Review Article

Potential interventions for the prevention of childhood pneumonia in developing countries: improving nutrition[1–3]

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ABSTRACT Acute respiratory infections are the leading cause of childhood death in developing countries. Current efforts at mortality control focus on case management and immunization, but other preventive strategies may have a broader and more sustainable effect. This review, commissioned by the World Health Organization, examines the relations between pneumonia and nutritional factors and estimates the potential effect of nutritional interventions. Low birth weight, malnutrition (as assessed through anthropometry), and lack of breast-feeding appear to be important risk factors for childhood pneumonia, and nutritional interventions may have a sizeable effect in reducing deaths from pneumonia. For all regions except Latin America, interventions to prevent malnutrition and low birth weight look more promising than does breast-feeding promotion. In Latin America, breast-feeding promotion would have an effect similar to that of improving birth weights, whereas interventions to prevent malnutrition are likely to have less of an effect. These findings emphasize the need for tailoring interventions to specific national and even local conditions. *Am J Clin Nutr* 1999;70:309–20.

KEY WORDS Protein-energy malnutrition, birth weight, breast-feeding, pneumonia, respiratory tract infections, children, review, developing countries

INTRODUCTION

Acute respiratory infections (ARIs) are the leading cause of death among children in developing countries and most of these deaths are due to pneumonia (1). Studies in various settings suggest that acute lower respiratory tract infections (ALRIs) are associated with 15–40% of all childhood deaths (1–3); globally, this figure is estimated to be 30.3%, based on 1990 mortality figures (1). ALRIs are also involved in a large proportion of childhood deaths due to measles, pertussis, and HIV-AIDS (1).

Adequate case management can substantially reduce pneumonia mortality (4) and has been adopted as the main control strategy by international organizations. It is also important, however, to consider preventive strategies. The present review of the role of nutritional risk factors in pneumonia is part of a series of reviews of the major determinants of childhood pneumonia in developing countries, which were commissioned by the World Health Organization in association with the London School of Hygiene and Tropical Medicine with support from the UK Overseas Development Administration and the United Nations Children's Fund (UNICEF). The present review synthesized material from 3 separate reviews: *1*) a review on preventing low birth weight (A Ashworth and S Rogers, unpublished observations, 1995), *2*) a review on preventing protein-energy malnutrition (RE Black and S Sazawal, unpublished observations, 1995), and *3*) a review on promoting breast-feeding (CG Victora, unpublished observations, 1995).

The review process and methods were described elsewhere (1). This review examines the relations between pneumonia morbidity and mortality in early childhood and low birth weight, underweight, and lack of breast-feeding, and estimates the potential effect on pneumonia mortality of reducing these nutritional risks. The potential effect of improving vitamin A status is discussed in a separate study (5).

Many of the studies identified herein used ALRIs—including pneumonia, bronchiolitis, and bronchitis—as the outcome and did not explicitly focus on pneumonia because pneumonia accounts for a large proportion of all ALRIs in young children. Note, however, that the definition of an ALRI varies enormously depending on the investigator, which may affect the interpretation of the findings discussed below. Studies in which the outcome variables were either all ARIs or just upper respiratory infections were not considered in this review, unless they referred to episodes for which the patients were hospitalized. Hospitalization usually indicates a severe illness and thus most patients hospitalized because of an ARI probably had pneumonia. Overall respiratory mortality was accepted as a reliable outcome in the review of mortality studies because most such deaths are due to pneumonia (1).

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TABLE 1
Median prevalences of low birth weight, malnutrition, and non-breast-feeding in different regions of the world

	Prevalence of risk factor		
	Low birth weight (<2500 g)[1]	Underweight (weight-for-age < −2 *z*-scores)[1,2]	Non-breast-feeding (12–15 mo)[3]
		%	
Region			
Sub-Saharan Africa	16	31	10
Middle East and North Africa	10	17	38
South Asia	34	60	22[4]
East Asia and the Pacific	11	26	
Latin America and the Caribbean	11	11	64
All developing countries	19	36	30
Prevalences used in the simulation models			
Lowest	10	11	10
Intermediate[5]	19	36	30
Highest	34	60	64

[1] Data from reference 6.
[2] For children aged <5 y.
[3] Unpublished data from Demographic and Health Surveys, United Nations Children's Fund (UNICEF), 1995.
[4] Available data were not sufficient to separate the 2 Asian regions.
[5] All developing countries.

NUTRITIONAL RISK FACTORS: DEFINITIONS, INDICATORS, AND MECHANISMS OF ACTION

The literature on risk factors for pneumonia is affected by a lack of consistency regarding terminology and definitions. These issues are discussed below.

Low birth weight

It is estimated (6) that 19% of all babies born in developing countries have a low birth weight, ie, a birth weight <2500 g. Median prevalences range from 10% in the Middle East and North Africa to 34% in southern Asia (**Table 1**). Low-birth-weight infants may be divided into 2 broad subgroups: preterm (<37 wk gestation) and small for gestational age (SGA). The operational definition of SGA (ie, an infant born at term with a weight less than the standard reference weight) is affected by a lack of consistency in use of not only cutoff points—some authors using 2 SDs below the mean for gestational age and others the 5th or 10th percentile—but also in different intrauterine growth references (7, 8). Limited data are available on length of gestation in developing countries, but most low-birth-weight infants appear to be SGA (9). This is in contrast with industrialized populations in which most low-birth-weight infants are born preterm.

There are 2 main mechanisms that predispose low-birth-weight infants to an increased risk of respiratory infections: reduced immunocompetence and impaired lung function. As is discussed below, low-birth-weight babies may have a higher incidence of pneumonia because low birth weight may lead to a short duration of breast-feeding and to poor nutritional status.

