The Interaction of Acute Respiratory Infections, Measles, and Nutritional Status

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Nutrition and infection bear the same close relationship to each other as the interdependent covariables in nature such as space and time, and mass and energy. We discuss the intricate web of relationships between nutrition, acute respiratory infections, and measles in this chapter, and conclude with suggestions for further research.

IMPACT OF ACUTE RESPIRATORY INFECTIONS ON NUTRITIONAL STATUS

Protein-Energy Malnutrition

In a longitudinal health and nutrition survey of 3,000 children (birth to 2 years of age) conducted in the Philippines, length and morbidity data were collected bimonthly over a 2-year period (1). Stunting (height for age > 2 SD below the World Health Organization [WHO] median) was found in 65% of the children, and the study showed that the likelihood of stunting was significantly increased by febrile respiratory infections. In a community-based study of 106 Kenyan children 18 to 25 months of age, being underweight (weight for age < 80% of expected) and stunted (height for age < 90% of expected) was positively associated with acute lower respiratory tract infections (2).

Vitamin A

Common acute respiratory infections have been noted to reduce vitamin A levels in various settings. Sommer et al. confirmed this in their prospective, community-based programs in Indonesia (3). Among rural preschool children followed-up for 18 months, those with respiratory disease were more than twice as likely to develop x-
rhopthalmia as the children who did not have respiratory disease (p < 0.05). This association was not detected in those under 3 years of age; among those above age 3 years, the relative risk ranged between 3.3 and 6.2 for different age groups. Protein-energy malnutrition did not influence this risk. Among hospital cases, acute respiratory infections often occurred together with xerophthalmia; the more severe the latter, the more frequent the respiratory infections. Shenai et al. have reported falling levels of vitamin A among low birthweight babies in the United States who have repeated lower respiratory tract infections.

A recent study from Bangladesh examined the impact of vitamin A supplementation (15 mg each dose) given at the time of primary immunization at 6 weeks, 10 weeks, and 14 weeks after birth (4). Despite supplementation, after 3 months, 61% of 33 children remained vitamin A deficient by the relative dose-response test. Acute respiratory infection episodes were more frequent in those who remained deficient, despite vitamin A supplementation; the odds ratio for postdose vitamin A deficiency in supplemented infants was 5.4 (95% confidence interval (CI) 0.33 to 87.3; p = 0.22) for acute respiratory infections. The authors interpret these results to mean that frequent respiratory infections reduced vitamin A levels despite supplementation.

IMPACT OF MEASLES ON NUTRITIONAL STATUS

Protein-Energy Malnutrition

Several studies have shown that measles has a negative effect on nutritional state (5,6). Accompanying fever increases the body’s need for protein and energy during a time of decreased food intake. Also seen is an increase in protein loss from the gut—it is estimated that up to 20% of protein intake is lost in the stools. A diet that was just adequate to allow growth before the illness may be inadequate to allow optimal growth during the recovery phase.

In a community study in Haiti (7) of 595 infants 6 to 12 months of age, it was shown that those infants who had serologic evidence of previous measles infection had a significantly worse nutritional status than those who had no evidence of previous measles (p < 0.01).

Vitamin A

The best evidence that an attack of measles profoundly affects vitamin A metabolism is the well-documented association between measles and xerophthalmia in many countries throughout the world. An acute measles episode produces a transient reduction in serum vitamin A, which recovers without supplementation once the disease is over (8-11). For example, in an Indian community-based study of 1,544 children under the age of 5 years who were prospectively followed, 318 cases of measles were seen and vitamin A concentrations measured (8). There was no supplementation with vitamin A. Serum vitamin A was lower during measles and became normal by 8 weeks after recovery. Retinol concentrations were lowest in those children with
measles who also had the most severe grade of protein-energy malnutrition. The decrease in serum vitamin A during measles has been found in both developing (8–11) and industrialized countries (12). The reasons for this decline are probably multifactorial; high metabolic demand caused by widespread infection, exuberant immune responses, and vigorous catabolism are likely to be critical. Measles results both in early death and in delayed mortality. The longer term consequences of measles on the gastrointestinal tract and respiratory system can cause a gradual deterioration in vitamin A status.

**IMPACT OF NUTRITIONAL STATUS ON ACUTE RESPIRATORY INFECTIONS**

**Protein-Energy Malnutrition**

Hospital-based studies conducted in Nigeria (13) and India (14) showed that malnutrition was a strong predictor of length of hospital stay and death from acute respiratory infections. The problem with hospital studies is that measurements are made at the time of diagnosis, therefore making it difficult to ascertain whether malnutrition is an acute response to infection or a pre-existing risk factor. Community-based, prospective studies are more helpful. A study in Bangladesh of 965 children (0 to 5 years of age), followed-up once a month for 4 months, showed that, among children who developed acute respiratory infections, 63% were malnourished compared with 37% among the noninfected controls (15). A similar study in Burkina Faso showed that malnutrition was a significant risk factor for developing acute respiratory infections. Two studies in India (16,17) that followed children under 5 years of age for 1 year found that malnourished children had a significantly greater risk of acute respiratory infection.

In a 10-month prospective study of children in Kenya (6 months to 10 years of age), nutritional status and cellular immunocompetence, determined by delayed-type hypersensitivity (DTH), were related to individual attack rates of acute respiratory infection (18). When examined separately, both nutritional status and DTH responsiveness were significant predictors of individual attack rates of acute respiratory infection; however, when the effects were simultaneously tested, only DTH responsiveness was significant. These results indicate that the effect of nutritional status on the occurrence of acute respiratory infection may be mediated by cellular immune function.

