Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions

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Abstract Inadequate nutrition and acute lower respiratory infection (ALRI) are overlapping and interrelated health problems affecting children in developing countries. Based on a critical review of randomized trials of the effect of nutritional interventions on ALRI morbidity and mortality, we concluded that: (1) zinc supplementation in zinc-deficient populations prevents about one-quarter of episodes of ALRI, which may translate into a modest reduction in ALRI mortality; (2) breastfeeding promotion reduces ALRI morbidity; (3) iron supplementation alone does not reduce ALRI incidence; and (4) vitamin A supplementation beyond the neonatal period does not reduce ALRI incidence or mortality. There was insufficient evidence regarding other potentially beneficial nutritional interventions. For strategies with a strong theoretical rationale and probable operational feasibility, rigorous trials with active clinical case-finding and adequate sample sizes should be undertaken. At present, a reduction in the burden of ALRI can be expected from the continued promotion of breastfeeding and scale-up of zinc supplementation or fortification strategies in target populations.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Estimation of the global burden of child mortality attributable to undernutrition has played a crucial role in refocusing the attention of researchers and policy-makers on the importance of optimal maternal–child nutrition for promoting neonatal, infant and child survival,[1–3] including the prevention of mortality due to severe acute lower respiratory infection (ALRI).[2–5] To advance the public health application of knowledge about the interrelated burdens of childhood ALRI and poor nutrition in developing countries, we have critically reviewed available data regarding the efficacy and effectiveness of specific nutritional interventions for reducing global childhood ALRI incidence, morbidity and ALRI-specific mortality.

Methods

Search strategy

This review included meta-analyses and large-scale randomized controlled trials of micronutrient supplementation, breastfeeding promotion, complementary food provision or counselling, and antenatal nutritional interventions, in which at least one childhood ALRI outcome (incidence, morbidity or mortality) was measured. Smaller studies or those with non-randomized designs were included where higher-quality data were unavailable. The literature review was based primarily on several systematic reviews that formed the evidence base for the *Lancet Undernutrition Series* (*LUS*) published earlier this year (available at: http://www.globalnutritionseries.org/web_appendices). To include articles published after completion of the systematic reviews, we searched PubMed (1990–January 2008) and reference lists of selected recent articles published on each topic. PubMed search terms included nutrient-specific keyword(s) and a string that broadly captured childhood ALRI-related articles ("ALRI" OR "ARI" OR "pneumonia" OR "lower respiratory tract infection" OR "lower respiratory infection" OR "bronchiolitis" OR "bronchopneumonia" OR "morbidity" OR "mortality") without age or language restrictions. Titles/abstracts were scanned for relevant interventional studies or key supportive articles, for which full-text articles were retrieved.

ALRI outcome definition

As there is no standard definition of childhood ALRI,[6] studies were included if they applied an outcome definition incorporating at least one specific lower respiratory tract sign reported by a caregiver or study personnel (fast or difficulty breathing, chest wall indrawing) and/or abnormal auscultatory findings (crackles/crepitations or bronchial breath sounds). Authors occasionally differentiated ALRI subtypes on the basis of wheeze versus crepitations/crackles (probable bronchiolitis versus pneumonia, respectively); however, viral diagnostics, isolation of pathogenic bacteria from a sterile fluid (i.e. blood culture, lung aspirate), or unequivocal radiographic findings (i.e. lobar consolidation or pleural effusion) were not documented in the reviewed trials.

Burden of disease

Estimates of the burden of ALRI attributable to selected nutritional factors were extracted from an analysis performed for *LUS*[3,7] [where "burden" refers to ALRI-related deaths and disability-adjusted life years (DALYs) lost], and are discussed in the context of

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Table 1. **Estimated ALRI deaths and disease burden in children under 5 years of age attributed to nutritional risk factors, in 2004**