The immune response of low-birth-weight infants is compromised. SGA infants are more adversely affected than are preterm infants and their impairment lasts longer (10–13). Impairment of the immune response may arise, at least in part, from nutritional deficits (11, 14–16). For example, preterm infants have low body stores of iron, zinc, copper, and other nutrients (17), whereas SGA infants have the disadvantage of notably smaller livers than preterm infants of similar birth weight (18).

Preterm infants tend to have impaired lung function during childhood. This impairment may be a consequence of mechanical ventilation for neonatal respiratory illness, with resulting bronchopulmonary dysplasia (19–21). However, impaired lung function has been observed in children born preterm who were not subjected to mechanical (or other) ventilation (22, 23). Bronchopulmonary dysplasia may be associated with a reduction in the diameter of major airways or an obstruction of peripheral airways. A possible mechanism is the disruption of the integrated development of airways and alveoli by preterm birth (23, 24).

Further research is needed to establish the relevance of the above mechanisms to low-birth-weight infants in developing countries. Bronchopulmonary dysplasia is largely confined to very-low-birth-weight infants (<1500 g), few of whom survive in developing countries; the other studies cited were restricted to children weighing <2000 g at birth, who represent a minority of infants with a low birth weight in developing countries. Indeed, it is possible that lung function may not be impaired in childhood among preterm infants with a birth weight >2000 g (25, 26).

Protein-energy malnutrition (underweight)

Protein-energy malnutrition refers to a condition resulting from an inadequate intake or utilization of energy or protein in the diet, or excess wastage, that is often accompanied by specific vitamin and mineral deficiencies (27). Protein-energy malnutrition is also often caused by childhood infectious diseases such as diarrhea and pneumonia (28).

All recent studies of the association between protein-energy malnutrition and respiratory infections relied on anthropometric criteria based on the US National Center for Health Statistics reference (29). Although it is desirable to separate the effects of stunting (low height-for-age) from those of wasting (low weight-for-height), most studies have reported their results solely in terms of underweight (low weight-for-age), which represents a combination of stunting and wasting. In developing countries, the positive predictive value of underweight as an indicator of protein-energy malnutrition is very high, ie, most

children who are underweight are malnourished because of either inadequate diets or frequent infections (29). Underweight, therefore, is a reasonable proxy for protein-energy malnutrition under these circumstances.

Published studies have also varied in terms of the scales used, ie, percentiles (often the 5th or 10th), percentages of the median reference value, or SDs (*z* scores). Whenever possible, SDs were used in this review. Authors also varied in their choice of categories for analysis, some using a dichotomous comparison of an underweight and a nonunderweight group of children and others using several categories in search of dose-response trends.

Although protein-energy malnutrition occurs throughout the world, its prevalence varies, being highest in the least developed countries. It is estimated (6) that ≈36% of children aged <5 y living in developing countries have a weight-for-age < -2 *z* scores compared with reference values. Regional prevalences range from 11% in Latin America and the Caribbean to 60% in southern Asia (Table 1).

Malnourished children have an impaired immunologic response (30–32) and consequently more severe infections. Protein-energy malnutrition may affect nonspecific and antigen-specific defense mechanisms. The cell-mediated immunologic response is particularly affected; changes include atrophy of the thymus and other lymphoid tissues, T lymphocyte reduction, depressed lymphocyte activation, and impaired delayed hypersensitivity reaction. The humoral response does not seem to be so markedly affected, although secretory immunoglobulin A concentrations in several organs, including the respiratory tract, are decreased. Other components of the immunologic system may also be affected by protein-energy malnutrition, including the complement system and phagocytosis.

Lack of breast-feeding

Authors also varied in their definitions of breast-feeding (33). Most treated breast-feeding as a dichotomous variable, separating children who received any amount of breast milk from all other children. Only 3 studies considered >2 breast-feeding categories. These studies are important because they show dose-response associations and also because grouping together children who are exclusively breast-fed with those receiving small amounts of breast milk may underestimate its protective effect.

The duration of breast-feeding varies markedly between developing countries. Special tabulations from the Demographic and Health Surveys of the Planning and Coordination Office of UNICEF (unpublished observations, 1995) were used to calculate the prevalences of breast-feeding at ages 12–15 mo (Table 1). Children were more likely to not be breast-fed at this age (64%) in Latin America and the Caribbean and least likely to not be breast-fed (10%) in Sub-Saharan Africa. The median value of non-breast-feeding children in 44 countries studied was 30%.

Breast-feeding protects against ALRIs because of breast milk's unique antiinfective properties. It provides passive protection against pathogens (antibacterial and antiviral substances including secretory immunoglobulin A, lactoferrin, oligosaccharides, and cells—macrophages, lymphocytes, and neutrophils), stimulants of the infant's immune system, and the bifidus factor, which inhibits colonization by Gram-negative species (34–37). In developing countries, exclusively breast-fed babies are less likely to be exposed to contaminated foods and may have a better nutritional status in the first months of life (38), which may contribute to the reductions in the incidence and severity of infectious diseases. Existing data show that the protection afforded by breast-feeding against ALRIs does not appear to vary with the infant's age (*see* below).

RISKS OF PNEUMONIA OR ALRI ASSOCIATED WITH NUTRITIONAL RISK FACTORS

In this section, the associations of each nutritional factor with pneumonia or ALRI are reviewed. Available evidence for associations between pneumonia or ALRI mortality (including studies of case fatality), morbidity, and hospital admissions are presented.

