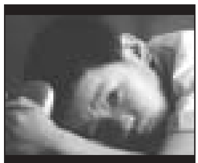

CHAPTER 3

RISK FACTORS FOR ACUTE LOWER RESPIRATORY INFECTIONS

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I. INTRODUCTION

Acute respiratory infections (ARI) are the single greatest cause of death among children throughout the world. They are responsible every year for the deaths of 4.3 million children under 5 years of age worldwide, which represents 21.3% of all deaths in this age group (*1, 2*). To reduce these appalling figures, preventive measures are needed to complement efforts directed at improved case management. This chapter will focus on the results of epidemiological studies on risk factors for respiratory infections in developing areas of the world, since most deaths from these infections occur there. Attention is given as well to studies from industrialized areas when necessary.

Acute lower respiratory infections (ALRI), including pneumonia, bronchiolitis, and bronchitis, are responsible for the vast majority of ARI deaths in developing areas. Priority has therefore been given to reviewing articles on ALRI rather than respiratory infections in general. However, there have been major inconsistencies in the case definitions of different investigators. Most studies rely on mothers' reports of the presence of cough and such signs of severity as accelerated or difficult breathing. Others record the presence of specific signs such as rales, chest retraction, or tachypnea, while only a few employ radiological criteria. Moreover, the number of studies on mortality is very limited, most being directed at reported morbidity, clinical care, or hospital admissions. Virtually none of the studies offer data on the validity of diagnoses. Therefore, despite the exclusion of studies with obvious flaws, this review is based on studies with various case definitions and uneven methodological quality.

For the purpose of the present review, risk factors for ALRI have been organized into demographic, socioeconomic, environmental, nutritional, and behavioral groupings. Vaccines also represent an important and promising strategy for ALRI prevention, including both new vaccines developed specifically against agents such as *Haemophilus influenzae* (type b) and pneumococcus, as well as the existing measles and pertussis vaccines. These, however, are reviewed elsewhere in this book.

II. Demographic risk factors

a) Gender

In a number of community-based studies, boys appear more frequently affected by ALRI than girls (*2, 3*). In clinical studies, however, the possibility of gender bias in seeking care cannot be ruled out.

The excess risk for boys was confirmed in two recent pneumonia case control studies from Brazil (*4, 5*). In one of these (*4*), male preponderance was inversely related to age; whereas 74% of the cases under 6 months old were boys, the proportion was 51% among 1-year-olds.

b) Age

Although the overall incidence of ARI is reasonably stable during the first 5 years of life, mortality is concentrated in infancy (*6*). In fact, about one-half of all respiratory deaths among children under 5 occur in the first 6 months after birth (*2*).

III. Socioeconomic risk factors

a) Income

The first indication that ALRI is associated with socioeconomic factors is the pronounced differences between countries. Although children under 5 throughout the world undergo approximately the same number of ARI episodes–about five per child per year (*2, 7*)—the annual incidence of pneumonia ranges from 3% to 4% in industrialized countries and 10% to 20% in developing countries (*2*). Primary childhood pneumonia deaths have been virtually eradicated from the industrialized countries.

Differences are also present within single countries and cities. In southern Brazil, the ALRI mortality rate for children from families earning under US$50 a month was 12 per 1,000; 16% of these children were admitted to a hospital with a respiratory infection by the age of 20 months. Among more than 600 children with a monthly family income above US$300, there were no pneumonia deaths and only 2% were admitted with ALRI (*8*).

b) Parental education

Low educational levels in mothers are associated with an increased risk of ALRI hospitalizations and mortality (*9*); this association was reduced but still remained significant after adjustment for confounding variables. In a pneumonia case control study in Brazil, however, the father's education was more strongly correlated than the mother's when both variables were included in an explanatory model (*5*). These findings suggest that although confounding factors may account for some of the crude data related to the mother's education, this variable has an independent role in the etiology of ALRI.

c) Place of residence

ARI incidence rates vary markedly between urban children (five to nine episodes per child per year) and rural children (three to five episodes) (*2*), which may be due to increased transmission as a result of crowding (see section IV.b below).

IV. Environmental risk factors

The most frequently studied environmental risk factors for respiratory infections include exposure to smoke, crowding, and chilling.

a) Exposure to smoke

Smoke includes several contaminants that affect the respiratory tract. The main sources of smoke affecting children in developing countries include atmospheric pollution, domestic biomass pollution, and passive cigarette smoking.

a.1) Atmospheric pollution

The well-documented rise in mortality due to respiratory diseases during the great London fog of 1952 (*10*) and other acute air pollution incidents (*7, 11*) has stimulated research on the association between air pollution levels and respiratory illnesses in children. These are particularly relevant to many cities in Latin America, such as Mexico City, Santiago, and São Paulo, where air pollution levels are often very high.

