Infection: How Important Are Its Effects on Child Nutrition and Growth?

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Malnutrition is a key determinant of childhood mortality, largely because it leads to an increased severity of recurrent infections that are acquired under poor environmental conditions (1). Malnutrition has other serious long-term consequences such as impaired cognition and psychobehavioral problems (2,3). The need to hasten the decline in the high rates of malnutrition in developing countries is therefore a high priority.

Low food intakes and the heavy burden of common infections limit the full realization of the genetic growth potential of children in developing countries (4–13). Deficient food intake is traditionally considered to be the primary cause. This is reflected in the fact that nutrition programs are targeted mainly toward increasing access to food among vulnerable populations (14). Infection is well recognized to be a factor in the development of malnutrition. There is, however, uncertainty about how much it contributes to the etiology of malnutrition, although attempts have been made to quantify its role in wasting and stunting (12).

The impact of food supplementation programs on children’s nutritional status has been less than anticipated, and a reassessment of the role of common illnesses in causing malnutrition is therefore warranted (13,15,16). The effects on growth of diarrhea, pneumonia, and helminthiasis have been investigated quite extensively, whereas less attention has been paid to the effects of measles, acute febrile illnesses, and malaria. As an illustration of a chronic infection during postnatal life, the recent studies of human immunodeficiency virus (HIV) are of particular interest.

Some investigators have determined the influence of the severity and duration of illness episodes on growth. Such knowledge could facilitate the development of case management approaches, which, if introduced early in the illness, might reduce growth faltering. For diarrhea, in particular, the adverse growth impact of infection with individual pathogens has been quantified in studies from Bangladesh (17–20).

Children in developing countries are often chronically colonized with bacterial or protozoal pathogens at their mucosal surfaces, such as the intestinal tract, without having overt symptoms of disease. Whether these subclinical infections have significant adverse effects on growth and nutrition is not established (19–22).
In this chapter, we consider issues related to the effects of infection on the growth and nutrition of young children.

**IMPACT OF INFECTION ON GROWTH**

**Impact of Common Childhood Infections**

The hypothesis that diarrheal and respiratory morbidity has an adverse impact on children’s growth has been examined in various studies in developing countries (23–34). Growth has been compared over defined intervals in children with some or no morbidity and in those with low or high morbidity. Weight and length gains were analyzed in relation to morbidity over short intervals (1–3 months) and long intervals (6–28 months) (Tables 1–3). Morbidity was also related to wasting or stunting at the end of the observation period by some workers. Analysis over long-term intervals is of greater importance as it reflects the cumulative effects of morbidity as well as the extent of catchup growth.

Two potential sources of bias are relevant to these analyses. First, it may not be possible to determine whether infection or poor growth came first. As an example, it is possible that children with high morbidity who were growing at a slower rate were, in fact, experiencing more morbidity because they were already faltering in growth. This has been taken care of, in some instances, by recruiting subjects at birth or by adjusting for previous morbidity. Second, socioeconomic and baseline nutritional status could act as confounding factors, associated as they are with both morbidity and growth. Adjustment for these factors was performed in only some of the studies.

**Impact of Diarrhea on Growth**

The effect of diarrhea on weight and length gain over short intervals is considered first. Eight of the nine studies showed a significant negative association of diarrhea with weight gain (Table 1); the one from Bangladesh reported the association only with a diarrhea prevalence greater than 30% (17). Comparison of the effect size across studies is difficult owing to differences in design and the way in which growth outcomes were expressed. We have estimated, wherever possible, the magnitude of the effect as a proportion of deficit in growth from the National Center for Health Statistics (NCHS) reference population as suggested by Black (12). Among studies that reported a significant impact on growth, between 8% and 80% of weight deficit over short intervals was attributable to diarrhea. Effects of larger size were reported in African studies than in those conducted in South East Asia or Latin America. In Zimbabwe (25) and Bangladesh (17), the effect size was assessed in relation to high or low diarrhea prevalence. It was seen that the magnitude of effect increased with increasing diarrhea prevalence.

To assess catchup growth, the impact on growth of diarrhea occurring during the first and second halves of an observation period was assessed in Zimbabwe (25) and Bangladesh (17). In both countries, weight gain was found to be related to diarrhea
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Analysis interval (mo)</th>
<th>Subjects’ age</th>
<th>Impact of diarrhea</th>
<th>Impact of respiratory infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia (23)</td>
<td>1997</td>
<td>1</td>
<td>0–12 mo</td>
<td>None</td>
<td>None 9% lower weight gain; AURI &amp; ALRI not differentiated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6–11 mo</td>
<td>None</td>
<td></td>
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<tr>
<td>Bhutan (24)</td>
<td>1995</td>
<td>1</td>
<td>1–38 mo</td>
<td>4.4 g/d lower weight gain</td>
<td>2.6 g/d lower weight gain</td>
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<tr>
<td>Zimbabwe (25)</td>
<td>1994</td>
<td>3</td>
<td>9–23 mo</td>
<td>Diarrhea prevalence 5–10%: 22% lower weight gain 11–20%: 23% lower weight gain &gt;20%: 50% lower weight gain</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Philippines (26)</td>
<td>1993</td>
<td>2</td>
<td>0–6 mo</td>
<td>None</td>
<td>Yes, only for febrile episodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6–24 mo</td>
<td>Yes</td>
<td>Yes, only for febrile episodes</td>
</tr>
<tr>
<td>Gambia (28)</td>
<td>1988</td>
<td>1</td>
<td>0–12 mo</td>
<td>50% of shortfall in weight</td>
<td>Yes, only for ALRI episodes</td>
</tr>
<tr>
<td>Sudan (27)</td>
<td>1987</td>
<td>3</td>
<td>0–12 mo</td>
<td>Yes, 32 g/d ill</td>
<td>Yes, 16 g/d ill, ALRI and AURI not differentiated</td>
</tr>
<tr>
<td>Bangladesh (19)</td>
<td>1984</td>
<td>2</td>
<td>6–48</td>
<td>Yes, those with highest disease burden (&gt;30% prevalence) had only 60–65% of expected weight gain</td>
<td>No; ALRI and AURI not differentiated</td>
</tr>
<tr>
<td>Uganda (29)</td>
<td>1977</td>
<td>1</td>
<td>&lt;3 yr</td>
<td>Yes</td>
<td>No impact of ALRI or AURI</td>
</tr>
<tr>
<td>Gambia (30)</td>
<td>1977</td>
<td>1</td>
<td>6–48 mo</td>
<td>Yes, 80% of weight deficit attributed to diarrhea</td>
<td>No impact of ALRI or AURI</td>
</tr>
</tbody>
</table>