Low birth weight

Association with pneumonia or ALRI mortality

Four studies from developing countries provided information on birth weight and infant mortality due to pneumonia or ALRI (**Table 2**): cohort studies from Brazil (39), India (40), and the Philippines (41) and a case-control study from Brazil that excluded early neonatal deaths (42). All of these studies showed clear patterns of decreasing pneumonia mortality with increasing birth weights. Relative risks for low-birth-weight infants were 1.5 in the Philippines, 1.6 in the Brazilian case-control study, 6.7

TABLE 2
Summary of community-based studies of mortality from acute lower respiratory infection (ALRI) and pneumonia and relative risks based on birth weight in children from Brazil, India, and the Philippines

	Country and reference			
	Brazil (39)	India (40)	Philippines (41)	Brazil (42)
Cause of death	Pneumonia	Pneumonia	ALRI	ALRI
Age (mo)	0–11	0–11	0–23	0.25–11
Design	Cohort	Cohort	Cohort	Case-control
Sample size				
Number of children	5914	659	9942	254[1]
Number of deaths	25	19	39	127
Relative risk based on birth weight				
≥2500 g	1.0	1.0	1.0	1.0
<2500 g[2]	6.7 (3.0, 14.9)	8.0	1.5 (0.7, 3.1)	1.6 (0.8, 3.3)
Comments	Unadjusted	—	Unadjusted	Adjusted for confounders

[1] Number of children in the control group.
[2] 95% CI in parentheses.

TABLE 3
Summary of community-based studies of mortality from acute lower respiratory infection (ALRI) and relative risks based on wieght-for-age *z* scores in children from Brazil, the Philippines, and the Gambia

	Country and reference		
	Brazil (49)	Philippines (41)	Gambia (50)
Cause of death	ALRI	ALRI	ALRI
Age (mo)	0.25–11	0–23	0–23
Design	Case-control	Cohort	Case-control
Sample size			
Number of children	254[1]	9942	270[1]
Number of deaths	127	39	129
Relative risk based on weight-for-age z scores			
>0	1.0	—	—
0 to −0.9	4.0 (1.8, 9.3)[2]	—	—
−1 to −1.9	5.5 (2.2, 13.8)	—	—
≤−2	21.5 (6.3, 73.6)	—	—
≥0	—	1.0	—
−1	—	1.9	—
−2	—	3.3	—
−3	—	5.9	—
≥0.75	—	—	1.5
−1.26 to 0.76	—	—	0.2
−1.87 to −1.27	—	—	0.8
≤1.88	—	—	1.0
Comments	Adjusted for confounders	Calculated from linear fit of *z* scores	—

[1] Number of children in the control group.
[2] 95% CI in parentheses.

in the Brazilian cohort study, and 8.0 in India. Studies with pneumonia as the outcome had higher relative risks than those in which the outcome was ALRI, and the higher estimates were provided by the 2 studies with the smallest number of deaths—the cohort study in Brazil and the study in India. The pooled relative risk of mortality, weighting these estimates by the total number of deaths in each study, was 2.9.

Association with pneumonia or ALRI morbidity

Neonatal respiratory disease is an important complication of low birth weight but the prevalence of respiratory infections during this period and its association with low birth weight are unclear. The association between low birth weight and pneumonia incidence throughout infancy is also poorly documented and only 2 studies were located. In an Indian cohort study of 659 infants followed over 1 y, there was no significant effect of birth weight on the number or duration of ALRI episodes (cough with rapid or difficult breathing, chest indrawing, or both), despite an 8-fold difference in respiratory mortality (40).

Three studies from developing countries provided information on hospital admissions, after adjustment for confounding factors. In China, low-birth-weight children had 1.9 times more respiratory admissions in the first 18 mo of life than did children in other countries with an age-appropriate birth weight (43). In Argentina, low-birth-weight children aged <5 y had 2.2 times more hospital admissions than other children (44). In Brazil, children below the 10th percentile of birth weight for gestational age had 1.5 times more ALRI admissions in the first 2 y than did heavier children (45). In this study, SGA and preterm infants showed similar risks of being hospitalized with pneumonia during the first 2 y of life. In the third and fourth years of life, however, preterm infants experienced a higher risk of pneumonia admissions than did SGA infants (45).

Two case-control studies from Brazil used radiologically confirmed pneumonia as the outcome while controlling for several confounding factors. In the city of Fortaleza, Brazil (46), children with a birth weight <2000 g had a relative risk of 3.2 and those with a birth weight between 2000 and 2499 g had a relative risk of 1.4 compared with children with a normal birth weight. In Porto Alegre, Brazil (47), low birth weight was associated with a relative risk of 1.4. In summary, the available epidemiologic evidence points to an effect of birth weight on pneumonia-associated morbidity and mortality.

Protein-energy malnutrition (underweight)

Association with pneumonia or ALRI mortality

Only 4 studies provided information on the role of malnutrition (underweight) as a risk factor for pneumonia mortality. One of these, reporting information from a study in Papua New Guinea, indicated that children who were <70% of their weight-for-age had an 8-fold higher risk of dying than did heavier children (48). Unfortunately, no data or additional information are provided in this publication. The other 3 studies are abstracted in **Table 3**. In Brazil, infants who died from an ALRI had their weight-for-age *z* scores at hospital admission compared with the *z* scores of control subjects from the same community (49). A clear dose-response pattern was observed. Relative to children with a weight-for-age *z* score >0, those with *z* scores <−2 had a relative risk of 21.5. These risks persisted after adjustment for confounding factors. In the Philippines, a prospective study showed that children with weight-for-age *z* scores <−2 had a relative risk of ALRI death that was 3.1 times that of all other children (41). In a study from the Gambia, children with weight-for-age *z* scores <−1.88 had a relative risk of ALRI mortality 5 times that of children with *z* scores between −1.26 and 0.76, a category that included most of the children surveyed (50). The risk

for heavier children, however, was higher than for children with *z* scores between −1.26 and 0.76.