**Nutritional Interventions**

A recent trial in Vietnam (19) used an intervention of encouraging home garden production and nutrition education in order to improve the nutritional status of children 1 to 6 years of age. Children in the intervention commune (n = 469) had a significant reduction (p < 0.0001) in the incidence of acute respiratory infections: 11.2% compared with 49.1% in the control commune (n = 251).
Vitamin A

Deficiency and Predisposition to Acute Respiratory Infections

Some early studies suggested that vitamin A deficiency may predispose to different types of respiratory infection. Several recent cross-sectional studies have also detected an association between varying degrees of vitamin A deficiency and respiratory tract infections (3,20–23). These infections include both upper and lower respiratory tract disorders. The data were derived from population-, clinic-, and hospital-based investigations in developing countries. On the other hand, some population-based projects have failed to detect an association between vitamin A deficiency and respiratory disease (24–26). A much clearer idea of this association emerges from the prospective, community-based studies conducted recently. Studies from Indonesia (27,28) and India (29,30) have shown an increased risk of respiratory disease in children with vitamin A deficiency.

Supplementation and Acute Respiratory Infections

Recent meta-analyses (31,32) have failed to detect a consistent impact of vitamin A supplementation on the incidence or mortality from acute lower respiratory tract infections. The Vitamin A and Pneumonia Working Group reviewed 12 large-scale field trials which had results available to January 1993 (32). Five of these trials had information on pneumonia incidence and prevalence. Overall, no significant impact was found of vitamin A supplementation on either the incidence or the prevalence of pneumonia (Table 1). However, a trend was seen showing a possible harmful effect of vitamin A supplementation on the incidence and prevalence of pneumonia in infants 6 to 11 month of age, and a possible beneficial effect on those 48 to 59 months of age. Most of the increased risk was contributed by data from one study. Furthermore, four of the nine studies (which had appropriate data) revealed a 5% to 10% excess of coughing in the group receiving vitamin A supplement. Only the Jumla, Nepal, study showed a significant impact of vitamin A supplements (33).

Three smaller trials, one in Thailand (23), one in China (34), and the other in Indonesia (35), showed a positive or marginal impact of vitamin A on respiratory mor-

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin A</th>
<th>Placebo</th>
<th>Rate ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morvita et al. (28)</td>
<td>0.55</td>
<td>0.48</td>
<td>1.14 (0.99–1.32)</td>
</tr>
<tr>
<td>Bahia et al. (36)</td>
<td>0.98</td>
<td>1.00</td>
<td>0.97 (0.86–1.09)</td>
</tr>
<tr>
<td>Delhi et al. (37)</td>
<td>1.58</td>
<td>1.67</td>
<td>0.95 (0.77–1.17)</td>
</tr>
<tr>
<td>VAST Ghana Study Team (77)</td>
<td>0.85</td>
<td>0.92</td>
<td>0.92 (0.82–1.04)</td>
</tr>
<tr>
<td>Jumla et al. (33)</td>
<td>0.61</td>
<td>0.91</td>
<td>0.77 (0.66–0.89)</td>
</tr>
<tr>
<td>Summary</td>
<td>—</td>
<td>—</td>
<td>0.95 (0.89–1.01)</td>
</tr>
</tbody>
</table>

* Episodes of pneumonia/number of child-weeks.
CI, confidence interval.
TABLE 2. Impact of vitamin A supplementation on pneumonia-specific mortality in children under 5 years of age

<table>
<thead>
<tr>
<th>Country (study)</th>
<th>Pneumonia-specific mortality</th>
<th>Design effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jumla et al. (33)</td>
<td>0.88</td>
<td>1.416 (0.38–2.05)</td>
</tr>
<tr>
<td>Madurai et al. (72)</td>
<td>0.66</td>
<td>1.329 (0.08–5.19)</td>
</tr>
<tr>
<td>Sarlahi (76)</td>
<td>1.10</td>
<td>1.187 (0.77–1.57)</td>
</tr>
<tr>
<td>Sudan (77)</td>
<td>0.43</td>
<td>1.000 (0.16–1.19)</td>
</tr>
<tr>
<td>Ghana (77)</td>
<td>1.10</td>
<td>2.003 (0.61–1.97)</td>
</tr>
<tr>
<td>Summary</td>
<td>—</td>
<td>0.98 (0.75–1.28)</td>
</tr>
</tbody>
</table>

* Where randomization was not at individual level, regression was weighted to allow for within-cluster homogeneity using design effects (31).

bidity. In China, 172 children 6 months to 3 years of age were given either a placebo or two doses (each dose 200,000 IU) of vitamin A in a 6-month period. The incidence and severity of respiratory disease were decreased in the treated group. This effect was observed only in those 12 or more months of age. The latter study has been criticized for design problems, which could have introduced bias in assessments. In the study of 269 urban Indonesian children 1 to 5 years of age, vitamin A supplementation (200,000 IU orally 6 monthly) had no effect on incidence or severity of acute respiratory infections (as defined by WHO). The duration of acute respiratory infections was slightly shorter in those in the supplemented group (35).