AURI, acute upper respiratory infection; ALRI, acute lower respiratory infection.

From Black RE et al. (17), Kolsteren PWV et al. (23), Bohler E et al. (24), May RJO et al. (25), Adair L et al. (26), Zumrawi FY et al. (27), Rowland MGM et al. (28,30), and Cole TJ and Parkin JM (29).
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Analysis interval (mo)</th>
<th>Subjects</th>
<th>Impact of diarrhea</th>
<th>Impact of respiratory infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia (23)</td>
<td>1997</td>
<td>1</td>
<td>0–12 mo 6–11 mo Farm laborers, low SES</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Zimbabwe (25)</td>
<td>1994</td>
<td>3</td>
<td>9–23 mo Low SES</td>
<td>Diarrhea prevalence 5–10%: length gain similar to controls 11–20%: 10% lower length gain &gt;20%: 20% lower length gain</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Philippines (26)</td>
<td>1993</td>
<td>2</td>
<td>0–6 mo 6–24 mo</td>
<td>None</td>
<td>Yes, only for febrile episodes</td>
</tr>
<tr>
<td>Gambia (28)</td>
<td>1988</td>
<td>1</td>
<td>0–12 mo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gambia (30)</td>
<td>1977</td>
<td>1</td>
<td>6–48 mo</td>
<td>Yes</td>
<td>No impact of ALRI or AURI</td>
</tr>
</tbody>
</table>

ALRI, acute lower respiratory tract infection; AURI, acute upper respiratory tract infection; SES.

From Kolsteren PWV *et al.* (23), May RJD *et al.* (25), Adair L *et al.* (26), and Rowland MGM *et al.* (28,30).
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Analysis interval (mo)</th>
<th>Subjects</th>
<th>Impact of diarrhea</th>
<th>Impact of respiratory infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe (25)</td>
<td>1994</td>
<td>22</td>
<td>0–12 mo</td>
<td>No difference in attained weights in those with high diarrhea frequency (&gt;9) vs. those with low diarrhea frequency (&lt;4)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Brazil (31)</td>
<td>1990</td>
<td>12–28</td>
<td>Birth cohort SES not low</td>
<td>Hospitalization due to diarrhea associated with 25 g/mo lower weight gain (6%)</td>
<td>Hospitalization due to pneumonia associated with 10 g/mo lower weight gain (2.4%) but not significant</td>
</tr>
<tr>
<td>Taiwan (32)</td>
<td>1983</td>
<td>6</td>
<td>0–12 mo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mexico (33)</td>
<td>1977</td>
<td>12</td>
<td>0–3 yr</td>
<td>Yes, 24% of weight deficit attributable to diarrhea</td>
<td>No impact of AURI or ALRI</td>
</tr>
<tr>
<td>Guatemala (34)</td>
<td>1975</td>
<td>6</td>
<td>&lt;7 yr</td>
<td>Yes, 10% reduction in weight gain</td>
<td>None</td>
</tr>
</tbody>
</table>

ALRI, acute lower respiratory tract infection; AURI, acute upper respiratory tract infection; SES. From May RJD et al. (25), Victoria CG et al. (31), Baumgartner RN and Pollitt E (32), Condon-Paolini D et al. (33), and Martorell R et al. (34).
during the second but not the first half of the observation period. This finding suggests a transient effect of diarrhea on weight gain, followed by good catchup growth.

There was a significant negative association between diarrhea and length gain over short intervals in three of the five studies (Table 2) (23,25–27,30). In the Philippines, a significant negative association was observed at age 6–24 months but not at younger ages (26). In the studies reporting some effect on linear growth, 8–15% of the deficit in length gain was related to diarrhea, which is substantially less than for weight gain. Contrary to the observations for weight gain, diarrhea morbidity in the first but not the second half of an observation period was associated with reduced length gain.

The long-term effect of diarrhea morbidity was examined in six studies; in five of these, an adverse effect on either weight or length gain was found (Tables 3 and 4). Of the total deficit from the NCHS median, 6–24% for weight and 10–20% for length were attributable to diarrhea.

An educational intervention aiming to reduce diarrhea through improved hygiene practices also reported a reduction in malnutrition (35). At the end of the study, the intervention site had substantially higher cleanliness scores, lower diarrhea morbidity, and a reduction in the proportion of children with weight-for-age z scores below –3.