Several studies have addressed the association between malnutrition (underweight) and pneumonia or ALRI case fatality (51–57), of which 4 provided relative risks. These 4 studies were hospital based and nutritional status was determined on admission. In the Philippines, children with weight-for-age *z* scores < −2 were reported to have an ALRI case fatality rate twice that of better-nourished children (53, 54). In Papua New Guinea, the case fatality rate from severe pneumonia was twice as high in undernourished children (55). In Bangladesh, undernourished children hospitalized with an ALRI had a relative risk of 1.7 (56). In Argentina (57), where the cutoff for weight-for-age was 90% of the National Center for Health Statistics median (29), a relative risk of 3.3 was found. Nutritional status, therefore, seems to be an important determinant of pneumonia case fatality and mortality.

Association with pneumonia or ALRI morbidity

Many studies have examined the relation between malnutrition, particularly low weight-for-age, and the incidence of pneumonia or ALRI. In an early study in Costa Rica, low weight-for-age was found to have a relative risk of 3.9 for pneumonia requiring hospitalization, but the sample size in this study was small (58). In a prospective community-based study in the Philippines (54, 59), children with weight-for-age *z* scores between −2 and −3 had a relative risk of 1.2 for ALRI, whereas those with *z* scores < −3 had a relative risk of 1.9. In Uruguay, the relation of underweight and ALRI was examined by age: children 0–17 mo old showed no increased risk, whereas those 18–35 mo old had a relative risk of 2.7 (59). A study in Papua New Guinea (60) found that the relative risk of ALRI was 2.1 for children with weight-for-age *z* scores < −2 (estimate based on the figures in the text).

In Guatemala, children with weight-for-height *z* scores < −2 had a relative risk of 3.5 (61). In Brazil, the effect of malnutrition (underweight) on hospitalization for pneumonia was determined in a cohort of >5000 children aged 24–48 mo (45). Compared with children with weight-for-age *z* scores >0, all other groups had at least a 2-fold increased risk of admission.

Two case-control studies from Brazil used radiologically confirmed pneumonia as the outcome. In the city of Fortaleza (46), children with a weight-for-age *z* score < −2 had 4.6 times the risk of children with *z* scores >0, whereas in Porto Alegre (47), the same group had 4.8 times the risk of children with *z* scores > −1. Most studies, therefore, point to an association between anthropometric status and pneumonia or ALRI morbidity. Several studies documented a dose-response trend.

Lack of breast-feeding

The review on breast-feeding and pneumonia was limited to studies from developing countries or from low-income populations from developed countries. The reason for this restriction is that the effect of breast-feeding on morbidity and mortality seems to be modified by many socioeconomic and environmental factors (62), leading to a stronger protective effect of breast-feeding in developing (63) than in developed (64) areas of the world.

Association with pneumonia or ALRI mortality

Three studies provided information on ALRI mortality on the basis of breast-feeding status (**Table 4**). In Brazil, a population-based study compared data from infants who died of an ALRI with data from control subjects from the same community (65). Attempts were made to control reverse causality, self-selection, and confounding. Children who were not breast-fed were 3.6 times more likely to die of an ALRI than were those who received breast milk but no other milk. Infants receiving both breast and non-breast milk had an intermediate level of risk: 1.6. Relative risks did not appear to vary by age of the infants. In the Philippines, a community-based cohort study failed to show an association between breast-feeding and ALRI mortality. The relative risk for non-breast-fed children aged 12–23 mo was 1.05 (66). A case-control study from Tanzania, however, showed a relative risk of 1.7 for non-breast-fed children (67).

One study from Rwanda reported on the case fatality of infants with ALRIs who were hospitalized. Non-breast-fed children were twice as likely to die of pneumonia than were those who were breast-fed on admission (68).

Association with pneumonia or ALRI morbidity

Five studies provided data on the association between breast-feeding and hospitalization for pneumonia or ALRI. In China,

TABLE 4
Summary of community-based studies of mortality from acute lower respiratory infection (ALRI) and relative risk based on breast-feeding status in children from Brazil, the Philappines, and Tanzania

	Country and reference		
	Brazil (65)	Philippines (66)	Tanzania (67)
Cause of death	ALRI	ALRI	ALRI
Age (mo)	0.25–11	0–23	0–59
Design	Case-control	Cohort	Case-control
Sample size			
Number of children	254[1]	9942	1160[1]
Number of deaths	127	39	39
Breast-feeding status			
Breast-fed	1.0	1.0	1.0
Breast-fed + non-breast-fed	1.6 (0.7, 3.6)[2]	—	—
Non-breast-fed	3.6 (1.7, 7.5)	1.05	1.7
Breast-fed compared with non-breast-fed	2.7	—	—
Comments	Adjusted for age and confounders	—	—

[1] Number of children in the control group.
[2] 95% CI in parentheses.

18-mo-old children who had never been breast-fed were twice as likely to be admitted than were those who were breast-fed for any period of time (43). Native American infants who were never breast-fed were also 3 times more likely to be hospitalized because of an ALRI than were infants who were breast-fed for any period of time (69). In a case-control study from Argentina, infants breast-fed for <1 mo had 4.1 times the risk of being hospitalized with an ALRI than those breast-fed for a longer time (44). The 2 hospital-based case-control studies from Brazil of radiologically confirmed pneumonia also provided information on the protective effect of breast-feeding after several confounding factors were controlled for (46, 47). Relative to breast-fed children, the risks for partially breast-fed and non-breast-fed infants were, respectively, 1.3 and 1.7 in Fortaleza (46) and 1.5 and 2.6 in Porto Alegre (47).