Studies from industrialized countries provide supporting evidence for the existence of effects from suspended particulates and sulfur dioxide, while the impact of nitrogen dioxide and ozone is still a matter of debate (*7*). Other pollutants have received less scrutiny.

One of the most important of these investigations was the Six Cities Study in the United States (*12*), which showed large increases in the risk of cough and lower respiratory illnesses, especially in association with particulates and suspended sulfates. A recent study from Utah (*13*) showed that children's hospital admissions for pneumonia, pleurisy, bronchitis, and asthma were 2 to 3 times higher in winters when a steel mill was open than when it was closed. Levels of fine particulate pollution were directly related to admission rates.

A recent ecological study from the Czech Republic (*14*) showed a strong association between postneonatal respiratory mortality and levels of total suspended particulates and possibly sulfur dioxide, after controlling for several confounding factors.

A Brazilian study (*15*) compared infant mortality from pneumonia with mean suspended particulate levels for 27 Río de Janeiro neighborhoods. A direct association (r = 0.30) was observed, independent of socioeconomic differences.

Studies on the health effects of air pollution have been affected by a number of methodological difficulties, including their ecological design, problems in air pollution measurement, and difficulties in separating infectious from noninfectious respiratory morbidity (*7*).

b.2) Domestic biomass pollution

The high costs and limited availability of electricity and fossil fuels in many developing countries lead to frequent domestic use of biomass fuels, including wood, manure, and agricultural waste. It is estimated that in developing countries, 30% of urban households and 90% of rural ones use biomass fuels as the major source of energy for cooking and heating (*16*). These are usually burned under inefficient conditions and often without any type of chimney. Particulate levels in these homes are about 20 times greater than in developed countries (*17*).

Studies from Nepal (*18*), Gambia (*19*), Zimbabwe (*20*), South Africa (*21*), Argentina (*22*), and the United States (*23, 24)* have reported higher respiratory morbidity among young children exposed to indoor pollution. In the Nepalese study, the incidence of ARI, particularly the severe cases, was directly associated with the number of hours each infant spent near a stove. Native American children under 2 years of age who were exposed to wood-burning stoves were about 5 times more likely to have radiologically confirmed pneumonia than children of the same age and sex from homes without these stoves. Smoking was uncommon in both populations, but the possibility of confounding by other variables cannot be ruled out.

There have also been disturbing reports concerning Papua New Guinea (*25*), North American school children (*26*), and Guatemalan children under 2 (*27*).

Most of these studies have been affected by problems such as small sample sizes, difficult exposure assessment, uneven exposure levels, and failure to adjust for confounding variables. Nevertheless, they do suggest the existence of an association between exposure to domestic biomass pollution and acute respiratory infections. This association seems to be present among young children, although perhaps not among school-age children.

b.3) Environmental tobacco smoke

Cigarette smoke contains measurable quantities of carbon monoxide, ammonia, nicotine, hydrogen cyanide, particulates, and a number of carcinogens. The concentrations of most of these products are higher in sidestream than in mainstream smoke (*28*). Smoking prevalence is rising in many developing countries, particularly in urban areas (*29*). In most of these countries, one-third of all women and one-third to one-half of all men are smokers (*30*).

The association between environmental tobacco smoke, often referred to as passive smoking, and respiratory illness in childhood has been clearly established by a large number of studies (*7, 31*). Children of smokers do not perform as well in pulmonary function tests and show 1.5 to 2.0 times greater incidence rates of lower respiratory infections than those of nonsmokers (*31*). Data on 4,500 Brazilian children followed during the first 2 years of life showed a 50% increase in ALRI hospitalizations among children with two smoking parents, compared to children of nonsmokers (*32*).

This association is stronger for infants than for older children, and also stronger for maternal than paternal smoking (*31, 33, 34*). It is unlikely that the association is due to confounding variables (*32, 35, 36*).

However, two recent studies from Brazil, both of which used radiologically confirmed pneumonia as the outcome (*4, 5*), failed to find a significant association with parental smoking. One possible explanation for this discrepancy is that most positive studies included bronchospastic conditions as well as pneumonia, whereas the latter two studies were restricted to children with alveolar infiltrates.

b) Crowding

Crowding, which is notably common in developing countries, contributes to the transmission of infections through respiratory droplets and has been clearly shown to be associated with respiratory infections (*7, 37*). Variables strongly associated with crowding, such as birth order (*38*) and the number of children under 5 in the household (*39*), are also associated with the risk of lower respiratory infections. A study from Brazil (*39*) showed that after adjustment for socioeconomic and environmental factors, the presence of three or more children under 5 in the household was associated with a 2.5-fold increase in pneumonia mortality.