**Impact of Respiratory Morbidity on Growth**

In three studies carried out before 1987, no significant association was observed between respiratory infections and weight gain over 1- to 3-month intervals (Table 1). In these studies, upper and lower respiratory infections were not differentiated. Most studies conducted thereafter differentiated upper from lower respiratory tract infections, and all reported a negative association of the latter with weight gain (Table 1). This relation was restricted to febrile episodes in one study and to 6- to 11-month-old children in the other (23,26). The short-term contribution of lower respiratory tract infection to the deficit in weight gain varied from 6% to 35%.

It is notable that the effect of lower respiratory tract infections on weight gain was no longer apparent when analysis was performed over intervals of 6 months or longer, thus indicating effective catchup growth. Severe pneumonia requiring hospital admission was, however, associated with a small but significant long-term reduction in weight gain in Brazil (Table 3) (31).

In most instances, it has been found that respiratory morbidity does not affect length gain, although it is possible that severe episodes do have some effect (Table 2) (17,25,33,34). In the Philippines, for instance, length gain was negatively associated with febrile respiratory infection episodes (26). Similarly, in Brazil, a significant negative association was observed for respiratory infections requiring hospital admission (31).

**Impact of Malaria on Growth**

The impact of malaria on growth in children has been examined in several observational and intervention studies (29,36–48). A study from Gambia reported a significant negative relation between malaria and weight gain but not length gain in
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Analysis interval (mo)</th>
<th>Subjects age</th>
<th>Impact of diarrhea</th>
<th>Impact of respiratory infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe (25)</td>
<td>1994</td>
<td>22</td>
<td>0–12 mo</td>
<td>No difference in attained length in those with high diarrhea frequency (&gt;9) vs. low diarrhea frequency (&lt;4)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Brazil (31)</td>
<td>1990</td>
<td>12–28</td>
<td>Birth cohort</td>
<td>Hospitalization due to diarrhea associated with lower length for age</td>
<td>Hospitalization due to pneumonia associated with lower length for age</td>
</tr>
<tr>
<td>Bangladesh (17)</td>
<td>1984</td>
<td>1 yr</td>
<td>6–48 mo</td>
<td>Yes, those with highest disease burden (&gt;30% prevalence) had 0.42 cm/yr lower length gain</td>
<td>No, ALRI and AURI not differentiated</td>
</tr>
<tr>
<td>Taiwan (32)</td>
<td>1983</td>
<td>6</td>
<td>0–12 mo</td>
<td>Yes, between 7 and 11 mo, none between 0 and 6 mo</td>
<td>None</td>
</tr>
<tr>
<td>Mexico (33)</td>
<td>1977</td>
<td>12</td>
<td>0–3 yr</td>
<td>None</td>
<td>No impact of AURI or ALRI</td>
</tr>
<tr>
<td>Guatemala (34)</td>
<td>1975</td>
<td>12</td>
<td>&lt;7 yr</td>
<td>Yes, 10% reduction in length gain</td>
<td>None</td>
</tr>
</tbody>
</table>

ALRI, acute lower respiratory tract infection; AURI, acute upper respiratory tract infection.
From Black RE et al. (17), May RJ et al. (25), Victora CE et al. (31), Baumgartner RN and Pollitt E (32), Condon-Paolini D et al. (33), and Martorell R et al. (34).
children aged under 3 years (29,48). In the same study, a significant negative relation for diarrhea was found both for weight and for length gain. In Melanesia, among children under 10 years of age, the risk of wasting increased by 2.4-fold in those who had experienced clinical attacks of Plasmodium vivax malaria; no such relation was observed for P. falciparum malaria. In this study, as well, clinical malaria caused by either species was not associated with stunting over the 6-month intervals (36).

There were four intervention trials. The interventions in the controlled trials included residual house spraying (37), chemoprophylaxis (38,42), or the use of insecticide-treated bed nets (ITBNs) in Kenya, the Gambia, and Tanzania, respectively (40,43,47). The residual house-spraying program in East Africa did not result in improved infant growth despite a significant reduction in infection rates and levels of anemia. One factor that may have affected the results is that the study was entirely clinic based and relied on passive self-referral for recruitment of infants, which is likely to have affected the estimates of nutritional improvement afforded by vector control at the community level. A positive impact on weight gain was achieved following institution of the two other malaria control strategies: the use of chemoprophylaxis and ITBNs. The Tanzanian study that used ITBNs reported 286-g greater weight gain in the intervention group than in the controls. Another ITBN intervention study from Kenya reported a 25% reduction in the proportion of underweight children at the end of the study. The Gambian study reported a significant difference in the mean weight-for-height z scores between the intervention and control children, but there was no impact on height for age.

Impact of Measles on Growth

There is a lack of epidemiological data documenting the impact of measles on growth. It is nevertheless widely assumed that growth falters during and after recovery from measles. A significant negative relation with weight gain was shown with clinical measles in Uganda (29) and with high-titer Edmonston–Zagreb (EZ) immunization in Senegal (49). In Uganda, in children younger than 3 years and over monthly intervals, a little under 15% of the deficit in weight gain could be attributed to measles (29). In Senegal, children randomized to receive high-titer EZ vaccine at 5 months had a 2.85 times greater risk of wasting than those who received the standard dose of Schwarz vaccine at 10 months (49). There was no increase in the prevalence of stunting in the group receiving high-titer EZ vaccine.