Six studies provided information on breast-feeding in relation to pneumonia or ALRI outcomes other than mortality or hospitalization. In the above-mentioned Argentinian study (44), a second group of patients was made up of outpatients with ALRIs. These infants were 3.5 times less likely to be breast-fed for ≥1 mo than were the control infants. In American Samoa (70), 20 children with clinically diagnosed ALRI (of whom 13 were positive for respiratory syncytial virus) were compared with 60 outpatient control subjects. A reanalysis of these data by the authors of the present review, excluding control subjects who might have diseases associated with weaning (ie, infectious diseases), showed no effect of ever breast-feeding (relative risk: 0.9).

A weekly follow-up of 70 Indian infants—35 of whom were breast-fed for ≥2 mo (median: 9.5 mo) and 35 of whom were bottle-fed from the first week of life—indicated 2 episodes of radiologically confirmed pneumonia among the breast-fed group and 8 episodes among the bottle-fed group (71). In a study of Polynesian infants (72), retrospective information on signs associated with ALRIs was collected from the mothers. By 2 mo of age, episodes of ALRIs were twice as common in non-breast-fed than in breast-fed infants.

Two other studies adjusted for several confounding variables. In Peru, urban infants were visited 3 times weekly (73) and ALRI was diagnosed on the basis of history and auscultation; the percentage of days ill was calculated according to feeding pattern. In infants aged <6 mo, the relative risk for all non-breast-fed compared with breast-fed infants was 1.4; in infants aged >6 mo, the relative risk was 1.9. In a retrospective assessment of clinical records of Native American infants in the southwestern United Sates (74), pneumonia was 1.5 times more common among children who were never breast-fed than among those breast-fed throughout the first year. Most studies, therefore, point to a protective effect of breast-feeding against ALRI morbidity and mortality.

INTERRELATIONS BETWEEN NUTRITIONAL RISK FACTORS

The study of the effects of nutritional risk factors on ALRI or pneumonia is compounded by the complex interrelations between these factors. A simplified framework for these associations is shown in **Figure 1**. The age ranges at which these factors have been assumed to operate and the percentage distribution of pneumonia deaths are also shown (1).

Low birth weight was a major determinant of nutritional status later in life (75; RE Black, PW Yoon, LH Moulton, and S Becker, unpublished observations, 1993). SGA infants were particularly likely to grow poorly in postnatal life (76–81) and this negative effect remained significant even after confounding factors were controlled for (82, 83). Low birth weight was also observed to be associated with a shorter duration of breast-feeding (84). Breast-feeding and underweight might also be associated, but the direction of this association is likely modified by age and socioeconomic status (85, 86). Studies from developed countries and middle-income countries showed that breast-feeding is associated with slower weight gains after 3–4 mo of age (29, 87). Additionally, slow growth is an important reason why breast-feeding is stopped in some societies (87, 88).

The issue is further complicated by the possibility that pneumonia 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 be affected by pneumonia (45). Only one study, in the Philippines, was identified that

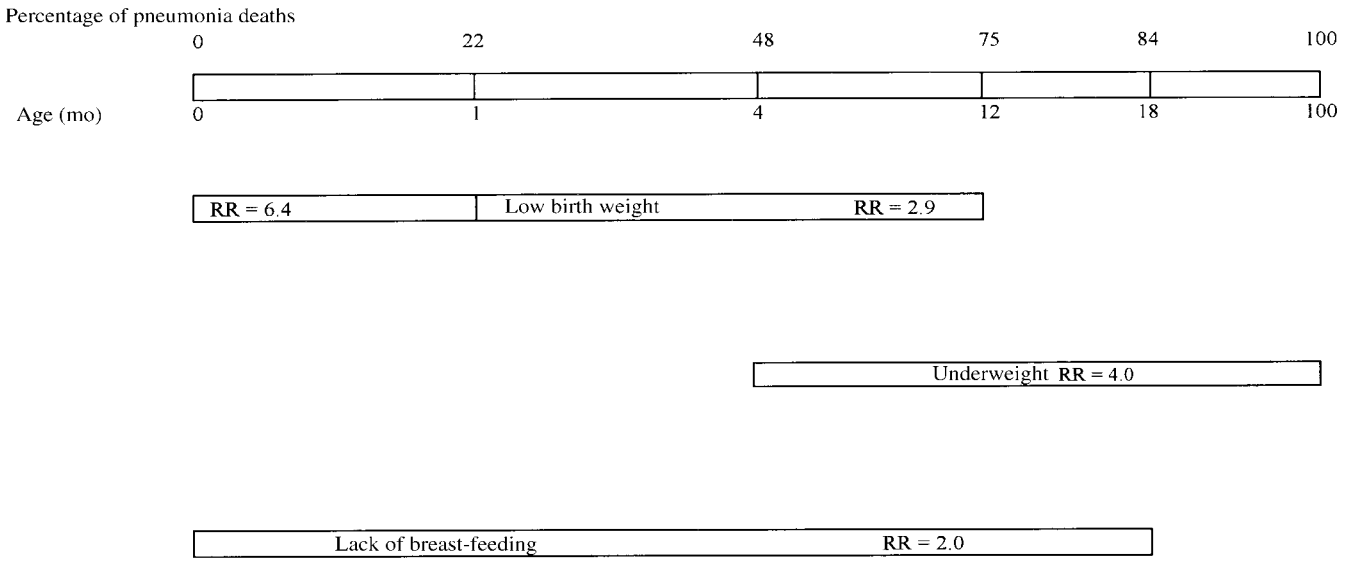

FIGURE 1. Relations between nutritional risk factors for pneumonia mortality and distribution of pneumonia deaths by age. RR, relative risk.

assessed the effect on ALRI mortality of the interactions between the different nutritional risk factors. The separate effects of the nutritional risk factors on ALRI mortality identified in this study were discussed in the sections above. Although there were no significant interactions between the 3 risk factors, the analyses suggested that the risk of mortality associated with not breast-feeding was higher for low-birth-weight babies than for those weighing ≥2500 g (66).