Day-care centers, which increase the contact between young children, are also associated with ARI (*40-42*). Of particular interest are two studies from Brazil showing a strong association between day-care attendance and pneumonia among children less than 2 years of age (*4, 5*). After adjustment for confounding variables, the increased risk was 12-fold in Porto Alegre and 5-fold in Fortaleza.

Crowding, therefore, whether at home or in institutions, is one of the best-established risk factors for pneumonia.

c) Exposure to Cold and Humidity

According to popular belief, cold weather brings about respiratory infections, as implied by the very words cold and flu (from Italian *influenza del frigore,* influence of the cold). In fact, deaths due to pneumonia are considerably higher during the winter months, as exemplified by data on infants in southern Brazil (*43*). In developed countries, however, the seasonal trends in infant mortality are now less marked than in the first half of this century (*44*).

It is not clear, however, that winter peaks in respiratory infections are directly caused by low temperatures. Volunteers infected with rhinoviruses who were exposed to cold and dampness were no more likely to develop respiratory infections than those kept in a warm, dry environment (*45, 46*). This is supported by two British studies which have failed to show an association between indoor temperatures and humidity and the incidence of respiratory infections (*47, 48*). The above evidence, however, relates basically to viral rather than bacterial infections.

It is possible that correlates of cold weather, such as crowding or domestic biomass pollution, may be largely responsible for the higher respiratory morbidity and mortality during winter months (*7*). Further research is needed on this topic since, although indirect evidence is overwhelming, actual studies showing a direct evidence of cold on ALRI are lacking.

A factor that is related to cold exposure is the quality of housing. The two Brazilian case control studies failed to find an association between pneumonia and housing quality (*4, 5*).

One important aspect of chilling refers to young infants. Newborn hypothermia is not uncommon in developing countries (even in warm climates), being associated with respiratory and other infections as well as with metabolic and clotting disorders (*49, 50*). It is not clear, however, whether hypothermia is a cause or a consequence of the accompanying infections.

d) Exposure to Other Adverse Environmental Conditions

Gas cooking, which is widely used in some urban areas of developing countries, is a source of carbon dioxide. It has been implicated as a possible risk factor for respiratory infections among children (*51, 52*), but this finding has not been confirmed by other studies (*53, 54*).

V. Nutritional factors

Nutritional factors that may influence the risk of ALRI include birth weight, nutritional status, breast-feeding, and levels of vitamin A and other micronutrients. These factors interact in complex ways. For example, low birth weight (particularly intrauterine growth retardation) is an obvious determinant of later nutritional status (*55-58*). Birth weight is also positively correlated to breast-feeding duration (*59*). Breast-feeding and nutritional status may also be associated, but the direction of this association varies with age and socioeconomic status (*60-62*). Micronutrient deficiencies, including for vitamin A, are also more common among malnourished children and may be affected by breast-feeding (*63*).

The issue is further complicated, however, by the possibility that ALRI itself may influence some of the above risk factors. Children may be weaned as a result of any severe illness such as pneumonia and nutritional status may also be affected by pneumonia (*64*). These complex interrelationships must be borne in mind when interpreting the results of observational studies on nutritional risk factors and ALRI.

a. Low Birth Weight

Approximately 20 million low birth weight (LBW) infants are born each year, representing 16% of all births (*65, 66*). The majority of these infants appear to be small for gestational age (SGA), but are born at term (*67*). This differs from the situation in industrialized countries, where most LBW infants are preterm. Two major mechanisms link birth weight to ALRI: reduced immunosufficiency and impaired lung function. The immune response of LBW infants is severely compromised, affecting particularly SGA babies (*68-71*). Preterm infants tend to have impaired lung function during childhood, due either to bronchopulmonary dysplasia secondary to mechanical ventilation (*72-74*) or to dyspnea, in which the integrated development of airways and alveoli is disrupted by preterm birth (*75*). The latter mechanisms may, however, have limited relevance for developing countries where most LBW infants are SGA and where severely preterm infants rarely survive.

Low birth weight is a well-established determinant of overall mortality for infants and children under 5 (*76, 77*). Preterm infants are at greater risk of death than SGA infants of comparable birth weight (*76, 78*), although in the second, third, and fourth years of life, the reverse may be true (*79, 80*).