Impact of Asymptomatic HIV Infection on Growth

The findings of studies that examined the effect of asymptomatic HIV infection on growth are summarized in Table 5 (50–56). The patients’ ages ranged from infancy to 19 years. HIV infection had a negative impact on weight gain in children in developing countries (50,51,53) but not in developed countries (52,54–56). Adequacy of nutritional support and specific drug treatment may have limited the impact, if any, of HIV on weight gain in the developed countries. On the other hand, there was a
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Subjects</th>
<th>Wasting</th>
<th>Stunting</th>
</tr>
</thead>
</table>
| Congo (60)    | 1999 | (1) HIV+ infants of HIV+ mothers  
(2) HIV infants of HIV+ mothers  
(3) Infants of uninfected mothers | Weight for length lower in Group 1 since birth, remained low till 20 mo  
HIV+ infants 950 g lighter than controls (42% of deficit from NCHS) at 20 mo | Length for age similar at birth but lower in Group 1 since 3 mo  
HIV+ infants 2 cm shorter than controls (33% of deficit from NCHS) at 20 mo |
| Brazil (61)   | 1998 | Anthropometry at 4 mo old of infants with:  
- Early symptoms (<3 mo)  
- Late symptoms (>6 mo)  
- Uninfected | -0.42 z  
-0.06 z  
+0.18 z | -1.38 z  
-0.89 z  
-0.09 z |
| USA (52)      | 1998 | Infants & children 3–168 mo:  
- Exposed but not HIV+  
- Asymptomatic HIV+  
- Symptomatic HIV+  
- HIV+ requiring nutritional support | 60%  
47%  
47%  
10% | 37%  
19%  
20%  
3% |
| Rwanda (53)   | 1996 | Longitudinal follow up till 36 mo:  
(1) HIV+ infants of HIV+ mothers  
(2) HIV– infants of HIV+ mothers  
(3) Infants of uninfected mothers | Weight for length lower in Group 1 vs. controls only at 3, 6, 24, & 36 mo | Impact of HIV infection on length for age greater & evident at all ages |
| USA (54)      | 1995 | HIV+ and controls followed from birth to 70 mo | No | Yes, appeared after 15 mo old |
| USA (55)      | 1994 | Hemophiliac boys 6–19 yr old:  
- HIV+  
- HIV– | +0.25 z  
+0.030 z | -0.56 z  
-0.01 z |
| USA (56)      | 1993 | 1–24 mo old:  
- HIV+ and controls | No | Yes, appears by 4 mo old |

NCHS, National Center for Health Statistics.
From Bailey RC et al. (50), Agostini C et al. (51), Peters VB et al. (52), Lepage P et al. (53), Saaredra JM et al. (54), Gertner JM et al. (55), and McKinney RE et al. (56).
consistent negative effect of HIV infection on linear growth irrespective of the study setting. The impact on length gain was observed in infants as well as in older children and following vertical and transfusion-acquired infection. The effect on length was more pronounced and appeared earlier than the effect on weight (50,51,53).

**Impact of Helminthiasis on Growth**

To determine whether there is a causal relation between helminthiasis and growth, we have examined the intervention trials with albendazole, a potent antihelminthic drug, carried out during the last decade (57–63). The prevalence of ascariasis and trichuriasis in these studies ranged from moderate to heavy and that of hookworm from low to heavy. All except the Indian trial enrolled school-aged children. The dosing schedules were a single dose in Haiti, four doses at 6-month intervals in India, and two doses at 3- or 6-month intervals in the other trials.

The impact on weight gain across studies was inconsistent (Table 6). Only three of the seven trials found a significant impact on weight gain when all enrolled children were included in the analysis. The maximum (1,000 g) increase in weight gain was reported from Kenya, where hookworm, ascaris, and trichuris infestation was highly prevalent (63). The burden of hookworm, ascaris, and trichuriasis was high in the two other trials that showed a positive impact of intervention (60,62), but it was also high in at least one of the negative trials (59,61).

There was no significant impact on length gain in any of the trials. The study from India reported a 9% reduction in the prevalence of stunting (57). There are two features in this study that merit consideration. First, the reasons for the gross imbalance in the allocation to the intervention and control groups were not explained. Second, the difference in the proportion stunted by the end of the study in the two groups (4%) was not significant. The reported estimate of a 9% reduction in stunting was computed by comparing the difference between the results at the end of the study and the baseline proportions within each group across the two cells. The validity of this approach is questionable.

The overall impression we gain is that the population impact of periodic deworming has not been consistently demonstrated. There is, however, evidence to suggest that treating infected children may result in some growth benefit.