Nutritional risk factor	Estimates[a]	UN region			All developing countries
		Africa[b]	Asia[b]	Latin America[b]	
Underweight[c]	**Deaths**	238 234 (24.3)	203 104 (28.1)	1 542 (3.1)	442 879 (25.3)
	DALYs x 10^3	8 335 (24.3)	7 262 (27.9)	65.69 (3.1)	15 662 (25.1)
Stunting[c]	**Deaths**	243 325 (24.9)	152 906 (21.1)	3 540 (7.0)	399 771 (22.8)
	DALYs x 10^3	8 510 (24.9)	5 479 (21.1)	150.0 (7.1)	14 136 (22.7)
IUGR-LBW[d,e]	**Deaths**	31 866 (11.9)	97 297 (22.0)	1 550 (5.2)	130 713 (17.6)
	DALYs x 10^3	1 092 (11.9)	3 330 (22.0)	53.97 (5.2)	4 475 (17.6)
Zinc deficiency[f]	**Deaths**	66 062 (6.8)	48 800 (6.7)	3 135 (6.2)	117 997 (6.7)
	DALYs x 10^3	2 350 (6.9)	1 840 (7.1)	159.2 (7.5)	4 349 (7.0)
Suboptimal breastfeeding (0–28 days of age)[e,g]	**Deaths**	115 193 (42.9)	198 128 (44.8)	14 394 (48.2)	327 714 (44.2)
	DALYs x 10^3	3 947 (42.9)	6 798 (44.8)	500.9 (48.2)	11 246 (44.3)
Suboptimal breastfeeding (> 1 month of age)[g]	**Deaths**	187 304 (19.1)	141 942 (19.6)	14 987 (29.8)	344 234 (19.6)
	DALYs x 10^3	6 536 (19.1)	5 036 (19.4)	578.3 (27.3)	12 150 (19.5)

ALRI, acute lower respiratory infection; DALYs, disability-adjusted life years; IUGR, intrauterine growth restriction; LBW, low birth weight.

[a] Values in parentheses are percentage of all under-five ALRI deaths or DALYs. Because nutritional risk factors are overlapping and often correlated, attributable fractions should not be directly summed across risk factors.

[b] UN region composition available at: http://unstats.un.org/unsd/methods/m49/m49regin.htm

[c] In these analyses, risks of children considered underweight [weight-for-age z score < -1 standard deviations (SD) on the WHO growth curve] or stunted (height-for-age z score < -1 SD) were compared with those classified as "normal" (> -1 SD on the respective growth curve).

[d] Risks among term neonates weighing between 1500 g and 2499 g were compared with those of birth weight ≥ 2500 g. Neonates weighing < 1500 g were excluded from the analysis because of the strong likelihood of preterm birth.

[e] Estimates for IUGR–LBW and suboptimal breastfeeding in the newborn period only apply to neonates 0–28 days of age and were based on the relative risk of the aggregate outcome "perinatal infections". Absolute numbers of deaths and DALYs were calculated by assuming that 80% of perinatal infections are ALRIs.[81]

[f] Estimates were applied to children aged 6–59 months of age, since the efficacy of zinc supplementation has not been demonstrated in infants < 6 months of age (see text).

[g] For the 0–5 month age range, infants not exclusively breastfed were compared with those exclusively breastfed. For infants 6–23 months of age, those receiving any breast milk were compared with those receiving no breast milk.

related interventions. The ALRI-specific attributable fractions (Table 1) were not reported in *LUS*.

Results

Breastfeeding promotion

A lack of exclusive breastfeeding in the first half of infancy is a risk factor for ALRI incidence, morbidity and death.[3,5] In the *LUS* analysis,[3] approximately 44% of infection-related neonatal deaths/DALYs (including those due to ALRI) and 20% of postnatal ALRI deaths/DALYs lost were attributed to suboptimal breastfeeding (Table 1). A causal effect of breastfeeding is plausible given the maternal–infant transfer of innate immune effectors (e.g. lactoferrin, lysozyme, secretory IgA, leukocytes)[8] and influences of breast milk on immune-system maturation.[9] Breastfeeding may enhance the antibody response to important pneumonia-causing pathogens (e.g. pneumococci, *Haemophilus influenzae*),[10] but the specific mechanisms by which breastfeeding ameliorates ALRI resistance are less obvious than those that underlie diarrhoea risk reduction.

