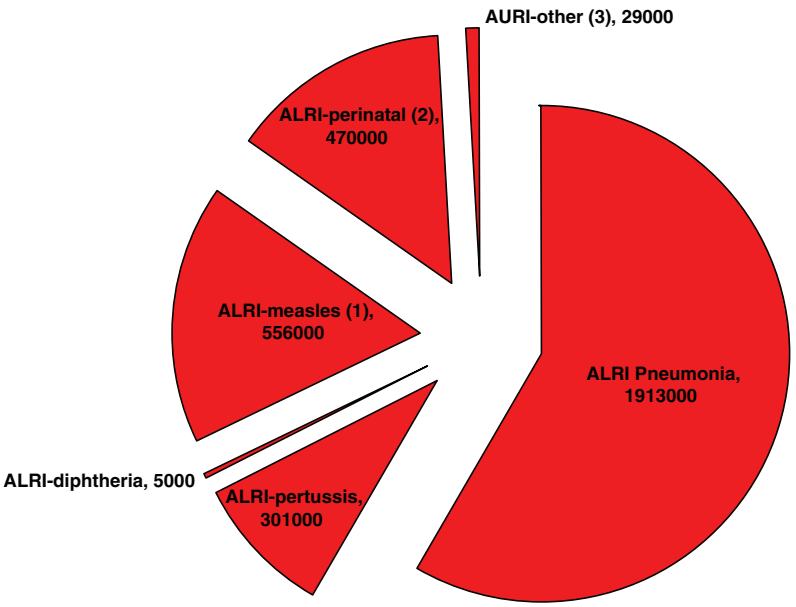

Fig. 7.1. Causes of acute lower-respiratory infection (ALRI) worldwide. (1) All measles-related deaths are assumed as due to ALRI. (2) All perinatal deaths not related to low birth weight or to birth asphyxia and birth trauma have been classified as ALRI. (3) All deaths due to acute upper respiratory infections (AURI) not due to otitis mostly represent croup. (Adapted with permission from [4].)

A common cause of pneumonia, pneumococcus (*Diplococcus* [*Streptococcus*] *pneumoniae*), was identified in 1881, and subsequent animal studies showed that it was involved in the causation of pneumonia [11]. By the turn of the century in the United States, it was estimated that mortality from pneumonia affected 1 of 500 individuals [12]. Antipneumoccocal sera were developed for the treatment of pneumonia; however, typing of the many pneumococcal strains was needed to ensure that the proper pneumococcal antisera were used. Sulfa antibiotics, which emerged in the late 1930s, were later shown to be more effective than serum therapy in the treatment of pneumococcal pneumonia [11]. Identification of many viral pathogens involved in acute respiratory infections, including respiratory syncytial virus (RSV), parainfluenza virus, and rhinoviruses, occurred in the 1950s [11].

7.4 EPIDEMIOLOGY

Several risk factors have been identified for acute lower-respiratory infections. These are reviewed briefly in this chapter (Table 7.1).

7.4.1 Risk Factors

7.4.1.1 Low Birth Weight

Low birth weight (LBW) (<2,500 g) is associated with increased morbidity and mortality from acute lower-respiratory infections. Case-control studies from Brazil [13, 14], Sri Lanka [15], Chile [16], and the Bedouins in Israel [17] have documented that LBW

Table 7.1
Risk factors for acute lower-respiratory infection

Low birth weight
Lack of breast-feeding
Malnutrition
Vitamin A deficiency
Selenium deficiency
Zinc deficiency
Vitamin D or calcium deficiency
Immunosuppression
Attendance at day care centers
Crowding
Exposure to cooking fire
Parental smoking
Outdoor contaminants
Low socioeconomic status, poor housing
Household dampness
Respiratory disease in the household
Prior respiratory infections
Young age
Males
Season
Lack of immunization
Human immunodeficiency virus (HIV/AIDS)
Sickle-cell disease

was associated with an increased risk of acute lower-respiratory infection. LBW infants appeared to have a 50% greater risk of pneumonia compared with infants with birth weight of 2,500 g or more [11]. These findings have been confirmed by longitudinal studies done in Pelotas, Brazil [18], and in China [19], where LBW children had higher hospital admissions for respiratory disease. LBW has also been associated with repeated episodes of wheezing disorders during the first year of life [20]. In a prospective study of premature infants with birth weight less than 1,500 g in Rio de Janeiro, Brazil, respiratory morbidity was associated with previous mechanical ventilation, prolonged oxygen use (more than 28 days), and pneumonia in the neonatal period [21].

Epidemiologic studies have also shown an association between LBW and increased mortality from acute lower-respiratory infections in Brazil [22, 23], India [24], and the Philippines [25]. Infants born at term weighing 2,000–2,499 g at birth had neonatal mortality ten times greater than that of infants weighing 3,000–3,499 g [26]. This increased risk of mortality owing to respiratory diseases seems to be greater among LBW infants who were stunted at birth [26].

The incidence of LBW is greater in developing countries than in developed countries for several reasons [26]; one is poor maternal weight gain during pregnancy. Maternal weight gain of less than 10 kg was associated with a 40% increased risk of hospitalization owing to pneumonia in Brazil [27]. This increased risk of morbidity and mortality among LBW infants may be owing to impaired immunity or lung function [28]. The incidence of LBW, especially those infants small for gestational age born at term, continues

to be an important public health problem in developing countries because of poor diet, infections, adolescent pregnancies, and other reasons.

7.4.1.2 Lack of Breast-Feeding

Lack of breast-feeding has been identified as a major risk factor for morbidity and mortality in children with acute lower-respiratory infections. Children in China who were not breast-fed were twice as likely to be hospitalized as breast-fed children [19]. Lack of breast-feeding was found to be a risk factor for acute lower-respiratory infection, including radiologically confirmed pneumonia, in case-control studies in Argentina [29] and Porto Alegre, Brazil [13]. Non-breast-fed children were 17 times more likely to be hospitalized for pneumonia than breast-fed children in Pelotas, Brazil; this risk increased to 61 times in infants under 3 months of age [30]. In a birth cohort study in poor rural areas of Malawi, early introduction of complementary feeding was associated with increased risk of respiratory infections, particularly among illiterate women [31]. Similar findings have been reported in cohort studies done in Iran [32] and Nigeria [33]. Studies in developed countries also indicated that exclusive breast-feeding during the first months of life protects against asthma at 6 years of age [34], an effect that may also exist in developing countries.

Epidemiologic studies have also documented the relationship between lack of breast-feeding and the risk of death in children with acute lower-respiratory infections. A case-control study in Pelotas, Brazil, showed that risk of death from respiratory infections was higher in infants who were not breast-fed [35]. In a large prospective birth cohort study in slum areas of Dhaka, Bangladesh, partial or no breast-feeding in the first months of life was associated with a 2.4-fold increased risk of death due to acute respiratory infections [36]. In a secondary analysis of a multicenter study done in Ghana, India, and Peru, non-breast-fed infants had a high risk (hazard ratio of 32.7) of death due to acute lower-respiratory infections [37] Breast-feeding may be protective against acute respiratory infections because of transfer of immunity by breast milk, the presence of antibacterial and antiviral substances in breast milk, and avoidance of pathogens from contaminated weaning foods [38–40]. Baby bottles are also known to be a risk factor for the development of acute otitis, diarrhea, and pneumonia [41].

7.4.1.3 Malnutrition

The relationship between malnutrition and the incidence of respiratory diseases has only been evaluated critically since the 1990s [42]. A study done in the Philippines found an increased risk of acute respiratory infections in children with a Z-score less than −3 in weight-for-age compared with the National Center for Health Statistics median reference population [43]. This study found that undernourished children had a relative risk of 1.2 for an increased incidence of any acute respiratory illness and 1.9 for acute lower-respiratory infections [43]. These initial findings were confirmed by subsequent studies done in Bangladesh [44] and India [41].