**Impact of Asymptomatic Intestinal Infections on Growth**

Many children in developing countries have increased bacterial counts in the upper small intestine, or they are colonized with putative pathogens without any overt symptoms for extended periods of time (19,20,22). It is plausible that at least some of these infections affect growth. Peruvian children with asymptomatic cryptosporidiosis, for instance, gained 162 g less weight during the first month of infection than children without diarrhea who were not yet infected (19,20). Notably, whereas symptomatic cryptosporidiosis retarded weight gain more than asymptomatic cryptosporidiosis, the latter was twice as common. Given the higher prevalence
<table>
<thead>
<tr>
<th>Country (ref.)</th>
<th>Year</th>
<th>Subjects</th>
<th>Baseline and end-study prevalence</th>
<th>Dosing</th>
<th>Weight impact</th>
<th>Length impact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ascaris</td>
<td>Trichuris</td>
<td>Hookworm</td>
<td></td>
</tr>
<tr>
<td>India (57)</td>
<td>2000</td>
<td>1.5–3.5 yr</td>
<td>10% &amp; 40%</td>
<td>—</td>
<td>—</td>
<td>6-mo for 2 yr</td>
</tr>
<tr>
<td>Haiti (58)</td>
<td>1999</td>
<td>Schoolchildren, grades 1–4</td>
<td>29% &amp; 0.5%</td>
<td>42% &amp; 20.1%</td>
<td>6.9% &amp; 0%</td>
<td>Single dose, assessment at 4 mo</td>
</tr>
<tr>
<td>China (59)</td>
<td>1999</td>
<td>Schoolchildren</td>
<td>56%</td>
<td>76%</td>
<td>44%</td>
<td>6-mo for 1 yr</td>
</tr>
<tr>
<td>Philippines, Kenya</td>
<td>1999</td>
<td>Schoolchildren</td>
<td>91% &amp; 53%</td>
<td>85% &amp; 73%</td>
<td>—</td>
<td>3-mo for 6 mo</td>
</tr>
<tr>
<td>Guatemala (60)</td>
<td>1998</td>
<td>Schoolchildren</td>
<td>91% &amp; 53%</td>
<td>85% &amp; 73%</td>
<td>—</td>
<td>3-mo for 6 mo</td>
</tr>
<tr>
<td>Jamaica (61)</td>
<td>1995</td>
<td>6–12 yr</td>
<td>42% &amp; 7%</td>
<td>100% &amp; 50%</td>
<td>—</td>
<td>3-mo for 6 mo</td>
</tr>
<tr>
<td>Kenya (62)</td>
<td>1994</td>
<td>Schoolchildren</td>
<td>29% &amp; 4%</td>
<td>84% &amp; 50%</td>
<td>93% &amp; 0%</td>
<td>3 doses on consecutive days; assessment after 9 wk</td>
</tr>
<tr>
<td>Kenya (63)</td>
<td>1993</td>
<td>Schoolboys</td>
<td>44% &amp; 18%</td>
<td>96% &amp; 85%</td>
<td>96% &amp; 44%</td>
<td>Single dose; assessment after 4 mo</td>
</tr>
</tbody>
</table>

From Awasthi S et al. (57), Beach MJ et al. (58), Olds GR et al. (59), Watkins WE and Pollitt E (60), Simeon DT et al. (61), Adams EJ et al. (62), and Stephenson LS et al. (63).
of asymptomatic cryptosporidium infection, its contribution to poor growth in a community may be greater than that of symptomatic infection. Asymptomatic cryptosporidiosis also showed a significant adverse effect on length gain.

Preliminary data from Brazil show that intestinal colonization with a putative pathogen, enteroaggregative Escherichia coli, is associated with an increase in fecal inflammatory markers such as lactoferrin, interleukin (IL) 8, and IL-1β and with growth impairment regardless of the presence or absence of diarrhea. As about 8–10% of children in many developing countries are colonized with enteroaggregative E. coli, this finding may have practical significance (21).

Summary of Effects on Growth

There is a considerable variability in the effect of diarrhea and other illnesses on growth that is not readily explained. Differences in study design and analysis and in the dietary intake, burden, and underlying etiology of the infection are among the possible contributing factors. In Colombia, for instance, diarrheal illnesses did not significantly affect the growth of children who were participating in a supplementary feeding program, whereas such effects were seen in those not supplemented (64). Similarly, breast-feeding has been found to limit the effect of diarrhea on growth, as breast milk intakes are not significantly affected during illness.

Recurrent morbidity may not allow sufficient time for catchup growth. Some readily available nutritious foods may be erroneously linked to recurrent morbidity and therefore withheld. Also, caretakers may alter meal consistency on their own initiative or on the advice of health care providers.

The etiology of illness is another determinant of the magnitude of its effect on growth. In Bangladesh, enterotoxigenic E. coli and shigella infections but not any other causative agent were associated with an adverse effect on growth (17).

Some public health specialists hold the view that the impact of food supplementation and related education programs has been less than was anticipated because infection makes a predominant contribution to growth in children in developing countries. A natural consequence of this view is that a major investment in infection control by itself will result in large reductions in the rates of malnutrition. There is good evidence that infections have a significant long-term impact on weight and length, but the magnitude of the effect does not suggest that infection control by itself is sufficient to have a major impact on malnutrition. This view, however, may not be entirely true if asymptomatic infections of the gastrointestinal or urinary tract or other local sites are found to impair growth. As the prevalence of subclinical infections is possibly larger than that of symptomatic infections, we could be underestimating the overall impact of infections on growth. This may be particularly true for linear growth, which is not entirely nutrient related. Drug treatment and nutritional support, for instance, appear to prevent adverse effects of HIV infection on weight gain more than on linear growth.

Factors other than infection may help explain the limited impact of food supplementation programs on growth in countries such as India, where food intake is
usually low. Net daily energy intakes do improve following such interventions, but some deficit in energy and specific nutrient intake remains because sociocultural factors strongly influence feeding behavior. It is important to appreciate that even a small deficit in daily intake has a large cumulative impact on growth. This is also evidenced by the fact that in India’s largest food supplementation programs, for example, there have been substantial reductions in the rates of severe but not moderate malnutrition over the years.