METHODOLOGIC LIMITATIONS

Evidence of the effects of birth weight, malnutrition (underweight), and breast-feeding on pneumonia or ALRI mortality or morbidity is based on nonexperimental studies. Experimental studies are prohibitively large and expensive because the disease outcome is rare and interventions for improving birth weight, malnutrition, or breast-feeding duration are only partially effective. Three main types of bias may affect the results of observational studies on nutritional factors and pneumonia or ALRI (89, 90).

1) Reverse causality bias: Breast-feeding and nutritional status may change as a consequence of the ALRI; this type of bias does not affect studies of the role of birth weight.
2) Confounding: Infants with the risk factor under study (eg, low birth weight) may differ from those without the risk factor in several other individual, maternal, and environmental characteristics that may also influence pneumonia. Low birth weight and malnutrition are usually associated with low socioeconomic status, as is pneumonia (91); this may lead to overestimation of the relative risk. Breast-feeding may be associated with either higher or lower socioeconomic status; this may lead to over- or underestimation, respectively, of the protection afforded by human milk.
3) Self-selection bias: This type of bias is particularly relevant to breast-feeding because illness or poor growth may lead to discontinuation of breast-feeding and once a child is weaned, relactation is unlikely.

These 3 types of bias may operate in the same or in opposite directions. The possibility of effect modification by other variables, such as socioeconomic and environmental factors, must also be considered because it may explain some of the inconsistencies observed between the results of different studies.

An additional problem affecting the study of pneumonia hospitalizations is admission bias, also known as Berkson bias (92). Children from low-income households may be preferentially admitted because home management of their condition would be difficult or impossible. Alternatively, when payment is required for hospitalization, the poorest children may be excluded.

The studies reviewed above range from simple investigations with unsophisticated designs and crude analyses to more complex studies taking into account the possibility of bias and confounding and attempting to control these in the design or analysis. It is reassuring that the associations between nutritional factors and pneumonia or ALRI were shown on the basis of different designs (cohort, case-control, and cross-sectional), different settings (communities, hospitals, and clinics), and different outcomes (morbidity, hospitalization, case fatality, and mortality).

In addition to the limitations of the studies reviewed, the review process itself had shortcomings that were impossible to avoid. These shortcomings included the limited number of existing studies, implying that pooled relative risks had to be based on as few as 3 studies, and the possibility of publication bias, ie, that negative studies failed to be published because of the lack of significant results.

ESTIMATED EFFECTS OF INTERVENTIONS

Estimation of the likely effect of nutritional interventions entailed the following steps.

1) Using recent data on the distribution of risk factors in many countries (Table 1), 3 different scenarios were defined: the lowest and the highest regional prevalences and the estimated prevalence for all developing countries. These prevalences are shown in the bottom rows of Table 1.
2) Relative risks of pneumonia mortality were estimated by pooling the results of the available studies (Tables 2–4), weighted by the number of deaths in each study. These represent global, not regional-specific, estimates.
3) Each risk factor was assumed to act on a particular age group (Figure 1). Its effect was then extrapolated to total pneumonia mortality for children aged <5 y by using the age distribution of these deaths (1).
4) On the basis of the above information, estimates were made of the proportion of pneumonia deaths among children aged <5 y that would be prevented with reductions of 10%, 20%, 40%, 60%, or 100% in the prevalence of each risk factor, as described in the introductory paper to the review series (1). No attempt was made to model the simultaneous effect of reductions in the 3 risk factors.

Reductions in the prevalence of low birth weight

Three scenarios were defined with low-birth-weight prevalences of 10%, 19%, and 34% (Table 1). The pooled relative risk of pneumonia death for low-birth-weight infants, calculated on the basis of the data in Table 2, was 2.9. Studies of overall mortality suggest that the relative risk for low-birth-weight infants during the neonatal period was 2.2 times greater than the relative risk during infancy (93). Because no studies of pneumonia mortality during the neonatal period were available, the relative risk of 2.9 was multiplied by 2.2 for use during the first month. On the basis of the data in Figure 1, it was assumed that the effect of birth weight would cease at 12 mo of age, thereby potentially affecting 75% of all pneumonia deaths in children aged <5 y.

Expected reductions in pneumonia mortality among children aged <5 y, according to different assumed percentages of low-birth-weight prevention, are shown in **Table 5**. For example, a

TABLE 5
Hypothetical reductions in pneumonia mortality that would be expected given different degrees of effectiveness of programs for improving birth weight according to the frequency of low birth weight (<2500 g)[1]

Assumed percentage of low-birth-weight birth prevented	Frequency of low birth weight		
	Low (10%)	Intermediate (19%)	High (34%)
		%	
10	1.6	2.5	3.5
20	3.2	5.0	7.0
40	6.5	10.1	14.0
60	9.7	15.1	21.0
100	16.1	25.1	35.0

[1] Assumed relative risks of mortality associated with low birth weight were 6.4 for deaths at age <1 mo and 2.9 for deaths at age 1–11 mo.

TABLE 6
Hypothetical reductions in pneumonia mortality that would be expected given different degrees of effectiveness of programs for improving nutritional status according to the frequency of underweight (weight-for-age < −2 *z* scores)[1]

Assumed percentage of underweight prevented	Frequency of underweight		
	Low (11%)	Intermediate (36%)	High (60%)
		%	
10	1.3	2.7	3.3
20	2.6	5.4	6.7
40	5.1	10.7	13.3
60	7.7	16.1	20.0
100	12.8	26.9	33.3

[1] Assumed relative risk of mortality of 4.0 for underweight children aged 4–59 mo.