These studies used a symptom-based definition of acute lower-respiratory infections without clinical or radiographic confirmation of pneumonia. In addition, an association between undernutrition and an increased risk of developing pneumonia seems to exist, as indicated by hospital-based studies done in the Gambia [45], Brazil [18], and Chile [46], where undernutrition was identified as a risk factor for hospitalizations owing

to pneumonia. In a case-control study done in the Gambia, the development of pneumococcal infections was associated with a history of poor weight gain prior to illness compared with community controls [47]. Malnutrition seems to increase the severity of acute lower-respiratory infection, increasing its probability of having bacteremia (in many cases with multiple microbial organisms), pleural effusion, and other complications [48]. In a review of ten cohort studies done in Africa and Southeast Asia, the relative risk of mortality due to pneumonia varied from 2.01 in children with −1 to −2 standard deviation (SD) weight-for-age to 8.09 in children with less than 3 SDs [2]. That review concluded that 52.3% of all pneumonia deaths in the world were attributable to undernutrition. In conclusion, poor nutritional status in children seems to be associated with a modest increased risk for developing any acute respiratory disease and a moderate risk for developing acute lower-respiratory infection or pneumonia, increasing its severity and therefore explaining an important proportion of deaths due to pneumonia worldwide.

7.4.1.4 Micronutrient Status

Micronutrient status has been implicated as a risk factor in acute respiratory infections. Respiratory disease has been associated with increased risk of developing vitamin A deficiency [49], and in turn, vitamin A deficiency has been associated with increased risk of developing respiratory disease in preschool children [50, 51]. However, when respiratory diseases were assessed in carefully controlled prospective trials of vitamin A supplementation, no major reduction occurred in the mortality or morbidity associated with respiratory diseases, as indicated in an initial meta-analysis of available studies [52]. These findings were ratified by two meta-analyses [53, 54]. The initial association between low serum retinol levels and pneumonia may be explained by vitamin A that is lost in the urine during these infections [55], probably by mechanisms similar to those documented for diarrheal diseases [56].

Children with low plasma zinc concentrations in an urban slum setting had a mean prevalence rate of acute lower-respiratory infections that was 3.5-fold higher than children with normal plasma zinc concentrations [57]. In a randomized, double-blind, placebo-controlled trial in Bangladeshi children 2–23 months of age hospitalized with severe pneumonia, 20 mg of elemental zinc per day was associated with increased recovery and shorter hospital stay and duration of antibiotic treatment [58]. This study did not publish treatment effects by gender, although most children (65%) were male. In another double-blind, placebo-controlled trial in Indian children 2–24 months of age, 10 mg of zinc as acetate was associated with reduction of severe illness and fever, but in boys, not in girls [59]. Finally, in another Indian study, using a similar study design in hospitalized children 2–23 months of age, 10 mg of zinc sulfate did not have a beneficial effect on the treatment of severe pneumonia [60]. It is not clear if these differences could be due to lower zinc doses in the Indian studies, compared to the study in Bangladesh, or to other biological differences. In a controlled, double-blind study in Indian children 9 months to 15 years of age hospitalized with pneumonia associated with acute measles, 20 mg of zinc acetate did not showed any clinical benefit [61].

Further studies are needed to clarify the role of zinc supplements in the treatment of severe pneumonia in children. It is important to mention that in the Bangladeshi study, zinc supplementation did not show any benefit for children with wheezing disorders,

only those with severe pneumonia [59]. It is now clear that zinc is important not only in growth but also in the immune function of children, which is affected in zinc-deficient children suffering diarrheal and respiratory diseases [62]. Most children in developing countries consume very little animal proteins—the dietary source of zinc with the highest bioavailability—explaining why zinc deficiency may be one of the most important nutritional disorders in children from developing countries [63].

Selenium deficiency may be a risk factor for the development of respiratory infections, particularly pneumonia, among critically ill patients and malnourished children. Premature infants may be particularly at risk. It is known that selenium serum concentration drops in premature infants after birth, especially in those who develop respiratory distress syndrome [64]. In a prospective study in LBW infants, low plasma selenium levels were associated with chronic lung disease and bronchopulmonary dysplasia, as well as with the total days of oxygen requirement. For each drop of 0.1 μmol/L of selenium in plasma, there was a 58% increase in days of oxygen dependency, controlling for gestational age and age when infants were fully fed orally [65]. Premature infants, especially those treated with oxygen, may warrant selenium supplementation. Supplementation with one dose of 1 mg sodium selenite to routine treatment of children hospitalized with pneumonia or wheezing disorders associated with RSV [66] or *Mycoplasma pneumonia* [67] has been found to have a beneficial clinical effect in China. Food additives containing selenium have also been reported to have a beneficial effect in children with pneumonia in Russia [68, 69]. Further clinical trials with selenium supplementation in children with pneumonia are warranted.

Other micronutrients may also play a role in susceptibility of children to pneumonia and other acute respiratory infections. In a case-control study done in Ethiopia, children with clinical or radiological evidence of rickets had a probability of pneumonia 13 times higher than did children without rickets, suggesting that vitamin D or calcium deficiency may also be important as a risk factor for pneumonia [70]. A review of the literature concluded that nutritional rickets was a risk factor for pneumonia in Ethiopian children [71]. In a case-control study done in Indian children, a low serum level of vitamin D was associated with severe acute lower-respiratory infections, adjusting for other risk factors [72]. Poor dietary calcium intake may potentiate the deficiency of vitamin D [73]. Clinical trials with vitamin D with or without calcium supplements should be done in areas where vitamin D deficiency is endemic.

7.4.1.5 Decreased Immunity

Some indicators of decreased immunity have been associated with the risk of acute respiratory diseases. Depressed cell-mediated immunity has been demonstrated to be an important predictor of both acute upper- (20% increased risk) [74] and lower- (80% increased risk) [44] respiratory infections in Bangladeshi children, controlling for nutritional status. A study done in Kenya found a similar association with acute respiratory infections (34% increased risk) [75]. This impaired immune capacity of children in developing countries seems to be related to micronutrient deficiencies (zinc in particular) and malnutrition.

7.4.1.6 Environmental and Socioeconomic Factors

Several environmental and socioeconomic factors have been associated with respiratory infections in children. Attendance at day care centers has been identified as a strong

risk factor for acute upper- and lower-respiratory tract infections in children in several studies, both in developed [76, 77] and developing countries [13, 14, 78]. Children in day care centers have between 5 and 12 times greater risk of pneumonia than those cared for at home. This increased risk is not only for bacterial pneumonia, but also for other causes of pneumonia like *M. pneumoniae* [79] and RSV [80]. The very low rate of invasive pneumococcal disease observed in Switzerland between 1985 and 1994 has been attributed to the lower rate of day care attendance of Swiss children compared to other European countries [81]. Day care centers increase the contact between young children and facilitate the transmission of infections through respiratory droplets.

Similar to attendance at day care centers, crowding (number of persons in the household, number of persons sharing the bedroom, number of siblings under 5 years of age, greater parity) also favors the transmission of respiratory infections, as documented in case-control [13–15, 80, 82, 83] and longitudinal [84, 85] studies. Even at the turn of the twentieth century, household crowding was associated with an increased risk of death owing to measles-associated pneumonia [84]. Increased contact with other children or adults, whether at home or at institutions, is a strong risk factor for pneumonia and other respiratory diseases.