**EFFECTS OF ACUTE AND CHRONIC INFECTION ON NUTRITION**

The effects of infection on nutrition are mediated primarily by alterations in dietary intake, nutrient absorption, or nutrient retention. There are also shifts in specific micronutrients within body compartments, the biological and particularly the clinical significance of which is not clearly known.

**Effects of Illness on Intake and Absorption**

The relation between infectious illnesses and dietary intake is seen to vary according to the type and severity of illness, the nature of the diet, child feeding practices, and other sociocultural factors (4–11). In Peruvian infants, total energy intake from complementary foods decreased by 20–30% during diarrhea or fever, but notably there was no effect on breast milk intake (4). Somewhat lower reductions in energy intake of 15–20% were reported in two studies from Guatemala in children who were no longer breast-feeding (8). On the other hand, in children receiving breast milk but only small amounts of complementary foods, as in Bangladesh, a substantial reduction in energy intakes during common illnesses was not observed (9). Overall, a 5–10% lower energy intake during acute illnesses is likely in partially breast-fed children and two- to threefold more in those consuming only non-breast milk foods. The decrease in energy intake was noted to be greater for measles and diarrhea than for respiratory infections (65).

Decreased intestinal absorption of macro- and micronutrients occurs in acute and persistent diarrhea. Bangladeshi children with acute viral diarrhea, for instance, absorbed only 45% of the nitrogen, 42% of the fat, and 55% of the total energy intake in their diet (66,67). Those with persistent diarrhea absorbed, on average, 68% of the energy and 53% of the total nitrogen intake. Nutrient absorption may take 1–3 weeks after cessation of symptoms to be fully restored to precollapse levels. The extent of nutrient malabsorption caused by different helminthic infections is variable. Steatorrhea and diminished vitamin A absorption have been reported in ascariasis (68,69). A study of Colombian children with a moderate helminth burden showed that administration of antihelminthic drugs was followed by decreased stool fat and nitrogen losses and improved xylose absorption (70). Malabsorption of some nutrients does occur in respiratory infections, but there is little evidence of significant fecal energy losses. Decreased intestinal vitamin A absorption was well demonstrated during acute lower respiratory infections (68,69). In an Indian study, for instance, children
with pneumonia absorbed 74% of a tracer dose of vitamin A compared with 99% by noninfected children. In the same study, rates of 70% and 80%, respectively, were reported in those with diarrhea and ascariasis. Even in asymptomatic infection with parvovirus and certain strains of *E. coli*, decreased vitamin A absorption has been reported (71). Absorption of β-carotene is also impaired in gastrointestinal as well as in respiratory infections (72).

Increased protein losses occur transiently in acute viral, enterotoxigenic *E. coli*, or shigella-associated diarrhea. Increasing the dietary protein intake substantially improved catchup growth following shigellosis (73–75). Measles exacerabates the protein-losing enteropathy in acute enteric infections as a result of its direct effect on the intestinal tract (76).

Fecal zinc wastage has been well documented during acute and persistent diarrhea (77). It is, however, not clear whether this reflects impaired absorption, direct losses into the lumen, or both. Blood loss during hookworm infection resulting in iron deficiency anemia is another illustration of nutrient losses during infection that are unrelated to malabsorption.

**Effects of Infection on Nutrient Utilization**

Increased energy expenditure may contribute to the weight loss associated with infections. Several studies have observed an increase in resting energy expenditure in acute infections. In HIV-infected children, an increased resting energy expenditure was reported that was accentuated when these children had a secondary infection (78,79). The origin of this hypermetabolism is not clearly defined. Increased levels of catabolic hormones and effects of proinflammatory cytokines have been suggested as possible mechanisms, but neither has been proved conclusively (80).

Abnormal utilization of available substrate and their increased losses may occur during infections, acute or chronic inflammation, and even vaccination (81-85). It has been known for a long time that urinary nitrogen output is increased during infection or trauma (82,83). *In vivo* studies have shown that this is explained by a disproportionate increase in protein breakdown over synthesis (83). In chronic infections such as HIV and in inflammatory bowel diseases, impaired physical growth is often difficult to explain on the basis of decreased intake and absorption alone (50–56,80). It is postulated that increased protein breakdown may be an important mechanism of growth failure in such situations. Concomitant reductions in food intake would have a synergistic effect, as amino acid intake is the main stimulus to protein synthesis. Food supplementation in chronic inflammatory bowel diseases increases protein synthesis and balance but does not affect breakdown rates (86). Plasma concentrations of insulin-like growth factor are decreased in shigellosis, persistent diarrhea, and inflammatory bowel disease. Notably, insulin growth factor-1 concentration is strongly correlated with protein balance (86–88).

Urinary losses of specific nutrients have been found in enteric and nonenteric infections. Urinary losses of vitamin A were found to be increased in sepsis, diarrhea, and pneumonia. Urinary loss of retinol-binding protein increases during infection, and retinol is probably excreted bound to it (89–91). The increase in
retinol-binding protein excretion may be linked to decreased serum transthyretin concentration or diminution in the mutual affinity of the two molecules (90). The association of retinol-binding protein with transthyretin in serum is necessary to prevent rapid clearance in the kidney as it is a low molecular mass protein. Serum transthyretin concentrations are decreased during infection. Increased urinary losses and decreased intake and absorption act synergistically during infection to aggravate vitamin A depletion, as has been observed for measles, chicken pox, acute respiratory infections, and particularly persistent diarrhea (92–97). Zinc, on the other hand, appears to be conserved during infection, and urinary losses have not been reported. Chronic infection and inflammation result in anemia, which appears to be related to impairment of iron metabolism but also to impaired erythropoiesis, which is believed to be more important (98). Immune activation with an infectious agent releases cytokines, which leads to the inhibition of colony-forming units–erythroid development and produces anemia (98,99). This reduction in erythropoiesis can be overcome with pharmacological doses of erythropoietin both in vitro and in vivo.