Five trials were conducted in which pneumonia mortality could be assessed (Table 2). The impact of vitamin A supplementation on pneumonia mortality varied, but the summary rate ratio was near unity (0.98). As pneumonia is a major cause of infant deaths, the impact of vitamin A supplementation was separately analyzed for this age group. The rate ratio for those 0 to 5 months of age was 0.88 (95% CI 0.51 to 1.51) and for those 6 to 11 months it was 1.08 (95% CI 0.57 to 2.03).

The effect of vitamin A in children aged less than 6 months remains unclear. In Indonesian infants given 50,000 IU of vitamin A at birth, the mortality was half that of the control group in the first year (38). In Tanzania (39), Fawzi showed no effect of vitamin A on pregnancy outcomes in women infected with the human immunodeficiency virus, despite a beneficial effect of multivitamin supplements on fetal mortality, low birthweight, prematurity, and fetal growth retardation. In the recent WHO/CHD randomized trial (CHD, Child Health Division), no benefit was found of vitamin A supplementation linked to immunization visits in infancy on respiratory or diarrheal morbidity, growth, or mortality (40). In our Durban studies (41), we tested the prophylactic value of vitamin A given to infants born to women infected with HIV as follows: 50,000 IU at 1 and 3 months of age, 100,000 IU at 6 and 9 months, and 200,000 IU at 12 and 15 months. Recall of morbidity was recorded monthly at each follow-up visit. Babies infected with HIV in the supplemented group had reduced diarrheal but not respiratory morbidity.
In summary, therefore, vitamin A supplementation apparently has no significant impact on pneumonia incidence, prevalence, or mortality in children between 6 months and 5 years of age. Data from these trials are insufficient to derive any firm conclusions on the impact of vitamin A on pneumonia mortality in infants of less than 6 months of age, although recent evidence strongly suggests no beneficial effect occurs. Trends showing possible detrimental effects of vitamin A supplementation (cough in all age groups; pneumonia in those 6 to 11 months of age) require further clarification.

The 1992 meta-analysis by Beaton et al. (31), undertaken when the results of some large trials were still incomplete, concurred with the finding that vitamin A supplementation did not reduce the incidence or duration of respiratory infections, nor had a beneficial effect on mortality from respiratory diseases.

Australian studies have suggested that preschool children with frequent respiratory infections (42), but not those with a previous respiratory syncytial virus infection (43), derived benefit from vitamin A supplementation—a 25% reduction in lower respiratory tract infections. Shenai et al. treated vitamin A-deficient, low birthweight infants with vitamin A and reduced the incidence of bronchopulmonary dysplasia (44). These results were not confirmed in another study of different design (45).

Various randomized, placebo-controlled studies have failed to show consistent and substantial beneficial effects of vitamin A treatment in infants and children with acute onset of lower respiratory tract infection. Some of the benefits and adverse effects are given in Table 3. These trials have been undertaken in Brazil (46), Guatemala (47), Chile (48), Peru (49), and the United States (50); they have included clinically (47) or radiologically (48) defined lower respiratory tract infections, and have assessed all-cause pneumonia (46,47) and respiratory syncytial virus specific infections (47,48). The children studied were vitamin A replete in the United States (50), Guatemala (47), and Chile (48), or marginally vitamin A deficient in Brazil (46). A bulging fontanelle, probably caused by giving vitamin A, was transient and was noted in 4% of the children treated in the Brazil study (46).

Zinc

The major associations with zinc deficiency are chronic diarrhea, growth retardation, and immunoparesis. Some studies have shown that low zinc levels are accompanied by upper respiratory tract infections. A recent study in India showed that low plasma zinc predicts the subsequent development of lower respiratory tract infection and diarrhea. Over a period of 90 days, the initial low plasma zinc predicted a 3.5 times higher mean prevalence rate of acute lower respiratory tract infection than in children with normal zinc (51).

Supplementation

The impact of zinc supplementation in children who are likely to have inadequate body zinc is primarily on (a) improved growth (linear growth and weight gain); (b) a
<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>n</th>
<th>Age</th>
<th>Vitamin A dose (IU)</th>
<th>Disease</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guatemala (47)</td>
<td>263</td>
<td>3 mo to 4 yr</td>
<td>100,000 infants 200,000 &gt; 12 mo</td>
<td>ALRTI</td>
<td>No benefit</td>
</tr>
<tr>
<td>United States (50)</td>
<td>239</td>
<td>1 mo to 6 yr</td>
<td>50,000 1-5 mo 100,000 6-11 mo 200,000 &gt; 12 mo</td>
<td>RSV infection</td>
<td>Longer hospital stay in those &gt; 12 mo in supplemented group</td>
</tr>
<tr>
<td>Chile (48)</td>
<td>180</td>
<td>1 mo to 6 yr</td>
<td>50,000 1-5 mo 100,000 6-11 mo 200,000 &gt; 12 mo</td>
<td>RSV infection</td>
<td>Duration of hospital stay and tachypnea shorter in supplemented subgroup with severe hypoxemia (p = 0.01 and p = 0.09, respectively)</td>
</tr>
<tr>
<td>Brazil (46)</td>
<td>472</td>
<td>6 mo to 5 yr</td>
<td>200,000 infants 400,000 &gt; 12 mo</td>
<td>Clinical or radiologic pneumonia</td>
<td>Less fever by day 3, fewer failures to first line antibiotics (p = 0.008 and p = 0.054, respectively)</td>
</tr>
<tr>
<td>Peru (49)</td>
<td>95</td>
<td>3 mo to 10 yr</td>
<td>150,000 infants 300,000 &gt; 12 mo</td>
<td>Radiologic pneumonia</td>
<td>Adverse effects of vitamin A: lower O₂ saturation, higher prevalence of retractions, more consolidation, greater O₂ requirement</td>
</tr>
</tbody>
</table>