Another mechanism by which crowding may affect the risk of respiratory diseases is the exposure to smoking and other indoor air pollutants. Exposure to smoke during cooking and parental smoking was associated with deaths owing to acute lower-respiratory infections in a case-control study in the Gambia [86]. Maternal smoking (greater than or equal to five cigarettes/day) was associated with upper- and lower-respiratory diseases in a longitudinal study in Chile [82]. In a large prospective study of 1,459 children less than 2 years of age in periurban Lima, Peru, even the exposure of a child to a very low level of household members who smoke (mean consumption 11 cigarettes/week, only 6% of mothers reported smoking) was consistently associated with an increased risk of cough and respiratory illnesses [87]. Environmental exposure to tobacco smoke has been associated clearly with an increased risk of pneumonia, bronchitis, bronchiolitis, chronic middle ear effusion, and increased frequency and severity of attacks among asthmatics [88, 89]. Maternal smoking during pregnancy increases the risk of sudden infant death syndrome (SIDS) [90]. The Comparative Risk Assessment Collaborating Group has estimated that smoking may explain 2% of the DALYs lost to lower-respiratory infections in the world [91]. Developing countries are rapidly increasing their rate of maternal and household smoking, the reduction of which should be considered a public health priority. Breast-feeding protects children from this increased risk of lower-respiratory diseases associated with exposure to environmental tobacco smoke [90, 92], which is another reason for breast-feeding promotion.

Many households in developing countries utilize biomass fuels (wood, manure, carbon, agricultural waste, etc.), mostly because more efficient fossil fuels or electricity are either not available or not affordable [93]. These fuels are usually burned in inefficient stoves or openly within the family room without the use of a chimney, especially in rural areas in the highlands. Children exposed to these sources of indoor air pollution have increased risk of respiratory illnesses. In Nepal, the risk of severe respiratory diseases increased with the number of hours each infant spent near a stove [94, 95]. In the Gambia, carriage of a child on the mother's back while cooking was associated with acute lower-respiratory infections [96], as was the use of wood-burning stoves by Native Americans [97].

An increased incidence of acute lower-respiratory infection was reported associated with the use of kerosene stoves in India [98], but not in Peru [87].

Among different combustion products, a high concentration of suspended particulates with 0.1- to 10-μ diameter (PM10) has been linked to an increased risk of pneumonia. This effect seems to be mediated through an inhibition of the inflammatory response of alveolar macrophages by PM10 exposure, as documented with RSV infections [99]. Not only may indoor sources of air contaminants be important, but also environmental air pollution may play a role as a risk factor for pneumonia, especially among atopic individuals [100]. It has been estimated that indoor smoke from solid fuels explains 36% of DALYs lost to lower-respiratory infections in the world [91], while urban ambient air pollution may explain about 1% of mortality due to acute respiratory infections in children less than 5 years of age in the world [101].

Because of all these reasons, the incidence of acute lower-respiratory diseases has been reported to be higher in crowded urban areas of low socioeconomic status, where most of these factors are combined [41]. Lower social class [41, 82, 102], race [102], parental education [13, 27, 41, 82], and poor housing [29, 83] are variables associated with lower-respiratory infections through crowding, indoor air pollution, and environmental exposure to tobacco, as well as other nutritional factors. The presence of a pet animal at home [15] as well as household dampness [87, 103] are particular risk factors for wheezing disorders and childhood asthma, most likely by favoring the growth of molds [104] and the presence of other household allergens.

7.4.1.7 Prior Infections

Several studies have reported an increased risk of pneumonia or acute lower-respiratory infections in children who have had a prior episode of pneumonia or wheezing [13–15, 29]. Viral infections, particularly with RSV or influenza virus, also predispose to invasive pneumococcal disease for a period of 4 weeks [105]. In a case-control study in Brazil, wheezing disorders were associated with a sevenfold increased risk of pneumonia in children, controlling for other factors [106]. On the other hand, prior acute lower-respiratory infections (croup, bronchitis, bronchiolitis, or pneumonia) were also a risk factor for wheezing in infancy [20]. But, prior infection does not always seem to be a risk factor. Infections in early life seem to be related to the chances of developing asthma and allergic disorders later in life. An initial report from Japan documented that children 12 years old who had a positive tuberculin response predicted a lower incidence of asthma, lower serum immunoglobulin E (IgE) levels, and the predominance of a cytokine profile not associated with atopy [107]. This report was used to postulate that the reduction of early childhood infections, such as tuberculosis, owing to development and better living standards may be one reason for the increase in asthma and atopy observed in developed societies in the last 20 years [108].

The hygiene hypothesis suggested that an early life exposure to a contaminated environment primes the immune system in the direction of a Th1 (T helper type 1) profile, associated with a nonallergic phenotype; living in a cleaner environment would prime the immune system toward a Th2 (T helper type 2) profile, an allergic phenotype [109]. Some studies in developing countries have found supporting evidence for this hypothesis, with higher prevalence of atopic diseases and history of asthma in children in urban areas in Turkey [110] and Chinese [111] children; in contrast, the history of acute gastroenteritis,

fever, and antibiotic use during infancy was associated with later development of asthma in Korean children [112]. Some have postulated that rather than environmental exposure to pathogens, persistent infections with certain microorganisms, like *Chlamydia pneumoniae,* may explain later development of asthma [113]. Others have suggested that lifestyle changes related to obesity may be the link with asthma and developed areas [114]. Systematic reviews of the literature also provided conflicting results regarding the hygiene hypothesis [115, 116], indicating that the association of an increased prevalence of asthma, eczema, and atopy in developed countries may be multifactorial, relating to the host, nutritional status, and environment, among other factors yet to be explained.

7.4.1.8 Other Factors

Other factors have been associated with pneumonia or acute lower-respiratory infections, like young age, male sex, young maternal age, and so forth. Infants and children under 2 years of age have the highest incidence of infections, particularly with RSV [80]. Mortality owing to lower-respiratory diseases is concentrated among infants under 6 months of age [1]. Males have a higher incidence of wheezing disorders or RSV infections in infancy than females [15, 80, 87, 117]. Those of young maternal age [13] and adolescent mothers [27] have been reported to have an increased risk of pneumonia in their children. Lack of immunization has also been associated with increased risk of respiratory morbidity [14, 41] and mortality [86].

The increased incidence of HIV infections in the heterosexual population is changing the epidemiology of respiratory infections in children from developed and developing countries. As the prevalence of HIV increases in women, the number of newborns infected with HIV through vertical transmission will also increase [118]. As documented in Haiti, a large proportion of HIV-infected newborns (60% in this study) will die before reaching 6 months of life, whether meningitis, sepsis, or pneumonia is the immediate cause of death [119]. Other conditions prevalent in developing countries, like sickle-cell disease, are also associated with an increased risk of invasive pneumococcal and *Haemophilus influenzae* infections [120]. Finally, lack of maternal antibodies is a risk factor for the development of infections in early infancy, as documented for RSV [80]. This association may offer the opportunity to protect newborns through maternal immunization, as discussed in Section 7.7.1.

7.4.2 Incidence

Before reviewing the information available on incidence of acute lower-respiratory infections in children, it is important to discuss briefly the definitions of pneumonia or acute lower-respiratory infection used in these studies because they have profound influence on the rates reported, as reviewed elsewhere [121]. Studies done in developed countries generally report cases diagnosed by physicians on clinical grounds, sometimes complemented by chest X-rays. In contrast, studies conducted in developing countries usually are based on diagnosis from respiratory signs and symptoms reported by the mother or identified by field-workers. Even though the presence of cough, rapid respiratory rates, and other respiratory signs are highly suggestive of pneumonia, as promoted by the World Health Organization (WHO) case-management guidelines, it is difficult to distinguish very clearly between pneumonia and other types of acute lower-respiratory infections, especially in community-based prospective studies [122, 123].

The methodology used in these studies is also critical. High variability exists on the normal respiratory-rate-by-age, which at some ages is very similar (within 1 SD) of the cutoff value used by WHO to consider that a child has tachypnea [124]. The technique used to measure the respiratory rate is also important [125]. Physical signs on chest examination have important variations when repeat observations are done with one or multiple observers [126]. Even chest X-rays may be negative in the presence of pneumonia proven by postmortem examination in children [127]. To complicate the issue further, rates will change if cases are identified at health facilities when mothers decide to bring their children for care (passive surveillance) as compared with frequent home visits by trained field-workers to identify respiratory infections (active surveillance). Because of these variables, studies using passive surveillance and chest X-ray to diagnose pneumonia report the lowest rates, and studies using active surveillance and symptom-based diagnosis of acute lower-respiratory infections report the highest rates. Because of these reasons, the comparison of acute lower-respiratory infection or pneumonia rates across studies and countries may not be valid and should be taken with caution if the methods used are not similar.