An acute-phase response accompanies infection or other medical or surgical disorders (100). This phenomenon, associated with activation of complement and stimulation of the immune system, may have important nutritional costs even though it appears to have the overall purpose of defending the infected individual. Acute-phase response to infection is characterized by a stereotyped set of metabolic responses. These include hypoxicemia and hypoferremia as a result of tissue sequestration and increased hepatic synthesis of acute-phase proteins, which is reflected in an elevation of C-reactive protein, α1-antitrypsin, haptoglobin, and α-acid protein. Human and animal studies show that the acute-phase response is mediated by cytokines such as IL-1 and tumor necrosis factor-α, which are secreted by activated macrophages and monocytes in response to infection or injury (101,102).

The decline in plasma zinc or iron is the result of increased tissue uptake. Metallothionein, an intracellular metal-binding protein, has been shown to be responsible for increased hepatic uptake of zinc. Activation of hepatic metallothionein results from stimulation by IL-6 and glucocorticoids, secretion of which is induced initially by IL-1 (103). In animal models, there is increased uptake of zinc by the bone marrow, spleen, and liver following injection of labeled IL-1 together with decreased uptake by bone, skin, and intestine (101). Clinical and experimental evidence suggests that the magnitude of the effects of infection on zinc homeostasis depends partly on the severity of the infection and the cytokine response (104). Furthermore, these changes may begin early in the prodromal phase of the illness (100). An important but unresolved issue is whether the decreased serum concentration of certain micronutrients results in reduced transport to target tissues. Deficiency of these micronutrients at tissue levels could affect immunological and other body defense functions.

It has been shown that proinflammatory cytokines increase nitric oxide synthase in leukocytes, resulting in the production of citrulline and nitric oxide by oxygenation of one of the guanido-nitrogen groups of arginine. One of the effects of nitric oxide is as a microbicidal (105–107).
Infection, Inflammation, and Bone Modeling

Active infection or inflammation can alter growth independently of nutritional factors. Circulating inflammatory mediators may play a role in this growth delay. Cytokines, including IL-1, tumor necrosis factor-α, and IL-6, promote bone resorption (13,108,109). In inflammatory bowel disease, tumor necrosis factor-α and IL-6 have been found in the intestinal mucosa and plasma, but their role in impaired growth is unclear. Koniaris et al. (110) evaluated the effect of experimental colitis on bone growth in a nutritionally controlled rat model. The colitis group had impaired linear growth; the resting zone was larger, the proliferative zone was smaller, and the terminal hypertrophic zone was reduced in this group. The levels of IL-6 were raised in the colitis group. IL-6 has an inhibitory effect on collagen and noncollagen protein synthesis in osteoblasts in addition to inducing bone resorption.

In another putative mechanism, infection or inflammation may alter bone growth by a dysregulating influence on myeloid cell development. One action of tumor necrosis factor-α may be to direct the development of progenitor cells preferentially to macrophages rather than to osteoclasts (108).

Last, a model of direct viral infection has been proposed in the pathogenesis of Paget’s disease (111). This mechanism is unlikely to be of relevance to the linear growth effects of recurring, acute infections common in children in developing countries.

CONCLUSIONS

The etiology of malnutrition is multifactorial. Weight and length at birth, dietary intake, and the quality and burden of infections largely determine the extent to which the genetic potential for growth is achieved by children. The individual contribution of each of these factors to faltering growth is large enough to be of practical significance.

The acute effects of infection include weight loss or decreased gain and deterioration in micronutrient intakes—for example, of zinc or vitamin A—in a variety of infections. These in turn increase the risk of acquiring further infections and, more importantly, the severity and duration of the subsequent illness and possibly the risk of death. It is conceivable that the acute perturbations in status of some micronutrients during infections may have other consequences, for example, on neuropsychological function.

There is sufficient evidence of the long-term effects of infection on weight and length gain. The magnitude varies depending on the nature, duration, and severity of infection, the quality of medical care, and the nutrient intake. Control of infections, based on current evidence, is unlikely to lead to a desired level of weight and length gain without concurrent improvement in normal dietary intake after the initial 6 months of life. Measures to improve intrauterine growth would further help to reduce the rates of wasting and stunting. It is important to bear in mind that the available reports are insufficient for estimating the effects of subclinical infections. The recent demonstration of the substantial weight deficit associated with asymptomatic
cryptosporidiosis (19,20) clearly shows that we are underestimating the overall effects of infection on growth and nutrition.

REFERENCES


DISCUSSION

Dr. Gottrand: One pathogen you did not discuss is Helicobacter pylori, which is very common in developing countries, where more than 80% of children are infected by 2 years of age. Data from developed countries show that infected children are shorter and lighter than noninfected children (1–4). Confounding factors have been evoked, such as low socioeconomic status. Do you know of any studies, especially interventional studies in developing countries, on the role of H. pylori in growth and nutrition?