ALRTI, acute lower respiratory tract infection; RSV, respiratory syncytial virus.
decreased incidence, duration, and severity of diarrhea; and (c) restoration of immunologic integrity (52). Zinc supplements may also enhance child development and reduce malaria morbidity (52). Zinc supplementation has not been shown to reduce mortality in children. With the exception of a well-conducted, community-based, randomized double-blind controlled trial in India (53), little evidence supports the notion that zinc has beneficial effects on lower respiratory tract infection or pneumonia. It is not even clear whether zinc supplements consistently decrease the incidence of upper respiratory tract infection.

Supplementation and Respiratory Morbidity: Community-Based Studies

Results of community-based studies are summarized in Table 4. In the study in India (53), zinc-supplemented children had 0.19 lower respiratory tract infections per child per year, compared with 0.35 episodes per child per year in the control group. Pneumonia incidence was reduced (odds ratio [OR] 0.44; 95% CI 0.27 to 0.74; p = 0.002), as was pneumonia prevalence (OR 0.49; 95% CI 0.29 to 0.83; p = 0.008). In the study in Brazil (54), with the higher dose, a trend was seen toward reduced prevalence of cough and shorter duration of hospital admission. Zinc had no effect, given alone or with iron, on the incidence or duration of respiratory tract episodes among Mexican children; most of the episodes (669 of 673) were upper respiratory tract infections (55). A trend was seen toward an increased incidence and prevalence of respiratory infection (14% and 38%, respectively) in the zinc-supplemented group in Guatemala (56). A report from Vietnam (57) recorded only upper respiratory tract infections and showed a beneficial impact of zinc. The supplemented group had significantly fewer upper respiratory tract infections (p = 0.002); a 2.5 times reduced relative risk for these infections was found in the treated group (p = 0.057). Gambian children did not appear to be zinc deficient and it is unclear whether upper or lower

<table>
<thead>
<tr>
<th>Country (study)</th>
<th>n</th>
<th>Age groups (months)</th>
<th>Zinc dose</th>
<th>Level of acute respiratory infections</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (53)</td>
<td>609</td>
<td>6-35</td>
<td>10 mg daily</td>
<td>LRTI</td>
<td>6 mo</td>
<td>Reduced incidence and prevalence of pneumonia</td>
</tr>
<tr>
<td>Brazil (54)</td>
<td>205</td>
<td>Low birthweight newborns</td>
<td>5 mg or 1 mg daily for 8 weeks</td>
<td>URTI/LRTI</td>
<td>6 mo</td>
<td>No significant impact</td>
</tr>
<tr>
<td>Mexico (55)</td>
<td>219</td>
<td>18-36</td>
<td>20 mg alone, or with 20 mg Fe daily, 10 mg daily</td>
<td>Mostly URTI</td>
<td>12 mo</td>
<td>No significant impact</td>
</tr>
<tr>
<td>Guatemala (56)</td>
<td>99</td>
<td>6-9</td>
<td>10 mg daily</td>
<td>URTI/LRTI</td>
<td>7 mo</td>
<td>No significant impact</td>
</tr>
<tr>
<td>Vietnam (57)</td>
<td>146</td>
<td>4-36</td>
<td>10 mg daily</td>
<td>URTI</td>
<td>5 mo</td>
<td>Reduced incidence URTI</td>
</tr>
<tr>
<td>Gambia (58)</td>
<td>110</td>
<td>6-28</td>
<td>70 mg twice weekly</td>
<td>URTI/LRTI</td>
<td>15 mo</td>
<td>No impact</td>
</tr>
</tbody>
</table>

* All sites were community based.
LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.
respiratory tract infections were assessed (58); in that trial, Bates et al. also used a bi-weekly rather than a daily dose of zinc. A trial in schoolchildren in Ohio, USA, failed to yield positive results of zinc supplementation on upper respiratory infections (59).

Supplementation and Respiratory Morbidity: Health Facility-Based Studies

Three smaller, clinic-based studies of zinc supplementation, given to moderately or severely malnourished children, do not provide any consistent evidence of a beneficial effect of zinc on lower respiratory tract infections (60–62). Two studies from Chile (60,61) showed no significant effects of zinc on lower or upper respiratory tract infections, although one reported a marginal benefit on otitis media (61). Zinc supplementation was associated with an increase in impetigo in one study (61) and a decrease in pyoderma in the other (60). Ecuadorian children experienced a short-term benefit (60 days) from zinc supplementation in reducing upper respiratory tract infection; paradoxically, cough was increased in the treated group (62). In a recent study, not yet published, from the International Centre for Diarrhea Disease Research (ICDDR), Bangladesh, a 2-week course of zinc (20 mg/d) given to 65 malnourished children with acute diarrhea had a positive impact over the next 2 months on a subgroup with stunting. In the latter, the children who received zinc supplement had fewer episodes of respiratory tract infection than controls (1.0 vs 2.4; \( p < 0.01 \)), and these were of shorter duration (1.6 vs 4.2 days; \( p < 0.01 \)). It is unclear whether these were upper respiratory tract or lower respiratory tract infections. Studies from the ICDDR have also made observations on respiratory disease rates in their evaluation of the effect of zinc on diarrhea. Although reductions in respiratory diseases were noted, the numbers of such cases were too few to attain significance.