The incidence of acute respiratory infections (mostly upper) in developing countries has been reported as between four and seven episodes per child per year, being similar in America [128], Africa [129], and Asia [130]. The incidence of pneumonia, as diagnosed by physicians with or without radiology, has been reported as 53 episodes per 100 child-years in children under 3 years of age in Guatemala [128]; 30 episodes per 100 child-years in infants and children under 2 years of age in Peru [122, 131]; and 16.5 episodes per 100 child-years in children under 5 years of age in the Gambia [132]. In a systematic review of 28 high-quality community-based studies published since 1961, the median incidence rate of clinical pneumonia in children less than 5 years of age was 0.29 episodes per child-year, giving an estimated number of 150.7 million cases per year, with 7–13% of these children hospitalized in developing countries in the world [133]. The incidence in developed countries was estimated as 0.026 episodes per child-year, suggesting that 95% of all cases of pneumonia occur in developing countries. The age-specific incidence rates for acute respiratory infections are generally highest in infants at 6–11 months of age.

7.4.3 Seasonality

Seasonal distribution for incidence rates of acute respiratory infections and acute lower-respiratory infections has been examined in several initial studies [134]. Patterns of acute respiratory infections appear to vary by location. The highest incidence of acute respiratory infections in Colombia and Thailand was observed from September through December. In Guatemala, the highest rates were noted from January through July. Two peaks were observed in the Philippines, one in January and one in October. Seasonality was also observed for acute lower-respiratory infections in different location, but the patterns did not necessarily coincide with that for acute respiratory infections overall [134]. This variation is most likely owing to the mixture of pneumonia and wheezing disorders that are combined by the methodology used in these initial studies. Wheezing disorders or infections by RSV are more seasonal than pneumococcal or *H. influenzae* infections in tropical developing countries, being more common in winter or cold months [82]. Mortality owing to acute lower-respiratory infections, more so in neonates, is also higher in winter months [135].

These observations have led people to believe that exposure to cold weather or high humidity is associated with an increased risk of developing acute lower-respiratory infections or pneumonia. Volunteer studies with rhinoviruses after exposure to cold and to high humidity failed to demonstrate an increased risk of infection com-pared to a warm and dry environment [136]. Epidemiological studies done in England have also failed to demonstrate an association between indoor temperature and humidity and respiratory infections [137]. Most likely, cold weather induces individuals to reduce ventilation indoors, and the crowding that results from remaining indoors increases the risk of respiratory infections rather than the cold directly affecting the health. There is a need to better document this lack of association to clarify this issue.

7.4.4 Duration

Most episodes of acute respiratory infections and acute lower-respiratory infections last less than 2 weeks [134]. In a prospective home surveillance study done in Peru of respiratory signs and symptoms by frequent (twice weekly) home visits by trained field-workers, it was shown that cough and phlegm started developing 10–12 days prior to the diagnosis of pneumonia by a physician or a positive chest X-ray. It was also found that patients took 10–12 days to recover after diagnosis [122]. Rapid breathing, fever, loss of appetite, and ill appearance, as reported by the mother, appeared between 5 and 8 days prior to diagnosis and lasted 5–8 days after the diagnosis (except fever that disappeared in 24 hours after starting antibiotics) [122]. Thus, the duration of symptoms is related to their severity as well as to early treatment with antibiotics. Based on this study, it could be said that most respiratory signs and symptoms associated with pneumonia in the community usually would last no more than 15 days if diagnosed early and treated appropriately.

7.4.5 Case Fatality Ratios

Case fatality ratios for acute lower-respiratory infections in different hospital-based studies have ranged from 0.8% [138] to about 20% [139–142] in developing countries. Higher case fatality has been associated with age under 1 year [143–146], malnutrition [143–145, 147], increased respiratory rate (>70/min) [147], cyanosis and low oxygen saturation [143, 144, 146, 147], rickets [72, 144], loose stools [145], and late hospital admission [148]. Females have been reported to have an increased case fatality [134, 143]. In malnourished children, pneumonia is a predictor of mortality [149]. Gambian children who were hospitalized with severe pneumonia and survived were followed up after discharge from the hospital [150]. It was found that children who were malnourished while in the hospital had a threefold greater risk of death after being sent home than children without malnutrition, indicating the importance of nutritional recovery in the hospital before a patient is sent home [150].

Owing to the increase in the prevalence of penicillin-resistant strains of *S. pneumoniae*, concerns of greater case fatality rates in infections with resistant strains have emerged [151]. However, in several studies [152–154] the mortality associated with resistant strains did not increase even when penicillin or related drugs were used owing to the high concentration these antibiotics achieved in the lung tissue, several levels above the minimal inhibitory concentration of the strains [155]. On the contrary, resistant strains have higher mortality rates in meningitis owing to the lower antibiotic concentration in the cerebrospinal fluid [154, 155]. As expected, appropriate case management can

reduce a high level of case fatality, as documented in Zambia when the WHO protocol for case management of pneumonia was introduced in a rural hospital [140].

7.5 CLINICAL FEATURES/PATHOPHYSIOLOGY

7.5.1 Clinical Presentation

Acute upper-respiratory infections are usually defined based on signs of at least one of the following: runny nose, sore throat, cough, or earache or ear discharge, without any findings of acute lower-respiratory infections [134]. Acute lower-respiratory infections are defined based on the presence of cough and at least one of the following signs: increased respiratory rate (>60 respirations per minute in infants under 2 months of age, >50 respirations per minute in infants 2–11 months old, and >40 respirations per minute in children 12 months and older); rales or crepitations; wheezing; stridor; or chest indrawing [134, 156–159]. The presence of cough and an increased respiratory rate or chest indrawing is about 70% sensitive and specific to identify pneumonia, especially in cases seen in an emergency room of a health facility [156–158]. In areas that do not have malaria, the presence of fever may increase the specificity without much drop in the sensitivity [123, 160], increasing its positive predictive value. The presence of chest indrawing, nasal flaring, and cyanosis are signs of more severe disease [122, 161, 162].

Severe and complicated pneumonia was associated with low weight, anemia, and a white blood cell (WBC) count below 15,000/mm^3 at the time of admission in Israeli children [162]. The presence of nasal mucus, of any color or consistency, was not associated with pneumonia in a longitudinal study in Peru [122], against the popular belief that purulent nasal discharge is associated with pneumonia. Bacteremic pneumococcal pneumonia is usually associated with high fever, increased WBC counts, and ill appearance [163]; in 80% of cases, they had a lobar pneumonia. However, in a prospective study done in Brazil, respiratory signs and symptoms did not distinguish bacterial from viral pneumonia [164]. Also, the majority of clinically diagnosed cases of pneumonia in outpatient settings in developing countries do not have an abnormal chest X-ray, even though they do respond to antibiotic treatment, indicating the importance of clinical judgment over X-ray or laboratory parameters [165].

In the laboratory, apart from a positive chest X-ray, children with pneumonia have an increased WBC count during the first 2 days of their clinical course, declining thereafter, reaching the lowest levels by day 4 [166]. The erythrocyte sedimentation rate follows an opposite course, being normal or mildly elevated during the start of the clinical course and increasing steadily thereafter [166]. Studies have documented the importance of hypoxemia in children with acute lower-respiratory infections, ranging from 6% to 9% in outpatient cases to 47% in children hospitalized with pneumonia, more so (72%) in children with a positive chest X-ray [167]. Hypoxemia is more frequent in children living in high altitude areas [167] and is frequently underrecognized in neonates [168].

7.5.2 Major Pathogens Involved in Acute Lower Respiratory Diseases in Children

Respiratory syncytial virus is the leading viral pathogen involved in acute lower-respiratory infections in children, isolated in 5–37% of patients [134, 138, 169–171].