Eliminating the fraction of the ALRI burden due to suboptimal breastfeeding relies on effective breastfeeding promotion and education; however, few studies have quantified the effect of breastfeeding programmes on ALRI risk reduction.[11] Four studies that reported respiratory outcomes did not distinguish upper and lower respiratory tract infections.[12–15] PROBIT, a large cluster-randomized trial of breastfeeding promotion (based on the WHO baby-friendly hospital initiative) in Belarus,[16] was the only study from which an effect of breastfeeding promotion on ALRI outcomes could be inferred. Success of the promotion efforts was evidenced by increased breastfeeding continuation and a significant 40% decrease in diarrhoea incidence in the intervention group. The trial showed a 15% decrease in respiratory-disease-related hospitalizations (presumably due to ALRI), but despite the large sample size (n = 17 046) and high event rate (20.5% of infants in control arm had ≥ 1 respiratory disease hospitalization), the reported confidence intervals crossed the null after adjustment for confounders and design effects (Table 2).

The overall benefits of breastfeeding promotion are now widely accepted, and it seems doubtful that future similar trials will be deemed ethical or be more rigorously conducted than PROBIT, even though the magnitude of the effect might differ across populations or alternative behaviour-change strategies. Therefore, we concluded that the benefit of breastfeeding promotion on ALRI morbidity in PROBIT was consistent with observational data, and alongside the other known health benefits of breastfeeding (e.g. diarrhoea prevention, lactational amenorrhoea), reinforces the need to continue to support breastfeeding promotion policies and programmes in resource-poor settings.

Table 2. **Estimated effects of selected nutritional interventions on ALRI incidence, morbidity or mortality**

Nutritional intervention	ALRI outcome	Effect size[a]	Source	Comments
Vitamin A supplementation	Incidence	0.95 (0.89–1.01)	Meta-analysis of five trials[23]	Recent systematic review confirmed the null effects on incidence and mortality[24]
	Mortality	0.98 (0.75–1.28)	Meta-analysis of five trials[23]	
Zinc supplementation	Incidence	0.80 (0.70–0.92)	Meta-analysis of four trials[44]	Included trials of supplementation for at least 3 months
	Mortality	0.85 (0.65–1.11)	Unpublished meta-analysis of three trials[3]	Effect size (95% CI) in individual trials: Bangladesh – cannot calculate relative rate [10 deaths in placebo group (*n* = 812) and 0 in zinc arm (*n* = 809)]; Nepal 0.90 (0.64–1.26); United Republic of Tanzania 0.88 (0.5–1.5)
Breastfeeding promotion	Hospitalization	0.85 (0.57–1.27)	Single large trial in Belarus[16]	Outcome ascertained by maternal recall
Iron supplementation	Incidence	0.97 (0.83–1.23)	Meta-analysis of eight trials[31]	Trials published since the meta-analysis have confirmed the null effect[32]
Iron and folic acid supplementation	Incidence	0.92 (0.7–1.09)	Single large trial in Nepal[34]	In a companion trial conducted in a malaria-endemic region (Pemba), iron-folic acid (with or without zinc) significantly increased the risk of death due to non-malarial infections (HR 1.61, 95% CI: 1.03–2.52), although the specific effect on ALRI mortality was not estimated[58]
	Mortality	0·88 (0.50–1.46)	Single large trial in Nepal[34]	
Iron, folic acid and zinc supplementation	Incidence	0.91 (0.76–1.08)	Single large trial in Nepal[34]	
	Mortality	0.80 (0.45–1.34)	Single large trial in Nepal[34]	
Multiple micronutrient-fortified milk	Incidence	0.74 (0.57–0.97)	Single trial in India[60]	Experimental milk contained higher concentrations of vitamins A, E, C, iron, zinc, selenium and copper than the control milk

ALRI, acute lower respiratory infection; CI, confidence interval; HR, hazard ratio.

[a] Relative risk or relative rate, odds ratio or hazard ratio, compared with placebo. Values in parentheses are 95% CI.