In the report of a meeting on Zinc for Child Health held in Baltimore, Maryland, USA, on 17–19 November 1996, R. Black concluded from available zinc intervention studies that the incidence of acute lower respiratory illness or pneumonia was decreased by between 3% and 60% (average 12%). Reductions were greater in those with initial zinc deficiency and malnutrition.

Interpretation of Results of Trials

Probably many reasons exist for the failure of most of these studies to show consistent benefits of zinc supplementation on lower respiratory tract infections or pneumonias. It is possibly a true effect that zinc supplementation, as with vitamin A supplementation, may not be of benefit for respiratory diseases. On the other hand, design issues may have obscured a positive impact. Sample sizes may have been too small; the levels of zinc deficiency, stunting, and wasting too variable; associated protein-energy malnutrition and other micronutrient deficiencies may have obscured the effects of zinc replenishment; and the risks of pneumonia were probably different in the regions studied. Furthermore, the optimal dose of zinc supplementation is not clear, and there may be gender differences in response.
Iron

Controversy has existed over the role of iron in infections. On the one hand, free iron is necessary for bacterial growth; on the other hand, iron is needed by natural killer cells, neutrophils, and lymphocytes for optimal function. It is to be expected, therefore, that in iron deficiency the initial establishment of infection may be unaffected or even rendered more difficult, owing to lack of available iron for the invading microorganisms; once infection is established, however, decreased immunocompetence will make it difficult to eliminate the infection. The clinical studies investigating the role of iron in acute respiratory infections have not been very helpful and this is an area that needs continuing research.

Intervention Trials and Acute Respiratory Infections

A study was conducted in Bangladesh in 349 children 2 to 48 months of age, who were divided into a treatment group receiving a daily supplement of 15 mg iron and multivitamins for 15 months, and a placebo group given only multivitamins (63). Results showed no difference between the iron-supplemented group and the iron-free group with respect to the number of acute respiratory infection episodes and the mean duration of the episodes. It should be noted that the effect of the multivitamins may have masked any additional effect of iron. Additionally, as a word of caution on prolonged iron supplementation, it was noted, in children under 12 months of age, that those in the iron-supplemented group had a 49% increase in the number of episodes of dysentery.

In another intervention trial in Indonesia—where children received 30 mg iron/d for 2 months as opposed to 15 mg/d used in the previous trial, and control children received only vitamin C—it was shown that respiratory infections were 2.5 times more frequent in the placebo group than in the intervention group (64). It was also observed that this effect on morbidity had an indirect effect on growth, as the children in the iron-supplemented group had a greater increase in height for age.

IMPACT OF NUTRITIONAL STATUS ON MEASLES

Protein-Energy Malnutrition

Hospital studies have reported that malnourished children (weight for age < 2 SD at admission) have a higher mortality (65). However, community studies from Bangladesh, Gambia, Nigeria, Guinea-Bissau, and Benin, which had information on nutritional status before infection, have not supported this association (66–69). Only one community study has postulated higher measles mortality among malnourished children (70); in that study, 2,019 Bangladeshi children 12 to 23 months of age were followed for 2 years. Those results may be confounded because they were based on measles deaths in relation to the total population rather than in relation to the number of children contracting measles in the two nutritional groups. However, as pointed out by Aaby et al., children from large families tend to have lower weight for age and
a higher risk of contracting measles because of increased exposure and, thus, a higher risk of dying from measles (68). Therefore, the association between malnutrition and higher measles case fatality rate in the hospital is likely to reflect the fact that children lose weight during the incubation period before any symptoms of measles occur.

Effect of Nutritional Interventions

During an intervention study in India (71) designed to look at the effect of a food supplement on growth (310 kcal/d plus 3 g/d protein for 1 year), a measles outbreak occurred, which provided an opportunity for an interesting observation. The control group, children who developed measles had the expected decrease in weight compared with those who did not develop measles. However, in the supplemented group the children with measles (82 of 306) had a weight gain similar to those who did not develop measles (224 of 306).

Vitamin A

Supplementation or Treatment Reduces Measles Mortality

Vitamin A deficiency renders preschool children vulnerable to severe measles and high mortality, conditions which are ameliorated or reversed by vitamin A supplements. Eight major controlled community-based trials comparing vitamin A supplements with placebo for reduction of early childhood mortality have been conducted in east Asia, south Asia, and Africa (29,33,72–77). All these trials were carried out in vitamin A-deficient populations. The cause-specific mortality is available in five of these trials (33,72,73,76,77) and a summary is provided in Table 5. The reduction in mortality from measles ranged from 18% in Ghana (77) to 76% in Nepal (33).

Three controlled trials (Table 6) have shown convincingly that treatment with vitamin A given early during the course of measles reduces mortality by about 50% (10,78,79). Most deaths were in children under 2 years of age, and the reductions in mortality across all three trials are not inconsistent when considering differences between them.