Of children infected with RSV, 30% have pneumonia; bronchiolitis is the most common clinical presentation [172]. The association of RSV with asthma and reversible reactive airway disease in early childhood has been clearly recognized [173]. Epithelial cells are initially involved in an inflammatory response, in which cytokines and chemokines released from inflammatory cells trigger further inflammatory responses, which are more common in susceptible children with a family history of asthma or atopy [173, 174]. Recent studies have suggested that RSV may enhance the development of an allergic inflammatory response in susceptible hosts when exposed to allergens after being infected with RSV [175]. Other important viral causes of acute lower-respiratory infections are adenovirus, parainfluenza virus, and influenza virus [176, 177].

In 2001, a new, previously unidentified virus causing acute respiratory tract infections was reported from the Netherlands and was called human metapneumovirus (hMPV) [178], from the paramyxovirus group [180]. Since its initial report, it has been associated with respiratory illnesses in Europe, North and South America, Asia, Australia, and South Africa [178]. It is isolated in between 1% and 25% of cases with upper and lower respiratory tract infections, having similar epidemiological characteristics as RSV and influenza virus [174, 178, 179].

In November 2002, a severe acute respiratory syndrome (SARS) was reported from southern China, a disease later discovered to be caused by a coronavirus, probably from an animal source [180]. In February 2003, the virus was brought to Hong Kong, and from there, it spread rapidly to more than 30 countries in several continents, causing more than 8,000 cases and 916 deaths (11% case fatality) before the epidemic ended in June 2003 [180–182]. Because of its long incubation period (mean 6.4 days, range 2–11 days), it allowed asymptomatic air travelers to spread the disease globally. In children, SARS caused milder disease, with nonspecific chest X-ray changes [183].

Several zoonotic paramyxoviruses have also caused outbreaks of severe respiratory diseases in humans. The first was caused by what is now called Hendra virus, a lethal zoonotic agent able to cause the disease in horses and humans, initially described in Australia in 1984, 1999, and 2004, with a high case fatality rate [184–186]. The second and most frequent one is called the Nipah virus, initially described as causing an outbreak of severe febrile encephalitis with respiratory symptoms in Malaysia and Singapore in 1999 and later in Bangladesh, where it caused several outbreaks between 2001 and 2005 [185–188]. Its reservoir is large fruit bats (also called flying foxes), and virus can infect humans from bats, pigs, or infected humans [188]. Since its reemergence in 2003 in several Southeast Asian countries, a highly pathogenic avian influenza A virus (H5N1) has caused severe disease in humans exposed to sick or dead chickens or wild birds [9, 10]. There have been more than 200 human cases reported, including children, with a high case fatality rate (about 50%), but human-to-human transmission has not been documented yet. A fear exists that a mutation of the A/H5N1 influenza virus could allow it to spread within humans, causing another severe pandemic influenza in the world [10].

Identification of the bacterial causes of pneumonia is limited by the low rate of isolation of bacteria in blood cultures and the impracticality and risk involved with needle aspiration of the lung for culture. Cultures taken from the trachea or throat are invalid because they are usually contaminated by bacteria that grow in those settings, not necessarily representing the cause of the pneumonia. In cultured specimens taken from sterile sites (blood or lung tissue) in children with acute lower-respiratory infections,

the most commonly identified bacterial pathogen has generally been *S. pneumoniae*, followed by *H. influenzae* [134, 138, 170, 171, 189]. Other important pathogens include *Bordetella pertussis* and *M. pneumoniae*. Pneumonia in cases with pertussis has been reported in 9.4% of cases, with the severity of the disease greater among infants less than 6 months old [190]. Pertussis in the very young infant or in individuals previously immunized can also occur. In very young infants, the disease is atypical and severe, requiring hospitalization [191]. In previously immunized individuals, pertussis is mild, prolonged (>4 weeks of symptoms), and atypical [192]. Despite the worldwide use of pertussis immunization, the incidence of pertussis has not been reduced as expected [193]. Pertussis still occurs, causing severe morbidity and mortality in unimmunized or partially immunized children, usually infected from adults or adolescents who have waning vaccine-induced immunity [194]. In some endemic areas, *Chlamydia trachomatis* should also be considered in cases with pneumonia, especially if the individual has concurrent conjunctivitis [195]. As with *M. pneumoniae*, *C. pneumoniae* is also a cause of pneumonia epidemics in schoolchildren and adults [196]. Mixed infections with different pathogens may occur.

Empyema can occur in *S. pneumoniae* pneumonia. However, *Staphylococcus aureus* is a common cause of empyema in developing countries, requiring thoracentesis and prolonged antibiotic therapy [197, 198]. Another complication of pneumococcal pneumonia is necrotizing pneumonia, usually associated with lung abscesses and cavitation, with better clinical course in children than in adults [199]. Croup in children is associated with older children (mean age 21 months), usually associated more with viral organisms than bacteria [200].

An important subgroup of children that has been recently studied in developing countries is infants under 3 months of age. In two studies done in Ethiopia [201] and Papua New Guinea [202], *Streptococcus pyogenes* and *S. pneumoniae* were the most common isolates, followed by *S. aureus*. RSV was the most common viral agent. Organisms frequently isolated in young infants in developed countries, like *Salmonella* group B and *Streptococcus agalactiae*, were rarely isolated. However, in a similar study done in the Philippines [203], *Salmonella* spp., *Enterobacter* spp., and gram-negative organisms were more common than *S. pneumoniae*, indicating that the pattern observed in developed countries may also be present in some developing countries. Further studies on the etiology of severe infectious diseases in infants under 3 months of age are needed. Because of the newly recognized need to protect against *S. pneumoniae* infection in young infants, WHO is now evaluating the use of maternal immunization to protect neonates [204, 205].

Klebsiella pneumoniae [206], blastomycosis [207], *Legionella* pneumonia [208], and melioidosis [209] are some of the opportunistic infections that may occur in premature babies and persons who are immunocompromised, have congenital diseases, or are given steroids. In some isolated rural areas with low immunization coverage, measles epidemics that are associated with up to 32% of pneumonia cases still occur [210].

7.5.3 Pathophysiology

The pathophysiology of acute lower-respiratory infections may vary depending on the pathogen involved. In general, the immune defenses in the lung are provided by a cough reflex, action of cilia in the tracheobronchial tree, mucus secretion by goblet cells,

and phagocytic activity by alveolar macrophages. Pneumonia occurs when pathogenic organisms overwhelm these host defenses and infection occurs in the lower-respiratory tract. In the affected portion of the lung, polymorphonuclear leukocytes, erythrocytes, and proteinaceous secretions are present, and consolidation occurs, which may appear as a homogeneous density on chest radiograph. In general, consolidation occurs less among young infants. The affected individual may develop fever, tachycardia, and cyanosis, and sputum production may be present. Phagocytosis, antibody responses, and other immune mechanisms usually allow recovery from pneumonia within several days to a couple of weeks.

A series of elegant experimental studies have clarified the physiologic changes occurring in the lung with lobar pneumonia. Studies in dogs with pneumonia induced by inoculation with *S. pneumoniae* [211] or *Pseudomonas aeruginosa* [212] revealed that the exudate produced in the site of infection reduces the gas exchanged by filling the alveoli, preventing them from inflation. This causes a reduction in the total lung capacity as well as in the functional residual capacity, proportional to the magnitude of the lung involved. The lung reacts with hypoxia-induced pulmonary vasoconstriction in the affected area, initially thought to be an attempt to divert blood to ventilated lung tissues to maintain a high oxygen tension in the blood [213]. This, however, is not effective, and blood goes through the pneumonic, unventilated tissue, creating an arterial-venous shunt, which explains the hypoxia seen in severe pneumonia [214]. This pulmonary vasoconstriction induces pulmonary hypertension, which in severe pneumonia causes right ventricular cardiac failure, a condition that is associated with increased mortality and that does not respond to digoxin therapy [215]. Very few children with right ventricular failure will manifest the typical clinical signs of hepatomegaly, tachycardia, raised jugular venous pressure, or peripheral edema. They usually only have dilation of the right ventricle on ultrasound examination of the heart [215].