Four studies showed clear dose-response patterns in which infant pneumonia mortality decreases as birth weights rise (*78, 81-83*). The median relative risk from these studies was 7.3 for LBW babies compared to those weighing 2,500 grams or more.

Only two studies on ALRI incidence according to birth weight were located. No association was found in an Indian cohort study, despite an 8-fold difference in ALRI mortality (*83*). A British study (*84*) showed that LBW children had twice as many lower respiratory infections in the first year of life as did matched controls; in the second year the two groups did not differ significantly.

Several studies reported relative risks of ARI admissions for LBW infants (*22, 84-89*), but only three included adjustments for confounding factors (*4, 5, 90*). Despite the possible diagnostic and selection biases affecting the investigation of respiratory admissions, all studies showed elevated relative risks ranging from 1.5 to about 8 for LBW infants.

SGA and preterm infants in Brazil have similar risks of being hospitalized with pneumonia during the first and second years of life. In the third and fourth years, however, preterm infants experience a higher risk of pneumonia admission than SGA infants (*90*).

The above results lead to the conclusion that LBW results in a higher rate of severe respiratory conditions, including pneumonia.

b) Malnutrition

Protein-energy malnutrition results from inadequate intake, poor utilization of calories or protein in the diet, or from childhood infectious diseases, such as diarrhea and pneumonia (*91, 92*).

In epidemiological studies, malnutrition is usually assessed by using anthropometric measurements. Studies of malnutrition and ALRI have varied considerably, however, in choosing which indicator to report: low height for age (stunting), low weight for height (wasting), low weight for age (underweight), or different combinations of the three. Investigators have also varied in their choice of the cut-off value chosen to represent malnutrition in the analysis, using either percentiles (often the 5th or 10th), percent of the median reference value, or the currently recommended standard deviation scores (Z scores). In the following discussion, moderate to severe malnutrition is equated with a Z score below -2, unless otherwise stated.

The prevalence of malnutrition is highest in developing countries. Data from the World Health Organization (WHO) on 1-year-old children from several countries (*93*) show that the median prevalence of stunting (Z scores below -2) ranged from 34% in Latin America to 47% in Asia; weight-for-age deficits varied from 23% to 53%; and wasting, which was less common, ranged from 3% to 19%, respectively.

There is overwhelming evidence that severely malnourished children have impaired immunological response (*94-96*), particularly at the cellular level, and consequently develop more severe infections than well-fed children.

The impact of malnutrition on overall child mortality has been the subject of a recent meta-analysis (*97*). Even mild anthropometric deficits are associated with an increased risk of death.

Only two studies seem to be available on respiratory mortality, one from Papua New Guinea showing an 8-fold increase for children under 70% of their weight-for-age (*98*) and a Brazilian study that shows a 20-fold increase for those with weight-for-age Z scores under -2 (*99*). Confounding factors were taken into account in the latter study, which also showed an increased risk for mildly and moderately malnourished children.

Four hospital-based studies have provided relative risks for ALRI case fatality according to nutritional status (*100-104*). Taken together, these studies suggest that low weight-for-age is associated with 2 to 3 times higher rates of case fatality.

A number of studies have examined the relationship between malnutrition, particularly low weight-for-age, and the incidence of pneumonia or ALRI (*22, 65, 101, 105-108*). Most studies relied on hospital admissions. Taken together, studies which used -2 Z scores as the cutoff found a 2- to 4-fold increase in pneumonia among malnourished children.

The case control studies from Brazil on radiologically confirmed pneumonia found that children with weight-for-age Z scores under -2 had a risk about 5 times greater than those with Z scores above -1, after adjustment for confounding variables (*4, 5*). Significant associations were also found for height-for-age and weight-for-height.

In summary, studies from several countries show an association between malnutrition and ALRI/pneumonia. Although most studies measured weight after the outcome had occurred, and some degree of wasting might be attributed to the illness, it would not explain the magnitude of the observed relative risks.

c) Lack of Breast-Feeding

Authors varied in their definition of breast-feeding (*109*), but most reports included in the present review have handled breast-feeding as a dichotomous variable. Only three studies have considered more than two breast-feeding categories.

The frequency of breast-feeding varies markedly among developing countries (*110*). Whereas among the rich and some urban poor areas median durations are short (about three months), in many poor rural areas and some poor urban areas breast-feeding is universal until

12-18 months, although supplements are often introduced early in life. Most of the populations from less developed countries lie between the two extremes.

Breast milk may protect against ARI through a number of mechanisms, including its antibacterial and antiviral substances, immunologically active cells, and stimulants of the infant immune system (*111-115*). In developing countries, exclusively breast-fed babies may also present a better nutritional status in the first months of life (*115*), which may contribute to reductions in the incidence and severity of infectious diseases.