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Vitamin A supplement</th>
<th>Relative risk of measles mortality: vitamin A vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal (76)</td>
<td>Large dose, 4 monthly</td>
<td>0.24</td>
</tr>
<tr>
<td>Nepal (33)</td>
<td>One large dose, follow-up at 5 months</td>
<td>0.67</td>
</tr>
<tr>
<td>India (72)</td>
<td>Weekly recommended dietary allowance</td>
<td>0.58</td>
</tr>
<tr>
<td>Ghana (77)</td>
<td>Large dose, 4 monthly</td>
<td>0.82</td>
</tr>
<tr>
<td>Sudan (73)</td>
<td>Large dose, 6 monthly</td>
<td>*</td>
</tr>
</tbody>
</table>

* No measles cases reported.
The beneficial effects of prophylaxis in vitamin A-deficient populations, the measles infection-induced reduction of vitamin A levels, and the positive impact of high dose vitamin A at the onset of clinical disease all suggest that vitamin A supplementation works by improving deficient or suboptimal levels of vitamin A.

Observational studies in Zaire (9) and the United States (12) have shown that lower serum vitamin A concentrations were associated with severity of measles and higher case fatality rates. In the Zaire study, the relative risk of mortality was 2.9 (95% CI 2.3 to 6.8) in those with reduced vitamin A levels. In the Milwaukee study (12) of 114 preschool children seen during an outbreak of measles, the degree of retinol depression correlated with measles severity as measured by hospital admission rates, the presence of pneumonia, and a standard assessment of physiologic instability (the PRISM score).

**Table 6. Effect of vitamin A supplementation on measles mortality rate**

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Dose of vitamin A</th>
<th>Vitamin A formulation</th>
<th>Relative risk of mortality (control:treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanzania (78)</td>
<td>200,000 IU orally on admission and on next day</td>
<td>Oil miscible</td>
<td>1.9:1</td>
</tr>
<tr>
<td>Cape Town, South Africa (10)</td>
<td>200,000 IU orally on admission and on next day</td>
<td>Water miscible</td>
<td>4.7:1</td>
</tr>
<tr>
<td>London, UK (79)</td>
<td>—</td>
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**Vitamin A Treatment Reduces Morbidity**

Various cross-sectional studies (population, hospital, and clinic based) have detected an association between vitamin A deficiency and morbidity in measles (20,21,24,25). However, one study in Bangladesh (26) and another in the Philippines (22) did not detect such a relation.

Two studies South African studies (10,11) show clearly the reduction in complications arising from measles with vitamin A treatment. The Cape Town study (10) revealed that the group of children on vitamin A had fewer complications, a shorter hospital stay, and required less frequent intensive care than the group on placebo. The Durban study (11) provided evidence of benefit in both the short and the long term. Hospitalized children with measles who were treated with vitamin A recovered more rapidly from pneumonia, diarrhea, fever, and other complications, compared with children on placebo. This advantage of vitamin A persisted for at least 6 months.

A smaller Kenyan hospital study (80) and a village-based study in West Bengal (81) found similar benefits of therapeutic and prophylactic doses of vitamin A on severity of measles. In the Kenyan study (80), the prevalence of complications was similar between vitamin A and control groups; however, mortality was higher in the latter compared with the treated group (13% vs 7%). Most of the deaths were from respiratory diseases (e.g., mortality from pneumonia was 15% in the control group...
and 8% in the vitamin A-treated group). This suggests that vitamin A supplementation decreased the severity of disease in these children.

The improved outcomes in children with severe measles treated with vitamin A are probably primarily mediated through immunopotentiation (82). The Durban children with measles were treated with placebo or high doses of vitamin A given on admission and on days 2, 8, and 42 thereafter (82); the serum IgG antibody response was significantly better on days 8 and 42 in the treated group. Lymphopenia, which is a good predictor of outcome in measles, was also reversed quicker in the treated children.

### Meta-Analyses of Vitamin A Supplementation and Measles Mortality

Meta-analyses have confirmed the beneficial impact of supplemental vitamin A in vitamin A-deficient populations on mortality in children under 5 years of age. However, two recent meta-analyses (83,84) differed with respect to the evidence that community-based interventions with vitamin A reduce measles mortality. Glasziou and Mackerras (83) concluded that community trials show a 55% reduction in measles deaths (p = 0.017), whereas Fawzi et al. (84) argued that, although the results of community-based studies suggest a protective effect, the relationship between vitamin A supplementation and measles-specific mortality is not statistically significant (p = 0.30). The major difference between these meta-analyses was in the choice of trials included. Glasziou and Mackerras excluded the very large study in Sudan (which showed no significant impact of vitamin A on child mortality or measles mortality) because of bias in the method of allocation. Moreover, it can be anticipated that the effects of vitamin A supplementation on measles mortality will depend on the contribution of this disease to mortality in children under the age of 5 years. This varies from region to region. However, more detailed information on measles from Ghana continues to raise uncertainties about community-based vitamin A supplementation and measles. A recent study from the Ghana Vitamin A Supplementation Trials group (VAST) (85) of measles fatalities in relation to premorbid vitamin A supplementation found no significant effect of vitamin A on measles incidence, acute measles case fatality, or delayed postmeasles mortality (median follow-up 8 months). Serum retinol concentrations were higher in the supplemented group than in the placebo group. This is a region of poor vaccine coverage, low measles vaccine efficacy, and high case fatality rates. It is also the district in which the VAST studies have previously shown a beneficial impact of vitamin A supplementation on child mortality and health services utilization.

### DIRECTIONS FOR FUTURE RESEARCH

We suggest that further study is needed in the following areas.