Oxygen administration reduces the vasoconstriction and increases the blood's oxygen tension through the preserved lung tissue, but the shunt remains unchanged because the pneumonic lung is not ventilated [216]. Intrapulmonary blood shunt is not the only reason for hypoxia because the pneumonic tissue increases its consumption of oxygen, and at the same time, fever and infection also increase the oxygen requirements in the rest of the body [217]. The involvement of lung tissue by pneumonia also causes a reduction of lung compliance and an increase in the work of breathing. In the dog model, administration of intravenous fluids that could increase the plasma volume and the pulmonary capillary wedge pressure is associated with large increases in lobar wet weights of the affected pneumonic lung, probably owing in part to transudation of plasma and crystalloid into alveolar spaces [218]. The magnitude of the intrapulmonary shunt may be increased by endogenous vasodilator mediators, exogenous systemically administered vasodilator drugs, positioning the patient with the affected lung down, and increasing the positive airway pressure by mechanical ventilation [219]. Factors that reduce shunt include effective hypoxic pulmonary vasoconstriction, inhaled locally acting vasodilators that act primarily on the ventilated lung, and positioning the patient with the affected lung up [219]. The blood's oxygen saturation is improved if the patient is in prone position rather than in supine position [220]. The administration of aerosolized vasodilators may be beneficial to patients by improving their ventilation in the ventilated lung, thereby improving the blood's oxygen tension [221].

The lung compliance of the remaining ventilated lung seems also to be reduced, possibly by a reduction in surfactant activity, further increasing the work of breathing [219]. Pulmonary surfactant is a complex material composed of lipids and proteins; it is found in the fluid lining of the alveolar surface of the lungs. Surfactant prevents alveolar collapse at low lung volume and preserves bronchiolar patency during normal and forced respiration [222]. It is also involved in the protection of the lung from injuries and infections caused by inhaled particles or microorganisms [222]. Pulmonary surfactant is absent in prematurity and is one of the reasons for respiratory distress syndrome and hyaline membrane disease in premature newborns [222]. But, surfactant abnormalities are also present in various degrees in asthma, bronchiolitis, pneumonia, cystic fibrosis, and HIV infections [222]. Natural and synthetic surfactants are now available for the prevention and treatment of respiratory distress syndrome in infants [223].

The recovery process in pneumonia is produced by clearing of fluids and other materials from the air space, improving ventilation, and in part by a reduction of perfusion of poorly ventilated areas of the lung [224]. The reduction of blood flow through the consolidated lung reduces the shunt and improves arterial oxygen concentration [219]. However, the lung is not always able to recover completely. Long-term consequences after childhood pneumonia have been reported in pulmonary function tests among adults, including a reduction of lung volume [225].

There have been discussions whether the abnormal pulmonary function seen with some acute lower-respiratory infections, like wheezing disorders, is a consequence of or a risk factor for the initial attack. In an elegant prospective study done in Taiwan, respiratory function was assessed by a single-occlusion technique and rapid thoracic compression technique in a group of infants at a mean of 2 months who were then followed for 2 years [226]. Infants who developed a subsequent attack of wheezing had low values of total respiratory compliance corrected for body weight compared with those infants who did not develop a wheezing attack. This study indicated that differences in lung function in early life, for reasons yet to be understood, predispose infants to acute lower-respiratory infection with wheezing disorders in their first 2 years of life.

7.5.4 Impact of Acute Respiratory Infections on Nutrition and Growth

Few studies have focused on the impact of respiratory diseases on nutrition and growth. Compared with tuberculosis, which has a prolonged course of illness with a pronounced impact on nutrition [227, 228], or diarrheal diseases, the role of acute respiratory diseases on the nutritional status of children has been not well documented. In a prospective study of a small cohort of Gambian children, acute lower-respiratory infections diagnosed by a pediatrician were associated with a loss of 14.7 g of weight per day of illness, greater than the reduction observed with diarrheal diseases [229]. Because of their higher prevalence, however, diarrheal diseases explained one half of weight loss, and acute lower-respiratory infections only accounted for 25% of observed weight deficit. One study in the Philippines documented the impact of febrile respiratory illness on weight gain [230]. In Papua New Guinea, weight gain was reduced during episodes of acute lower-respiratory infections in young children [231]. A large longitudinal study in Brazil suggested that hospitalization for pneumonia and subsequent height-for-age are significantly associated [18], and acute respiratory infections had a negative impact on weight gain in Guatemala [232].

Acute respiratory illnesses have been associated with a 10–20% reduction in food intake [233]. This could be caused by a reduction in the child's appetite—as has been well documented in a study in Peru [234]—the same mechanism that is postulated for the reduction of weight after a diarrheal episode or a febrile illness [235]. As with these other illnesses, catabolism may also play a role. Based on these studies, we can conclude that acute lower-respiratory illnesses, especially those associated with fever, have a negative impact on the nutritional status of children if the child's appetite is reduced, and there is a subsequent reduction of dietary intake. Further studies are needed to quantify the magnitude of this negative relationship between acute lower-respiratory infection and growth.

7.6 TREATMENT

7.6.1 Case Management of Pneumonia

A case management approach for pneumonia in children has been developed by WHO and is based on the assumptions that the main causes of fatal pneumonia are *S. pneumoniae* and *H. influenzae* [236], and that antibiotic treatment of pneumonia can reduce case fatality rates [237]. An algorithm based on clinical signs was developed to facilitate the recognition and management of acute respiratory infections by non-specialist doctors working in small hospitals with limited facilities [238, 239]. Several intervention studies using a case-management strategy for pneumonia were conducted in several developing countries. A meta-analysis of intervention trials on case management of pneumonia in nine community settings showed that the case-management strategy has a substantial effect on neonate, infant, and under 5 mortality rates, at least in settings where infant mortality rates are 49/1,000 live births or greater [240, 241]. Despite differences in study populations (location, immunization coverage, diarrhea management, prevalence of malnutrition, health services availability, maternal literacy, and infant mortality rates) and antibiotic (penicillin, ampicillin, cotrimoxazole) treatment in the different intervention trials, there was a consistent impact of case management on pneumonia mortality in neonates, infants, and children 1–4 years old. Case management of pneumonia was associated with a summary estimate from the pooled studies of 42% reduction (95% confidence interval [CI] 22–57%) of neonatal pneumonia mortality, of a 36% reduction (95% CI 20–48%) of infant pneumonia mortality, and of a 36% reduction (95% CI 20–49%) of pneumonia mortality among children 0–4 years old [241]. Reductions of total mortality by 27% (95% CI 18–35%) in neonates, 20% (95% CI 11–28%) in infants, and 24% (95% CI 14–33%) in children 0–4 years of age were also observed [241].

7.6.2 Nutritional Interventions for Treatment of Acute Respiratory Infections

7.6.2.1 Zinc

As described in Section 7.4.1.4, zinc supplementation given to children hospitalized with severe pneumonia was found effective in reducing pneumonia severity and shortening hospital stay in Bangladeshi [58] and Indian children [59], findings that were not confirmed in another Indian study [60]. No effect on wheezing disorders was observed in these trials [59]. Zinc gluconate glycine lozenges have been suggested as a therapy

for the common cold [242–244]. Initial meta-analyses of randomized, controlled clinical trials have suggested that zinc lozenges may be effective in the reduction of cold symptoms in adults and children, but the studies had many problems, including zinc dose; inadequate placebo control, and various formulations of the lozenge, which may include citric acid, sorbitol, mannitol, or tartaric acid, which may bind free zinc ion in the mouth, reducing its therapeutic effect [242, 243]. Initial zinc lozenges were associated with adverse effects in general, with bad taste and nausea as prominent symptoms [245]. Recent done trials, however, have documented that zinc lozenges were associated with reduction of duration and severity of cold symptoms [246, 247], especially when administered within 24 hours of the onset of common cold symptoms [248]. The use of zinc nasal sprays, gels, or lozenges given intranasally have caused important side effects and are not recommended [249, 250].