Complementary food supplementation or counselling

A large body of literature has established strong links between malnutrition, immune dysfunction and infectious diseases.[4,17,18] The *LUS* analysis estimated that one-quarter of under-five deaths and DALYs lost were attributable to undernutrition (represented by underweight or stunting) and could theoretically be prevented by dietary interventions that normalize anthropometric indices in early childhood (Table 1). These estimates suggest that in addition to an optimal prenatal environment and breastfeeding practices, improvements in the density, diversity and quality of complementary foods may reduce the risk of ALRI incidence or mortality. However, there is a surprising lack of intervention research addressing this question. We found only one study that measured the impact of complementary feeding education or food supplements on ALRI incidence,[19] but the low statistical power limited interpretation of its null findings. There were also few published studies of the effect of comprehensive community-based nutrition programmes on ALRI outcomes. Two studies from Viet Nam reported ALRI outcomes,[20,21] but interpretation of their findings was limited by methodological weaknesses (i.e. small sample size, quasi- or non-randomized designs, non-specific outcome ascertainment and incomplete presentation of findings).

Single micronutrient interventions

Vitamin A

Vitamin A is involved in immune function and respiratory epithelial cell differentiation,[22] yet the impact of high-dose supplementation on under-five mortality cannot be accounted for by its effects on ALRI outcomes. A rigorous meta-analysis of five large trials concluded that routine vitamin A supplementation did not affect ALRI incidence or mortality (Table 2),[23] inferences that have not changed over time.[24] Estimates of the effect of routine early neonatal vitamin A supplementation remain imprecise and inconsistent,[25–27] and await clarification by as-yet unpublished findings from a large study of early neonatal vitamin A supplementation in Bangladesh. In the treatment setting, infants and children with non-measles-related ALRI do not benefit from adjunctive high-dose vitamin A administration.[24,28,29]

Iron and folic acid

The interplay between iron and infection has been the subject of enduring debate in nutritional immunology, primarily because iron deficiency impairs components of cell-mediated immunity but can also inhibit the growth of bacterial pathogens.[30] Nonetheless, the epidemiological data regarding the effect of iron supplementation on ALRI incidence quite convincingly reveal its effect to be null (Table 2).[31,32]

A recent prospective study in India found serum folate status to be independently associated with the risk of ALRI,[33] but we did not identify any trials assessing the effect of folic acid supplementation alone on ALRI outcomes. However, in a large trial in Nepal, the combination of daily iron and folic acid (IFA) supplementation modestly reduced ALRI incidence and mortality compared to placebo (Table 2).[34] Given the lack of effect of iron supplementation alone and biological mechanisms by which folates may be implicated in immune function,[35] the benefit may have been attributable to improvements in folate status; however, the wide confidence intervals that included the null indicate that the observation requires confirmation.

Vitamin D and calcium

Nutritional rickets, caused by dietary deficiencies of vitamin D and/or calcium, has been strongly associated with severe ALRI in hospitalized children in some settings.[36,37] Case-control studies in developing countries have found low vitamin D status to be associated with the risk of ALRI in Indian children[38] and Turkish neonates,[39] but not with the risk of viral bronchiolitis in young Canadian children.[40] The active form of vitamin D affects a variety of immune functions,[35] including the synthesis of endogenous antimicrobial peptides.[41] However, interventional trials of the effect of maternal or infant supplementation with vitamin D, with or without calcium, on the incidence of infant ALRI have not yet been reported.

Zinc

Infant and child zinc supplementation has been intensively studied because dietary zinc deficiency is highly prevalent in developing countries[42] and zinc is involved in the maintenance of skin and mucous membranes, leukocyte function and cytokine expression.[43] A recent meta-analysis of randomized efficacy trials conducted in South Asia confirmed that routine oral daily or weekly zinc supplementation for at least 3 months significantly reduces the incidence of childhood ALRI (Table 2),[44] an effect that may be specific to non-wheezy ALRI (i.e. cases that are more likely to be pneumonia than viral bronchiolitis);[45] this effect appears to increase with greater severity of disease,[45] and was not evident in infants less than 6 months of age.[46]