1. The impact of vitamin A given in the late antepartum period and during infancy on maternal and child health and disease, including respiratory infections
2. Large scale, multicenter field trials in developing countries to assess the impact of zinc supplementation on respiratory and other morbidity
3. Community-based studies to evaluate the impact of other micronutrients on lower respiratory tract infections and other diseases
4. Impact of micronutrient supplementation on pneumonia and other diseases in children infected with, or exposed to HIV
5. Comparison of the impact on populations of micronutrient interventions and broader development initiatives
6. The effect of iron deficiency on immune function and whether this leads to increased severity of infection in a properly controlled large scale clinical study

REFERENCES


DISCUSSION

Dr. Fawzi: You mentioned that, in general, the vitamin A trials seem to indicate no beneficial effect on pneumonia or on its prevention. Studies even suggest that vitamin A may in some cases be harmful in pneumonia. For example, the randomized, placebo-control study in Peru showed that vitamin A supplements resulted in an increased oxygen requirement, whereas in a study from Ecuador, a significant increase was seen in respiratory infection among well-nourished children; in our study from Tanzania, a nonsignificant increased risk of mortality was found among children admitted to the hospital with pneumonia (1–4). Could you comment on the potentially harmful effects of vitamin A?

Dr. Coovadia: As you say, the evidence is that you can occasionally produce harmful effects if you give vitamin A. My understanding is that in these field trials, the incidence was extremely low (< 2%), but still detectable. It is easily recognizable clinically, and it does not diminish the need for vitamin A on a public health intervention scale; the benefits outweigh the negative effects. I am, however, worried about the newborn and the infant in the first year of
life, because the meta-analysis suggested that in that period mortality might increase (5). One area of further research is the impact of vitamin A in infancy. Just to emphasize how complex this subject is, Dr. Brown gave a multicomponent mixture and it had a negative impact, whereas your study showed no impact of vitamin A and yet an impact of multivitamins. I think those are very important areas of research, otherwise you will not know what to do about current recommendations for vitamin A for mothers, who are supposed to be given 200,000 IU within a few days of birth. I think we need to know a lot more about this.

**Dr. Suskind:** You mentioned the lower levels of vitamin A and zinc in acute respiratory infections and measles. I am wondering about the effect of infection on visceral protein synthesis, on the production of the acute phase reactants, and on zinc status. Vitamin A is transported by a visceral protein, retinol-binding protein, which has been found to be very sensitive to external influences. Perhaps the decrease in vitamin A in measles and acute respiratory infections reflects a decrease in the carrier protein. In fact, many of these patients have adequate stores of vitamin A in the liver; perhaps it is just not getting into the circulation. The same might be true for zinc. We recognize that zinc, as well as iron, is decreased in infection. The observation is an important one, but the interpretation is also important. I would like your comments on that.

**Dr. Coovadia:** I would like to pass this question to my co-author Dr. Anna Coutsoudis.

**Dr. Coutsoudis:** In our original measles trial, we did measure retinol-binding protein. A definite reduction in retinol-binding protein very closely correlated with the reduction in serum retinol. I think that would account for why we sometimes see an impact of supplementation and sometimes not. Serum retinol could be reduced purely as a marker of subclinical infection, and not necessarily because the child is deficient.

**Dr. Suskind:** It is worthwhile commenting on the observation that vitamin A does not necessarily have an impact on respiratory infections or diarrheal disease. I wonder if the impact of vitamin A on small bowel overgrowth has been investigated. Perhaps the impact of vitamin A on small bowel overgrowth, and other aspects of the immune system, is reflected in a decrease in mortality that is not necessarily related to a specific effect on respiratory or gastrointestinal infections.

**Dr. Coovadia:** One can readily imagine that vitamin A stimulates the immune system, but I know of no studies looking at small bowel overgrowth and the impact of vitamin A treatment. The field trials had minimal information on these sorts of items.

**Dr. Fawzi:** An animal study on rotavirus showed much more severe intestinal infection in cases of vitamin A deficiency (6).

**Dr. Wasantwisut:** I would like your views on the nature of supplementation. The doses of vitamin A that are given are usually massive, in contrast to zinc which is more likely to be provided on the basis of the daily required dose. Do you think this pharmacologic versus physiologic dose regimen affects the way the body responds to certain types of infection?

**Dr. Coovadia:** The trials vary considerably in the way they gave the vitamin A, so that was a critical variable. Some gave it at 6-month intervals, some at 4-month intervals, and I think the Indian study gave it weekly. In the meta-analysis that I referred to, this was examined and the conclusion was that giving it more frequently was probably more effective.

**Dr. Meydani:** I would like to emphasize the need to learn more about the mechanism of how vitamin A may protect against certain pathogens. Without that information, consistent and effective strategies cannot be developed and you end up producing more and more data that will probably just cloud the issue even more. It does seem to me that there is a lot of inconsistency.

**Dr. Coovadia:** That is an important question. My only difficulty is that I work in a country where I see real problems. I could spend a lifetime looking at mechanisms, but it may be bet-
ter for me to gather evidence from field trials. That is the dilemma for all of us who work in
the field. It is an impossible dilemma to solve. About 20 years ago, we looked at protein-energy
malnutrition and thymolymphatic atrophy. Frankly, I do not think those studies have had
a major impact on the welfare of children 30 years later. Children have been helped because
Thailand has become a bit richer. That is the dilemma we have to find our way out of. I am
sorry I am not responding to you directly, but I am trying to indicate that we need a combina-
tion of both field trials, which are imperfect, and basic research.