The review on breast-feeding was limited to studies from developing countries or from poor areas of developed countries. This is because its effect on morbidity and mortality seems to be modified by a number of socioeconomic and environmental factors (*116*), leading to stronger protection in developing areas of the world (*117*) than in more industrialized regions (*118*).

Most studies concerning the association between breast-feeding and overall infant mortality in developing countries show a protective effect (*117*). A single study provides information on ALRI-specific mortality relative to breast-fed infants (*119*), those who also received artificial milk had a risk of 1.6, and non-breast-fed infants a risk of 3.6. The introduction of food supplements, regardless of the type of milk being consumed, was associated with a 3-fold reduction in the risk of ALRI death.

Among children hospitalized with pneumonia in Rwanda, breast-feeding was associated with a 50% reduction in case fatality (*120*).

Five studies provided data on the association between breast-feeding and hospital admissions due to pneumonia/ALRI in China (*121*), in a Canadian Indian reservation (*122*), in Argentina (*22*), and in Brazil (two studies) (*4, 5*). All showed that infants not breast-fed had 1.5 to 4 times greater risk of being admitted. The same ratios were described for studies of ALRI/pneumonia outcomes in addition to mortality and admissions (*22, 123-126*).

d) Vitamin A Deficiency

Unlike most risk factors for pneumonia, the evidence on the role of vitamin A deficiency results mainly from randomized controlled trials. This evidence has been recently reviewed by Beaton, et al. (*63*). Although vitamin A supplements reduce overall childhood mortality in areas where deficiency is present, no reduction on ALRI morbidity or mortality has been shown. In fact, there was an earlier report of increased respiratory morbidity among children receiving supplements (*127*), but this has not been confirmed (*63*).

Although other micronutrients (including iron, zinc, copper, and vitamin D) may play a role in the causation of ALRI, epidemiological data are very limited.

VI. Behavioral factors

Sociocultural and behavioral characteristics are likely to influence exposure to the above risk factors. For example, local perceptions of causes of illness may affect practices related to exposure to chilling. In many countries ARIs are attributed to exposure to cold or to abrupt changes in weather. Mothers therefore take care not to leave children uncovered or bathe them in very cold weather. Such concern about temperature, however, may lead to exposure to other risk factors, such as crowding and domestic biomass pollution for heating.

Patterns of child care may also affect the level of exposure to environmental risk factors. Where mothers tend to carry infants on their backs throughout the day, as in Bolivia or Gambia, these children may be at risk of exposure from cooking fires. On the other hand, exposure to cigarette smoke may be less intense where women are prohibited from smoking and where men's and women's activities are more segregated, such as in some Muslim countries.

An understanding of the social and cultural context in which exposure to environmental risk factors occurs is needed if effective interventions are to be developed.

VII. Summary of risk factors and possible intervention

Information on risk factors, along with feasibility and cost considerations, is essential for guiding preventive strategies against respiratory infections.

Demographic risk factors, such as age and gender, may be important for defining high-risk groups but are not amenable to intervention. Socioeconomic factors represent the ultimate determinants of a large proportion of the burden of severe ARIs, but interventions against factors such as low income or low educational levels fall outside the scope of the health sector. Available epidemiological evidence, however, should be used to support the political struggle against inequality.

Of environmental factors, environmental tobacco smoke, air pollution (especially particulate levels), and crowding are clearly associated with respiratory morbidity among young children. Although further studies are required on the effect of domestic biomass pollution, these are likely to confirm its causal role. Chilling and humidity, on the other hand, have not been established as independent determinants of respiratory infections. Possible effective interventions for reducing respiratory morbidity and mortality include air pollution control, anti-smoking campaigns, and improved biomass-burning stoves, as well as birth spacing and improved housing to reduce crowding.

Regarding nutritional factors, low birth weight, malnutrition, and lack of breast-feeding constitute independent risk factors, while vitamin A supplementation does not appear to have an effect on ALRI. A recent review by the World Health Organization (*128*) concludes that interventions to improve LBW in children and promote breast-feeding appear to have similar potential effects on pneumonia mortality, whereas improvements in nutritional status would have less effect. The cost-effect ratio of promoting breast-feeding is probably higher than that of efforts to fight LBW or malnutrition.

It should be noted that most of the above interventions would have other beneficial effects in addition to their impact on respiratory infections among young children. Further work is needed to establish the cost-effectiveness of possible interventions, taking into account their multiple benefits.

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