Several studies not included in the published meta-analysis have shown null or non-significant effects of routine zinc on ALRI incidence in Latin America,[47,48] South Africa[49] and Nepal.[50] Although it is possible that the heterogeneity is due to characteristics of the study populations, it is notable that ALRI was ascertained on the basis of either maternal report or WHO criteria alone (elevated respiratory rate) in these null studies. In an updated meta-analysis of routine zinc supplementation trials, we found that incidence of ALRI was substantially reduced by zinc supplementation when the diagnosis was established by active prospective case-finding and a clinical exam that included pulmonary auscultation (relative rate, RR 0.78; 95% confidence interval, CI: 0.68–0.91; based on three of the four trials included in the published meta-analysis), whereas the effect was absent in trials that ascertained ALRI on the basis of either elevated respiratory rate alone (RR 0.99; 95% CI: 0.89–1.09) or caregiver recall of ALRI signs or symptoms (RR 1.02; 95% CI: 0.97–1.09) (Roth & Black, unpublished findings). Null findings may thus be biased due to non-specific outcome definitions[51] or “contamination” by episodes of upper respiratory tract infections.

If the magnitude of the benefit of zinc prophylaxis on ALRI incidence is limited to bacterial pneumonia or increases with greater disease severity,[45] a large relative decrease in ALRI-specific mortality would be expected; however, the estimated reduction upon pooling available data for children aged 1–59 months was only 15% (Table 2).[3] The discrepancy could be purely methodological (i.e. misclassification of causes of death), or perhaps reflects the failure of zinc to prevent disease in those children with the highest baseline risk of ALRI fatality (i.e. young infants). An alternative explanation is that zinc supplements may increase the case fatality rate in a small subset of children who acquire ALRIs of certain bacterial etiologies, as suggested by Coles et al. who hypothesized that specific zinc–pathogen interactions may deleteriously alter the host response in severe pneumonia.[52]

In summary, routine zinc supplementation to young children prevents about one-quarter of ALRI cases, which likely translates into a modest reduction in ALRI-related mortality. Scaling-up zinc supplementation to all regions with high prevalence of zinc deficiency could avert an estimated 7% of ALRI deaths and DALYs lost (Table 1).

In contrast to its prophylactic effect, there is no strong evidence of a benefit of zinc supplementation in the treatment context. Of three published randomized controlled trials evaluating zinc supplementation as adjunctive treatment in children presenting to hospital with ALRIs, one found a relative reduction in the duration of severe disease equivalent to about one day in hospital,[53] one study showed no benefit,[54] and a third study found that zinc caused a slightly reduced duration of fever and severe illness in boys, but not in girls.[55]

Multiple micronutrient interventions

Children in resource-poor settings often exhibit concurrent deficiencies of multiple micronutrients,[56] many of which function as cofactors or regulatory molecules in immune or inflammatory cascades (e.g. vitamins C, D, selenium).[35] Therefore, multiple micronutrient supplements may theoretically augment the effect of zinc on infectious disease resistance in resource-poor settings.

Addition of zinc to IFA supplementation

Routine infant/child IFA supplementation is currently recommended by WHO for regions with a high prevalence of iron-deficiency anaemia,[57] so it is of primary interest to know whether including zinc in a daily IFA regimen would reduce ALRI-associated morbidity or mortality. In a large factorial trial in Nepal, zinc minimally strengthened the effect of IFA on ALRI incidence and mortality relative to placebo (Table 2);[34] however, in the United Republic of Tanzania, the addition of zinc to IFA did not notably alter the risk of non-malarial infection-related adverse events (hospitalization or death) compared to placebo.[58] In a third study involving children aged 1–23 months in Delhi (n = 94 359), but in which a placebo arm was not included, adding zinc to routine daily IFA supplementation for up to 12 months did not significantly impact the risk of ALRI-related hospitalizations (RR 1.09; 95% CI: 0.94–1.25) compared to IFA alone.[59] In the latter trial, adding zinc was associated with reduced ALRI-related mortality (RR 0.73; 95% CI: 0.55–0.96; confidence limits unadjusted for the likely negligible effect of intrahousehold clustering), but the authors emphasized that overall mortality and the distribution of causes of death did not significantly differ between the IFA + zinc and IFA-treatment arms, suggesting this estimate should be interpreted with caution.