Dr. Meydani: I did not mean that it has to be an either or situation. I think you need to do
both types of study in parallel. Ignorance of the mechanism and inconsistent results will only
increase the number of people who question the need for any of this research.

Dr. Coovadia: I would certainly be very worried about continuing single nutrient studies
without looking at the impact of broader interventions.

Dr. Farthing: One thing that struck me is that some of these studies look underpowered. I
do not know of many major clinical intervention studies, for instance, that only have 32 sub-
jects in them. I wonder whether with a meta-analysis with underpowered studies you end up
with an underpowered meta-analysis. My other point comes out of a study that we did in adults
infected with HIV with persistent diarrhea in Zambia (7). We supplemented them with vitamin
A and saw no effect. This was a large study of nearly 200 individuals, so we think it was prob-
ably powerful enough to show an effect if one existed. When we looked at the vitamin A sta-
tus of these individuals, as best we could, we found we had made no impact whatsoever on
plasma indices, including the binding proteins, which made me wonder whether the vitamin A
was actually getting where it needed to be. Vitamin A, was used, after all, as a very sensitive
test of intestinal absorption in the 1940s and 1950s. My question is, are there ways in which
you can assess the efficacy of your intervention not just in terms of morbidity and mortality
but of whether you have actually delivered the nutrient to the body?

Dr. Coovadia: Regarding your first point about which of the studies are reliable, that was
the reason why I separated all the studies into the smaller ones (hospital-based studies and clin-
cial studies) and field trials, implying that latter were the gold standard. The field trials were
all sufficiently powered and they have been analyzed individually and collectively, so no ques-
tion exists about the sample size being insufficient to pick up the problems they were trying to
detect. The reason I put up the smaller studies was precisely to show you that some may not
be sufficient. Anna Coutsoudis can comment on your other question about vitamin A absorp-
tion.

Dr. Coutsoudis: I think that serum retinol is clearly not accurate enough to measure what is
happening once you give vitamin A. That is why we have to use other measures. These include
pool size using isotopes, and the modified relative dose response. If you want purely to mea-
sure whether the vitamin A is being absorbed, you would have to measure serum retinol within
about 7 hours. It is no use coming along 3 weeks later, which most of us do; by then, if the per-
son was actually vitamin A sufficient and infection had been cleared, probably no difference
would be found in the serum retinol. However, we do know that during infection retinol is re-
duced.

Dr. Marini: I would like to say a word in favor of vitamin A in the lamb. The results of a
multicenter study from the United States on vitamin A for the prevention of bronchopulmonary
dysplasia were recently published (8), and showed that 10,000 IU of parenteral vitamin A sig-
nificantly reduced the problem of bronchopulmonary dysplasia in extremely low birthweight
infants.

I have a naive question for the people working in the field. Do you think that other very sim-
ple clinical tools could enhance your results? For instance, the ratio between arm circumfer-
ence and head circumference, or evaluation of respiratory rate or heart rate when the baby is sleeping. You can collect these data in the field, and maybe they would give you additional information about energy wastage and so on.

Dr. Coovadia: The short answer is that it is always useful to do simple tests in the field. I spent most of my studies on measles looking for the simplest test. The lymphocyte count on admission turned out to be best. I spent a lot of time showing that it was a really good indicator and predictor (this was before the days of HIV and CD4), and that information is available in most hospitals and clinics.

Dr. Chandra: Two brief comments. First, animal data and some in humans show that large doses of vitamin A produce a period of immunosuppression, which can last for 7 to 20 days. I think it might be useful to analyze the studies in which a negative impact or higher mortality was seen after vitamin A to see if most of the problems arose shortly after giving a large dose. Second, one should remember that in all intervention studies just a visit by the child or family to a healthcare center reduces morbidity and mortality, as we learned from the Montreal Dispensary study 40 years ago and a number of other studies. So, the mere fact of contact with a health worker in these field trials may have useful benefit.

Dr. Griffin: It seems to me that if you are going to introduce something on a global scale, then it should have no adverse effects at all, but we do have some evidence of adverse effects of vitamin A—the decrease in response to hepatitis A vaccine, the transient decrease in immunity, and so on. There is another form of adverse effect as well, which I think is perhaps even more crucial. That is the concern that the introduction of an intervention such as supplementation with vitamin A could affect the childhood vaccination program. The use of vaccines may be compromised in some places where there are severe economic constraints. I was at a vaccine meeting recently where this question was addressed, and the major players in the field had no doubt that vaccination programs could be adversely affected. You then have to make a judgment of how important that would be compared with what seem to me to be the quite marginal benefits of vitamin A.

Dr. Coovadia: That is an issue for a week’s discussion. I am not unaware of it, but the range of priorities is a difficult if not impossible thing for scientists to solve. But I would stress that the impact of vitamin A on mortality in certain population is so good and is achieved at such low cost that it is a really worthwhile public health intervention. I come from a country that is not giving zidovudine to pregnant women with HIV, so I know all about these priorities. For us, the use of vitamin A is not in question and in fact is going to be implemented.

Dr. Tontisirin: I believe we should apply basic research and implementation in parallel. We always need to have an understanding of mechanisms to help us avoid harmful consequences of our actions—for example, the use of large doses vitamin A may cause imbalance and create some kind of a negative effect. In terms of application, I think eventually we have to come down to community-based programs, although with nutrition, this becomes very complex.

REFERENCES