40% reduction in low birth weight would prevent 6.5% of pneumonia deaths in a region with a low (10%) proportion of infants with a low birth weight, 10.1% of pneumonia deaths in a region with an intermediate (19%) proportion of infants with a low birth weight, and 14.0% of pneumonia deaths in a region with a high (34%) proportion of infants with a low birth weight. Total prevention (100%) is the etiologic fraction or population attributable risk, ie, the expected reduction in mortality if low birth weight were completely eliminated. Thus, 25% of all pneumonia deaths might be prevented if there were no infants born with low birth weight in developing countries.

Reducing the prevalence of protein-energy malnutrition (underweight)

Estimates of the effect of reductions in malnutrition (underweight) on pneumonia mortality are presented in **Table 6**. Because of the lack of consistency in the way the anthropometric categories in Table 3 are presented, it was not possible to calculate weighted averages of the relative risks. However, these studies suggest that one can assume a relative risk of 4 for children with weight-for-age *z* scores < −2, excluding the unexpected rise in mortality for the heaviest children in the Gambian (50) study. It was also assumed that malnutrition would exert its effect from 4 to 59 mo, an age range encompassing 51.8% of pneumonia deaths in children aged < 5 y. The lower age limit was set at 4 mo because this is the earliest recommended age for introduction of complementary feeding.

Elimination of malnutrition (underweight) in a region in which it is highly prevalent, such as southern Asia, would prevent ≈33% of childhood deaths from pneumonia, whereas in a region in which there is a low prevalence of malnutrition, such as Latin America, ≈13% of deaths would be prevented (Table 6). Of all pneumonia deaths in developing countries, just > 25% would be prevented by eradicating malnutrition (underweight). An intervention that prevented 40% of cases of malnutrition (underweight) would lead to a 5.1–13.3% reduction in deaths from pneumonia, depending on the region. If 6 mo had been used as the lower age limit for the effect of the nutritional interventions, the reductions would be ≈20% smaller.

It is important to stress that underweight is being used as a proxy for malnutrition because of the limitations of existing data, and that interventions against malnutrition—including improved diets, control of infections, and improved child care—are likely to also improve other anthropometric indicators such as height-for-age and weight-for-height as well as clinical and biological indicators of nutritional status. It is also important that the timing of nutritional interventions be considered because, to be most effective, these interventions should take place early in the child's life when growth impairments are more likely to be reversible (29).

Reducing the prevalence of not breast-feeding

The weighted average of the relative risks of pneumonia deaths due to lack of breast-feeding was 2.0 (Table 4). This value was used to calculate the expected effect on pneumonia deaths resulting from interventions that reduced rates of not breast-feeding by from 10% to 100%. The calculations shown in **Table 7** are presented according to the 3 different patterns of breast-feeding described earlier (low, intermediate, and high). As assumed in Figure 1, breast-feeding would affect pneumonia mortality up to 18 mo of age, by which time 84% of pneumonia deaths in children aged < 5 mo would have occurred.

To estimate effect, it was necessary to calculate the point prevalence of not breast-feeding of children aged < 18 mo of age in different regions. The data available (Table 1), however, only provided the prevalence of breast-feeding at 12–15 mo so that further assumptions had to be made about the shape of the curve for other ages between birth and 18 mo. Results of the World Health Organization's Collaborative Study on Breast-feeding (94), carried out in the 1970s in 9 countries, were used for this purpose. This study described in detail 3 patterns of breast-feeding duration. Pattern 1 (median duration: ≈3 mo) was typical in industrialized countries and urban elite groups from some developing countries. Pattern 2 (median duration: 10 mo) was observed in some poor urban groups as well as in some rural populations, and one-third of the children were still being breast-fed at 18 mo of age. Pattern 3 was typical in rural areas of Africa and southern Asia as well as in some poor urban populations; breast-feeding was universal up to 1 y of age and > 80% of the children were still being breast-fed at 18 mo of age. All regions with recent data were characterized between patterns 2 and 3 (Table 1). For each region, breast-feeding prevalences at each month of age up to 18 mo were therefore interpolated from these 2 curves, based on the available prevalence data at 12–15 mo of age. Prevalences of

TABLE 7
Hypothetical reductions in pneumonia mortality that would be expected given different degrees of effectiveness of programs for improving breast-feeding according to breast-feeding pattern[1]

	Frequency of breast-feeding		
	Low	Intermediate	High
		%	
Age			
0 to < 6 mo	0	7	19
6 to < 12 mo	2	16	40
12–18 mo	12	31	62
Assumed percentage of infants not breast-fed, prevented			
10	0.1	0.8	1.8
20	0.3	1.7	3.5
40	0.5	3.3	7.0
60	0.8	5.0	10.5
100	1.3	8.3	17.6

[1] Assumed relative risk of 2.0 for non-breast-fed children aged < 18 mo.

TABLE 8
Hypothetical reductions in pneumonia mortality according to different nutritional interventions, assuming a 40% reduction in prevalence of the risk factor

Region	Risk factor		
	Low birth weight	Malnutrition	Non-breast-feeding
		%	
Sub-Saharan Africa	9.0	10.0	0.5
Middle East and North Africa	6.5	7.0	4.3
South Asia	14.0	13.3	—
East Asia and the Pacific	6.9	9.1	2.2[1]
Latin America and the Caribbean	6.9	5.1	7.0
All developing countries	10.1	10.7	3.3

[1] Available data were not sufficient to separate the 2 Asian regions.

not breast-feeding from birth to 18 mo of age were given by the areas above the interpolated curves.