Multiple micronutrient supplements or fortificants

In a recent trial involving children aged 1–3 years in Delhi, India, a commercial milk powder fortified with additional vitamins A, C, E, iron, zinc (7.8 mg more than control group), selenium and copper led to a significant reduction in the incidence of clinically confirmed ALRI compared to the standard milk powder (Table 2).[60] Three other studies of multiple micronutrient supplements or fortificants had null results but were inadequately powered to detect moderate differences in ALRI incidence between treatment and control arms.[49,61,62]

In summary, the only multiple micronutrient intervention with a clear benefit on ALRI incidence or mortality was a milk powder fortified with zinc and six other micronutrients, but the effect size was comparable to that achieved by supplementation with zinc alone. Null findings in trials using non-food-based supplements that combined iron and zinc (i.e. attenuation of the expected zinc effect) may be partially attributable to the inhibitory effects of supplemental iron on absorption of zinc supplements.[63] Where food fortification is not feasible, a proposed approach to avoid intraintestinal mineral interactions is alternate-day zinc and iron supplementation.

Antenatal nutritional interventions

Low birth weight (LBW: birth weight < 2500 g) in term-infants is a surrogate marker of intrauterine growth restriction (IUGR) and an established epidemiological risk factor for ALRI incidence and hospitalization.[5] In the *LUS* analysis,[3] an estimated 17.6% of ALRI-related deaths and DALYs lost in term neonates (birth to 1 month of age) were attributable to LBW (Table 1).

The biological plausibility of the association between LBW and respiratory morbidity is supported by observations of impaired immunocompetence in infants born small-for-gestational[64–66] and the association of fetal growth restriction with structural alterations that may affect lung anatomy and function.[67–69] However, the causal nature of the association between LBW and ALRI is complex, particularly given that LBW represents the cumulative and aggregative effect of a range of nutritional and non-nutritional prenatal exposures.[70,71] Wilcox[72] and others[73] have persuasively questioned the use of LBW as a biomarker of the effect of antenatal exposures on neonatal morbidity and mortality, suggesting it is of more practical relevance to directly consider the modifiable maternal nutritional and dietary factors that are hypothesized to "programme" the fetal immune system.[9] Unfortunately, at present there are insufficient data to recommend antenatal nutritional interventions on the basis of their effects on infant ALRI outcomes. Trials of antenatal zinc,[74] multiple micronutrients[75] and vitamin A[76] did not have statistically significant impacts, but may have lacked sufficient power to demonstrate subtle, but potentially meaningful, effects.

Discussion

Observational evidence of an association between inadequate growth and the risk of experiencing or dying from ALRI in early childhood is strong and consistent,[2,3,5] suggesting there could be a potentially large impact of nutritional interventions on ALRI morbidity and mortality. However, evidence-based public health policy and practice ideally rely on efficacy and effectiveness data from well conducted trials.

Based on a critical review of the literature, we were able to reach conclusions about only a few of the potential nutritional interventions. First, oral zinc supplementation in children > 6 months of age was the only intervention for which high-quality trial evidence has demonstrated a significant reduction in childhood ALRI incidence and a trend towards a reduction in mortality. Important feasibility issues remain to be resolved, including attenuation of the effects by concurrent iron supplementation, potential effects on case-fatality due to ALRIs of specific etiologies, and the optimal mode of community-based delivery (i.e. fortification, supplementation). Large-scale cluster-randomized effectiveness trials in Bangladesh[77] and India[78] have demonstrated that programmatic implementation of the WHO recommendation to incorporate a two-week course of zinc supplementation into case management algorithms for children with acute gastroenteritis has the added benefit of reducing the burden of severe ALRI in the community. Scale-up of this approach is therefore suggested as a feasible and effective strategy for improving zinc status in at-risk populations.