7.6.2.2 Vitamin A

Recent meta-analysis of trials evaluating the clinical effect of vitamin A supplementation in nonmeasles childhood pneumonia indicated that there was no effect [53, 54]. One study even showed vitamin A supplementation associated with more severe disease compared with placebo recipients [251]. These studies indicated that vitamin A supplementation has no role in the therapy of pneumonia.

7.6.2.3 Selenium

Selenium may play a potentially important role in acute lower-respiratory infections, and this relationship has only been partly explored. In humans, it was recognized early that patients on total parenteral nutrition who developed selenium deficiency had a marked reduction in erythrocyte and granulocyte glutathione peroxidase activity, which inhibits the cell's capacity to metabolize H_2O_2, abnormalities that returned to normal after selenium supplementation [252]. In critically ill patients admitted to intensive care units, the frequency of ventilator-associated pneumonia, organ system failure, and mortality (especially in those who developed a systemic inflammatory response syndrome), were three times higher in patients with low plasma selenium concentration on admission [253]. This fall in plasma concentration of selenium seems to occur mostly in patients with septicemia or pneumonia compared with those who develop viral infections [254, 255]. In a double-blind, controlled trial in Chinese children, selenium supplementation in children hospitalized with pneumonia or bronchiolitis associated with RSV resulted in a faster recovery rate of specific respiratory signs or symptoms [66]. Selenium supplements have also improved clinical signs of children with *M. pneumoniae* [67], and food additives containing selenium have improved symptoms in children admitted with pneumonia in Russian hospitals [68, 69]. Further trials are needed to document the value of selenium in the management of acute lower-respiratory infections in children.

7.7 PREVENTION

Potential interventions for the reduction of morbidity and mortality of pneumonia in children under 5 years old include immunization, improving nutrition, reducing environmental pollution, reducing transmission of pathogens, and improvement of child care practices [28].

7.7.1 Immunization

Measles and pertussis are still causing an important proportion of acute respiratory infection-related deaths in the world's children under 5 years old [1]. Increasing immunization coverage with measles vaccine and with diphtheria-pertussis-tetanus vaccine would be expected to lower the deaths from these two vaccine-preventable causes of acute respiratory infections [256]. The seven-valent conjugated pneumococcal vaccine has been safe and effective against pneumonia and invasive pneumococcal disease in children in the United States and was introduced for universal immunization in children in 2000 [257]. The effect of this vaccine introduction was greater in adults not vaccinated but protected by herd immunity by their children's immunization [257]. A protective effect was also observed for antibiotic-resistant invasive pneumococcal infections in children and adults in the United States [258]. This vaccine also reduces the prevalence of nasopharyngeal carriage of vaccine-type *S. pneumoniae* serotypes, which are replaced by nonvaccine types [259]. Recent reports from the United States indicate that these replacing serotypes are causing a greater proportion of invasive disease than before, which is a concern over the long-term benefits of this vaccine [257, 258]. The effect of this vaccine on the prevention of acute otitis media is questionable [260], although it may reduce tympanostomy tube placement in children [261]. A nine-valent conjugate pneumococcal vaccine was tested in a large group of infants in the Gambia, where it was documented not only to be 37% effective against radiological pneumonia, 77% effective against invasive pneumococcal disease caused by vaccine-related serotypes, and 15% against all-cause hospital admissions, but also was 16% effective in reducing mortality [262]. This nine-valent vaccine was also effective in South African infants, mostly among those who were not infected with HIV [263]. The seven-valent vaccine is now licensed for commercial use in several developing countries, but due to its high price, its use in public immunization programs will not happen soon. Other pneumococcal vaccines are under the horizon that may allow their introduction in developing countries.

Haemophilus influenzae type b (Hib) vaccine has been effective in reducing childhood pneumonia and meningitis in some industrialized countries, and a trial in the Gambia showed that a conjugate Hib vaccine was 95% protective against all invasive Hib disease and 100% protective against Hib pneumonia [264]. Although Hib causes only a small proportion of pneumonia, the vaccine was able to be 21% protective against any type of radiologically defined pneumonia in young children, indicating its potential to control diseases in children and infants from developing countries. This newly available vaccine has been rapidly introduced to developed countries, followed a few years later to most countries in Latin America. With the support of the Global Alliance for Vaccines and Immunisation (GAVI), the Hib vaccine is being introduced in poor countries [265].

Another vaccine that was introduced in developed countries that may be widely used in developing countries is an inactivated, trivalent influenza vaccine. In 2002, it was recommended to be used in US children 6–23 months of age [266], and several Latin American countries have also introduced it in young children. A new, cold-adapted, live influenza vaccine has proved not only immunogenic in young infants but also more effective in preventing influenza illness than the inactivated influenza vaccine [267]. However, the use of the cold-adapted trivalent intranasal influenza virus vaccine in children and adolescents has been associated with an increased risk of asthma or reactive airway

disease in children younger than 36 months [268]. This risk may be related to the intranasal route of administration since the use of a live attenuated trivalent influenza vaccine in children and adolescents has not been observed to increase the risk of asthma [272], including when it was tested in children and adolescents with asthma [270]. Finally, the use of the BCG vaccine in infants has been cost-effective in preventing severe childhood tuberculosis and should continue to be used [271].

The protection of the fetus by transplacental transfer of maternal antibodies has allowed the protection of infants against tetanus by maternal immunization. Similar approaches are also being considered to protect neonates against pneumococcal diseases, pertussis, group B streptococcal infections, and Hib infections [204, 272]. Other vaccines against human parainfluenza virus type 3 and RSV are also under development and may become available in the near future.

7.7.3 Nutrition

7.7.3.1 Breast-Feeding

Promotion of breast-feeding has been found to protect against acute respiratory infections in infants from developing countries [36]. It has been estimated that breast-feeding would significantly reduce the mortality due to diarrhea and acute lower-respiratory diseases in the world [256]. An estimated 1.45 million lives and 117 million DALYs are lost due to suboptimal breast-feeding in developing countries [273].

7.7.3.2 Prevention of LBW

The prevention of LBW may hypothetically decrease pneumonia mortality in developing countries, depending on the prevalence of LBW and the magnitude of the reduction in LBW [28]. There is a need to identify effective ways to reduce the prevalence of LBW in developing countries. Zinc supplementation has shown some promising results.

7.7.3.3 Reduction of Malnutrition

The reduction in malnutrition among infants and young children has been estimated to prevent 40% of pneumonia deaths in the world [28, 91]. The improvement of the weaning diet of children 6–24 months of age is a public health priority [2]. A pivotal study demonstrated that an intervention in well-baby clinics of the Ministry of Health in Trujillo, Peru, has been effective in improving nutrition in children [274], a study that needs to be replicated in other parts of the world. Food supplementation has been considered as an alternative approach by many developing countries, whereas food fortification is used in very few countries in the developing world.

7.7.3.4 Zinc Supplementation

Daily zinc supplementation of 10 mg to infants and 20 mg to older children younger than 3 years has been proven to reduce the incidence of pneumonia by 26% in Indian children [275]. A single 70-mg dose given weekly to Bangladeshi children 60 days to 12 months of age at enrollment and followed for 12 months reduced the incidence of pneumonia by 17% and prevented pneumonia-related deaths [276]. Zinc fortification followed by zinc supplementation has been cost-effective in developing countries [277]. Zinc deficiency has been estimated to explain 1.9% of the global burden of disease worldwide

and 16% of the lower-respiratory infections [91]. Eliminating zinc deficiency is now considered a priority for developing countries [256]. Effective and sustainable ways to increase the dietary intake of bioavailable zinc in developing countries are needed.