As might have been predicted, important reductions in pneumonia mortality would only occur in areas with high prevalences of not breast-feeding, where about one-fifth of deaths could be prevented, theoretically, if all children were breast-fed for ≥18 mo (Table 7). In areas such as Sub-Saharan Africa, where most children are breast-fed beyond 18 mo of age, promotion efforts would obviously have a limited effect. For all developing countries (intermediate duration in Table 7), only ≈8% of pneumonia deaths might be prevented by universal breast-feeding. A reduction of 40% in the prevalence of not breast-feeding in infants aged <18 mo of age would theoretically prevent 0.5–7.0% of pneumonia deaths.

Limitations of the effect estimates

The above estimates of effect may have been affected by some of the assumptions underlying the simulation models and they are discussed below.

1) It was necessary to define an age range for the effect of each risk factor; these age ranges were "best-guess" estimates because precise data on the duration of each effect were lacking.
2) There may be an interaction between the particular risk factor and age; for birth weight, a greater effect was assumed for neonates, but data on breast-feeding and malnutrition (underweight) were not sufficient for modeling risk according to age.
3) Three typical scenarios had to be defined regarding the prevalences of the risk factors; the data for describing these scenarios were not necessarily accurate and some populations certainly fell well outside the range used in the estimates, as may be the case for extremely short breast-feeding durations in some urban poor areas.
4) Data on relative risks were based on few studies and were assumed to be constant throughout the world, whereas their magnitude likely varied substantially from one setting to another. In fact, the differences observed in Tables 2–4 may be partly explained by this variability.
5) Risk factors were treated as dichotomous variables and there was likely a trend in risk. If this trend were ignored by combining values from the intermediate- and low-risk categories, the true effects might be underestimated.
6) The calculations of effect assumed a causal relation between the nutritional factors and pneumonia mortality. However, because the efficacy of nutritional interventions was not evaluated in most cases, it was not possible to conclude with certainty that elimination of these risk factors would necessarily reduce pneumonia mortality.
7) Despite these limitations, the simulation exercises were repeated after both the magnitude of relative risks and the prevalences of risk factors were varied. The results were proven to be fairly robust to changes in these assumptions.

Effect of interrelations between nutritional risk factors

The calculations of effect were carried out separately for each risk factor. However, as discussed previously and as illustrated in Figure 1, the risk factors are interrelated. This must be borne in mind when considering intervention approaches and possible associated effects. For example, the increased mortality of low-birth-weight babies during their first year of life may have been due to one or more of the following:

1) There was a direct risk associated with low birth weight.
2) Because of the negative association between low birth weight and duration of breast-feeding, there was an indirect risk associated with not breast-feeding.
3) The increased risk for low-birth-weight infants was partly or fully due to confounding variables, such as low socioeconomic status and poor maternal education, which are associated with the infrequent use of health care facilities and low immunization rates.
4) During the second 6 mo of life, there was a risk associated with undernutrition because of continued poor nutritional status.

Although interventions to prevent pneumonia and ALRIs involving one of the nutritional risk factors mentioned above may lead to changes in another of these risk factors, it is still valid to examine the potential effect of each risk factor separately. Care must be taken when considering concomitant interventions involving 2 or 3 nutritional risk factors; these interventions may have overlapping rather than additive (or multiplicative) effects because the same pathways may be operating. For example, the effects of an intervention to reduce the prevalence of low birth weight and another to reduce the prevalence of underweight should not be considered additive because some of the effect of the intervention to reduce the prevalence of low birth weight will be mediated through an improvement in nutritional status.

CONCLUSIONS

This review suggests that low birth weight, malnutrition (underweight), and lack of breast-feeding are important risk factors for pneumonia and ALRI morbidity and mortality in developing countries. The hypothetical effects on pneumonia mortality during childhood that might be expected from a 40% reduction in each of these 3 nutritional risk factors in different regions of the world,

based on the prevalence data from Table 1, are summarized in **Table 8**. It is not equally feasible to prevent each of the different risk factors in any given setting. Interventions aimed at preventing low birth weight in developing countries include improving maternal nutrition, preventing teenage pregnancies, improving maternal education, and controlling malaria and tobacco use (9); none of these interventions are particularly easy to implement. On the other hand, recent data suggest that malnutrition is being reduced effectively in most regions, exception in Sub-Saharan Africa (95). Likewise, breast-feeding rates are increasing in many countries, including developing countries (96, 97), and specific interventions appear to be effective in extending the prevalence and duration of lactation (98, 99).

For all developing countries, and for all regions except Latin America, interventions against malnutrition (underweight) and low birth weight appear to be potentially more promising for reducing pneumonia and ALRI mortality than does breast-feeding promotion. In Latin America, breast-feeding promotion and improvements in birth weight would hypothetically have equal effects, whereas interventions against malnutrition (underweight) are likely to have less of an effect. These findings emphasize the need for tailoring interventions to specific and even local conditions.

Nutritional interventions may have a sizeable effect in reducing pneumonia deaths. Other papers in this series commissioned by the World Health Organization are producing comparable sets of estimates for other preventable risk factors. Preliminary results (BR Kirkwood, unpublished observations, 1999) suggest that 2 highly effective preventive strategies are being developed— pneumococcal and respiratory syncytial virus vaccines—that might each prevent 10–20% of ALRI deaths. Two additional interventions—the measles vaccine and prevention of biomass (indoor) pollution—are considered to be intermediately effective and are proposed to theoretically prevent 5–15% of these deaths. All other potential interventions were estimated to have little or no effect (<7% of ALRI deaths prevented). These data, along with cost-effectiveness considerations, will help each region or country to prioritize preventive interventions against the major killer diseases of children aged <5 y. Additional benefits of reducing the prevalences of nutritional risk factors—relative to outcomes other than pneumonia and ALRI—should also be considered when designing preventive strategies.

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