Second, despite the limited available trial data, there should be little hesitation in including ALRI risk reduction in the list of benefits of exclusive breastfeeding, given the strength and consistency of observational findings and the evidence of a modest reduction in ALRI-related hospitalizations in the only rigorous trial of breastfeeding promotion. Third, there was strong evidence that vitamin A supplementation (after the neonatal period), or iron supplementation alone, do not reduce the risk of ALRI incidence or mortality.

We found insufficient evidence of efficacy of other specific nutritional interventions for ALRI risk reduction. However, the strength of the association between anthropometric indices and ALRI mortality suggests that a range of interventions (not limited to dietary changes) that reduce the prevalence of LBW, underweight or stunting[79] would be expected to consequentially diminish the burden of ALRI. Rigorous assessments of the effect on ALRI outcomes of improved feeding practices or comprehensive nutrition education programmes should be considered, since multicomponent interventions are most likely to improve overall nutritional status. In future trials, two major methodological issues need to be addressed. First, non-specific outcome ascertainment based on maternal recall or WHO criteria alone may nullify true effects, strongly suggesting that lower respiratory tract morbidity be prospectively assessed by active case-finding and clinical criteria. Second, trials need to have adequate power to detect meaningful intergroup differences in ALRI incidence. Even if a relatively large effect size is expected (e.g. hazard ratio = 0.7), over 800 child-years of follow-up are required in each group (e.g. 800 children treated and monitored for one year), under optimal conditions of a high baseline incidence rate (i.e. 0.3 episodes per child-year), minimal loss to follow-up, and conventional statistical assumptions (i.e.

5% risk of type I error, 80% power). Sufficient sample sizes are of particular importance in trials of multiple micronutrient supplements, food fortification or integrated nutrition programmes, because these trials cannot readily be pooled post-hoc due to non-uniformity of the interventions. The logistical, ethical and financial challenges of conducting large trials with active surveillance emphasizes the importance of building a strong scientific rationale for testing a specific nutritional intervention,[80] based on translational research (e.g. effects on immune function biomarkers), preliminary dose-finding trials (e.g. efficacy in improving biomarkers of micronutrient status), and qualitative feasibility studies (i.e. to establish that the intervention is acceptable to communities and could reasonably be scaled-up if shown to be effective).

Conclusion

As with other interventions to prevent ALRI discussed elsewhere in this issue of the *Bulletin*, nutritional interventions such as micronutrient supplementation or breastfeeding promotion can have a broad range of child health benefits.[79] Implementation and rigorous evaluation of multicomponent nutritional intervention programmes should be a high priority – to reduce the incidence and mortality associated with severe ALRI, as well as the overall disease burden that persists among children in developing countries. ■

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Competing interests: None declared.

Résumé

Infections aigues des voies respiratoires inférieures chez l'enfant : possibilités de réduire la charge mondiale d'ALRI par des interventions nutritionnelles

La malnutrition et les infections aiguës des voies respiratoires inférieures (ALRI) sont des problèmes sanitaires interdépendants et imbriqués, qui affectent les enfants des pays en développement. Sur la base d'une analyse critique d'essais randomisés étudiant les effets d'interventions nutritionnelles sur la morbidité et la mortalité par ALRI, nous avons conclu que (1) la supplémentation en zinc des populations déficitaires en ce métal prévient environ un quart des épisodes d'ALRI, d'où éventuellement une diminution modeste de la mortalité associée ; (2) la promotion de l'allaitement fait baisser la morbidité due aux ALRI ; (3) la supplémentation en fer ne suffit pas seule à réduire l'incidence des ALRI ; et (4) la supplémentation en vitamine A au-delà de la période néonatale ne diminue ni l'incidence des ALRI, ni la mortalité qui leur est imputable. Les éléments disponibles à propos des autres interventions nutritionnelles potentiellement bénéfiques étaient insuffisants. Concernant les stratégies bénéficiant d'une justification théorique solide et probablement réalisables sur le plan opérationnel, il conviendrait d'entreprendre des essais rigoureux, avec une recherche des cas active et des échantillons de taille appropriée. On pourrait à présent s'attendre à une baisse de la charge d'ALRI comme conséquence de la promotion permanente de l'allaitement et du passage à l'échelle supérieure des stratégies de supplémentation ou d'enrichissement en zinc, menées parmi les populations cibles.