7.7.3.5 Vitamin A Supplementation

As reviewed in Section 7.4.1.4, vitamin A supplementation appears to have little impact on acute respiratory diseases in preschool children. When respiratory diseases were assessed in carefully controlled prospective trials of vitamin A supplementation, no major reduction occurred in the mortality or morbidity associated with respiratory diseases, as indicated in a meta-analysis of all available studies [52]. Vitamin A does not have any role in the prevention of respiratory diseases in children.

7.7.3.6 Selenium Supplementation

Selenium supplementation may have possible benefit in reducing the morbidity and mortality of acute respiratory diseases in humans. Dietary supplementation with selenium for dairy cattle has become a standard practice and has been associated with a reduction of calf losses owing to respiratory diseases [275]. In patients with major burns, supplementation with selenium combined with copper and zinc was associated with fewer bronchopneumonia infections and with a shorter hospital stay in a double-blind, placebo-controlled trial [276]. Selenium has also been incriminated in the pathogenesis of asthma. It has been postulated that the combination of dietary, environmental, and genetic factors that decrease the cellular reducing capacity will increase tissue vulnerability to oxidant stress. This will result in inflammation and tissue damage in the respiratory system and later in immune damage, leading to an increased risk to develop asthma [277]. Severely malnourished children often have very low plasma selenium concentrations and low erythrocyte and plasma glutathione peroxidase activity, which may predispose them to the development of serious infections [278]. Controlled, randomized, double-blind trials are needed with selenium supplementation for treatment or prevention of respiratory illnesses in children; toxicity should be also closely monitored [279].

7.7.4 Other Measures

Reducing indoor and outdoor air pollution, elimination of environmental tobacco smoke, and reduction of crowding are potential interventions that may prevent childhood pneumonia in developing countries [280]. Modifications of child care practices, including improvement of care-seeking, better maternal education, and increased child spacing, is also a potential area that may have an impact on reducing pneumonia in children. All these potential interventions require evaluation in controlled studies in developing countries before they can be considered.

7.8 FUTURE DIRECTIONS

As reviewed in this chapter, a series of studies is needed to be able to answer many of the questions raised. The most important ones are listed next.

7.8.1 Risk Factors for Pneumonia and Acute Lower-Respiratory Infection

- The impact of acute lower-respiratory infections on subsequent nutritional status and growth needs further elucidation in developing countries.

- There is a need to perform properly conducted studies to prove or disprove the relationship between cold or high-humidity exposure and pneumonia and other acute lower-respiratory infection.
- Further studies are needed to clarify if abnormal lung function precedes or is a consequence of pneumonia or acute lower-respiratory infection or both.
- There is a need to understand better the pathophysiology of intrauterine growth and how LBW could be avoided.
- The relationship between maternal immune status and the protection of neonates by transplacental immune mechanisms needs further study.
- Only zinc and vitamin A have been evaluated in relation to pneumonia and acute lower-respiratory infection. Other micronutrients, like selenium, vitamin D, and calcium, deserve further studies. There is a need to study further the relationship between indoor air pollutants and acute lower-respiratory infection, identifying the combustion products that are more closely related to these diseases, and describing their pathophysiology.

7.8.2 Clinical Aspects

- There is a need to standardize the methodology and definitions of pneumonia and acute lower-respiratory infection for the conduct of longitudinal prospective studies of acute lower-respiratory infection epidemiology.
- There is a need to improve the diagnostic capabilities of bacterial pathogens as causes of pneumonia and invasive diseases in infants and children to facilitate the clinical management of patients and the conduct of epidemiological studies.
- The results of the WHO-sponsored studies on the etiology of severe infections of infants under 3 months of age have indicated the need to reevaluate the clinical management of these cases in developing countries.
- The increased prevalence of antibiotic-resistant bacteria strains is worrisome. There is a need to monitor this trend and at the same time try to diminish the inappropriate use of antibiotics. Alternative methods for the treatment of these infections may be needed in the near future.

7.8.3 Prevention

- There is a need to replicate effective interventions that have improved weaning food practices and improved the nutritional status of children in developing countries from Africa and Southeast Asia and to study their impact on the incidence and severity of pneumonia and other acute lower-respiratory infections.
- The protective efficacy of breast-feeding promotion on pneumonia and other acute lower-respiratory infections needs further evaluation and documentation.
- Although zinc supplementation has been proven to reduce the incidence of pneumonia and acute lower-respiratory infection, there is a need to document its impact on mortality, which should facilitate the development of a sustainable approach to improve the zinc status of children in developing countries.
- Prospective studies as well as double-blind, placebo-controlled clinical trials with selenium as a treatment or prevention of respiratory diseases in children, particularly in premature or LBW infants, are needed.
- Maternal immunization seems to be a promising intervention for the control of infections in the neonatal period. Proposed vaccine candidates should be evaluated in properly designed studies.
- The search for effective and affordable vaccines against the most prevalent childhood illnesses for children in the developing world should continue.

- Ways to reduce the risk of transmission of respiratory pathogens in crowded areas and in day care centers are urgently needed. Effective interventions should be developed and tested in developing countries.
- The exposure of children in developing countries to indoor air pollutants, including environmental tobacco smoke, needs further evaluation. Appropriate interventions (such as improving stoves) should be developed and tested for their efficacy in preventing pneumonia and other acute lower-respiratory infection.

7.9 CONCLUSIONS

Acute lower-respiratory diseases are some of the most important diseases of infants and young children in developing countries and are closely associated with high morbidity and mortality. A series of factors that increase the risk of developing pneumonia and other types of acute lower-respiratory infections have been identified, whereas others require further studies. Although a considerable number of studies have been conducted to measure the incidence and clinical characteristics of these illnesses, there is still a need to standardize the methodology to be used in the field. Physician-based diagnostic methodologies seem to be preferable to symptom-based definitions of pneumonia, which are not capable of adequately separating pneumonia from wheezing disorders and other acute lower-respiratory infections; this explains the great variability of the rates reported in studies using that methodology. Recently conducted studies on the etiology of severe infections in infants less than 3 months of age have identified the increased rate of pneumococcal diseases even from the neonatal period. Maternal immunization may be an important public health tool to reduce severe infections during the neonatal and early postneonatal periods of infants.

Despite the considerable knowledge on risk factors for pneumonia and other acute lower-respiratory infection, there are relatively few proven interventions to prevent them. The most promising ones are vaccines. The new pneumococcal conjugate vaccines, combined with the Hib vaccine, may be important interventions to control severe invasive diseases caused by these bacteria.

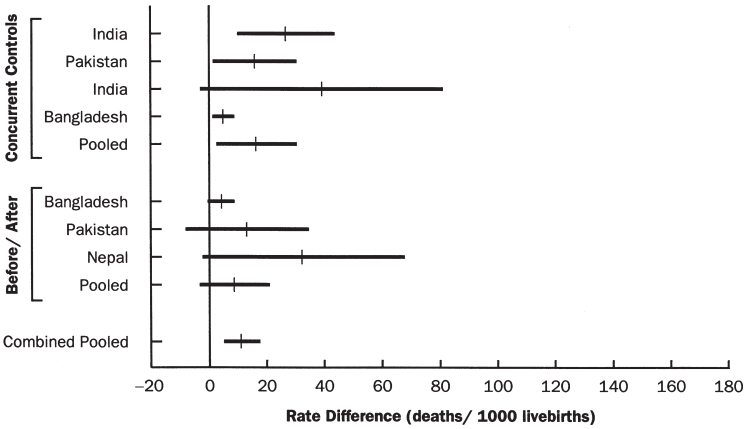

Fig. 7.2. Case management and acute lower-respiratory infection mortality in infants. (Adapted with permission from [240].)

While new vaccines are developed, tested, and implemented, other interventions are also needed that will focus on nutrition and the control of micronutrient deficiencies. Further studies are needed to identify sustainable interventions to improve the general nutritional status of children in developing countries as well as their families. The deficiencies of zinc, selenium, calcium, and vitamin D in children are also important and should be controlled. These studies also need to document their impact on pneumonia and other acute lower-respiratory infections in the affected population.

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