Resumen

Infecciones agudas de las vías respiratorias inferiores en la niñez: oportunidades para reducir la carga mundial de morbilidad mediante intervenciones nutricionales

Problemas interrelacionados que se solapan, la mala nutrición y las infecciones agudas de las vías respiratorias inferiores (IAVRI) afectan a los niños de los países en desarrollo. A partir de una reseña crítica de los ensayos aleatorizados sobre el efecto de las intervenciones nutricionales en la morbilidad y mortalidad por IAVRI, llegamos a la conclusión de que: (1) la administración de suplementos de zinc en las poblaciones con déficit de ese elemento previene aproximadamente una cuarta parte de los episodios de IAVRI, lo que puede traducirse en una reducción moderada de la mortalidad por IAVRI; (2) el fomento de la lactancia materna reduce la morbilidad por IAVRI; (3) la administración de suplementos de hierro por sí sola no reduce la incidencia de IAVRI; y (4) los suplementos de vitamina A superado el periodo neonatal no reducen la incidencia de IAVRI ni la mortalidad por esa causa. La evidencia respecto a otras intervenciones nutricionales potencialmente beneficiosas era insuficiente. Cuando las estrategias tengan una justificación teórica sólida y probabilidades de ser operacionalmente viables, deberían emprenderse ensayos rigurosos con procedimientos de búsqueda activa de casos clínicos y tamaños de muestra adecuados. Por el momento, cabe prever una reducción de la carga de IAVRI como consecuencia del fomento continuo de la lactancia materna y de la extensión masiva de las estrategias de uso de zinc como suplemento o como enriquecimiento de los alimentos en las poblaciones objetivo.

ملخص

التهابات الجهاز التنفسي السفلي لدى الأطفال: فرص خفض العبء المرضي العالمي بالتدخلات التغذوية

ثـمَّة علاقة متبادلة ومتـراكبة بين قصور التغذية والتهاب الجهاز التنفسي السفلي وبين المشكلات الصحية التي تصيب الأطفال في البلدان النامية. وبناءً على مراجعة دقيقة للتجارب المعشاة التي أجريت على تأثير التدخلات التغذوية على المراضة والوفيات الناجمة عن التهاب الجهاز التنفسي السفلي، وصلنا إلى الاستنتاجات التالية: (1) إن إضافة مكملات الزنك إلى غذاء السكان الذين يعانون من عوز الزنك يقي ما يقرب من ربع السكان من هجمات التهاب الجهاز التنفسي السفلي، والذي قد يظهر في شكل انخفاض طفيف في الوفيات الناجمة عن التهاب الجهاز التنفسي السفلي. (2) تشجيع وتعزيز الرضاعة من الثدي يقلص المراضة الناجمة عن التهاب الجهاز التنفسي السفلي. (3) إضافة مكملات الحديد لوحده لا تقلص حدوث التهاب الجهاز التنفسي السفلي. (4) إضافة مكملات الفيتامين Aبعد مضي الدورة الوليدية لا يقلص حدوث التهاب الجهاز التنفسي السفلي أو الوفيات الناجمة عنه. وهناك بينات يعتد بها إحصائياً حول المنافع المحتملة للتدخلات التغذوية. وينبغي إجراء تجارب ذات مصداقية عالية وتحر فعال للحالات السريرية مع توفير عينات ذات أحجام مناسبة وذلك من أجل وضع استـراتيجيات ترتكز على أساس نظري قوي وتكون ممكنة التطبيق من الناحية العملية. ويمكن في الوقت الحاضر توقع حدوث نقص في العبء المرضي الناجم عن التهاب الجهاز التنفسي السفلي بفعل التعزيز المتواصل للرضاعة من الثدي وبفعل النهوض باستراتيجية إضافة مكملات الزنك لدى السكان المستهدفين.

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