Dr. Bhan: I intentionally did not mention helicobacter. Helicobacter infection begins at about 3 months of age, and by 1 year, almost 50% of children are infected in India. When you do endoscopy, most of these children have a mild degree of gastritis—in fact, I have rarely seen a gastric biopsy from a child whom I endoscoped where no gastritis was reported; it’s another form of inflammation. Those studies that have suggested that helicobacter has an impact on growth seem too speculative to me, when you consider that the determinants of helicobacter infection and poor growth are the same. So, I would say that we need to wait for better studies to be sure that those associations are causal. It is true that there have been intervention studies with treatment targeted toward H. pylori that have tried to prove the hypothesis (1–4). The trouble with intervention studies is that when you give antimicrobials to these children, you also eliminate bacterial overgrowth and many other bacteria, so it’s not easy to prove that the growth impact is related to H. pylori infection. It’s an open issue at the moment, but I personally do not consider the evidence to be anything more than speculative.

Dr. Koletzko: You showed that symptomatic and asymptomatic infections of the gastrointestinal tract and to a lesser extent of the respiratory tract are associated with reduced growth, but the intervention studies—for example, the deworming studies—are less convincing. One wonders whether there are other factors that come into play, in addition to nutrient intake, absorption, metabolism, and so on. One of the first questions one would want to raise is the extent to which infections and growth problems are both associated with lifestyle, housing, crowding, number of siblings, position in the family, and other factors that determine both the risk of infection and the risk of malnutrition. Have some of these studies dissected out the role of infection versus other confounding factors to estimate the relative importance of infection as a determinant of malnutrition? The example you showed of asymptomatic HIV
infection being related to poor growth in developing countries, but much less so in developed countries, raises the same question. Isn’t it likely that this is related to the nutritional state of the HIV-infected mother and her socioeconomic status? Is it really true that asymptomatic HIV infection causes growth deficit?

**Dr. Bhan:** With regard to the types of study you refer to, there are two main concerns: One is reverse causality, and the other is confounding. Reverse causality was handled in some of these studies by selecting both the cohorts. Some have adjusted for baseline morbidity, but many have not. So, qualitatively, it’s a mix. Many of the studies have adjusted for socioeconomic factors, but when I compared studies that had done this and those that had not, I found that the effects were generally consistent between the two. So, I think these factors have some effect, but the association is rather general. With regard to HIV, I think the impact on linear growth in developed countries is very marked. It’s only the effect on weight that is not seen, and I attribute that to the fact that those children were given excellent nutritional support. This means that the effect of infection on growth is conditional upon the quality of nutritional support available. That would be true for any developing country in relation to other infections: In Colombia, for example, the association between diarrhea and growth was not seen in children who were participating in a food supplementation program. So, my conclusion that infection control by itself would not have a major impact on growth is based on the assumption that the conditioning factor is the kind of feeding that goes on in the background.

**Dr. Lala:** With regard to HIV and the differences you noted in children from developing countries compared with children from developed countries, my feeling is that these differences are largely attributable to the fact that children in developed countries have access to antiretroviral therapy. I think this in itself accounts for most of the differences. Some of the data in developing countries have been disappointing in that when HIV-infected children are given intensive nutritional supplementation, the effects on growth have been really very minimal unless antiretroviral therapy is also given. Having said that, I’m not aware of any trials—certainly no randomized trials—that have looked at the effect of micronutrient supplements in HIV-positive children. These might have a positive effect on growth through their actions in decreasing the severity of infections.

**Dr. Bhan:** There has been talk about micronutrient supplementation in HIV-infected children for a long time, but there are no published data yet to show that they have an important impact, so at the moment, I really don’t know the answer to that.

**Dr. Guesry:** You have emphasized the role of asymptomatic infection, and indeed this is very important. But under field conditions, I wonder how you differentiate asymptomatic infection from a carrier state. It seems that each time you find a pathogen, you diagnose asymptomatic infection, but I think finding a pathogen is insufficient to establish a diagnosis of infection.

**Dr. Bhan:** That’s an excellent question. First of all, I would like to emphasize that I’m not in any way saying that asymptomatic infection has been shown to make a large contribution. My message is simply that the burden of infection is very large, and so it is worthwhile having a look at this aspect. I gave some illustrations for cryptosporidium, but that does not mean the same is true for everything else. The ways the controls are chosen is important: In these studies, the control children were asked whether they had diarrheal symptoms in the last 6 weeks. That was the basis for choosing the controls. We have enormous experience with weekly
cultures in Bangladesh and India, on huge numbers, and if you are implying that a child with diarrhea may be excreting the pathogen for a long period, I can tell you that not even 5% of the children, even with persistent diarrhea, pass the same pathogen if you culture them every fifth day. The syndrome of chronic persistent infection explaining chronic intestinal disease simply does not hold up—these are all new pathogens each time. But if the infection is clinically mild and does not produce obvious diarrhea, even though there may be some degree of malabsorption or a mild acute-phase response, then we call it “asymptomatic” or subclinical. What we are really saying is there is a bug in the stool and we don’t know what infection to call it. In the case of enteroaggregative E. coli, it has been shown that there is inflammation, so it is a minimally symptomatic or subclinical infection, or whatever you would like to call it.

Dr. Martorell: Several times in this meeting, you have issued a challenge: You looked at what we have been able to achieve in terms of reducing growth failure and improving nutrition, and you’ve said we haven’t been very successful. You said that you believe that controlling infection by itself is not going to make much of a difference, but perhaps one should say that we really don’t know. You showed, for example, that asymptomatic infections are very common, but you also said that we really haven’t studied their influence. Maybe we simply don’t know what would happen if such infections were tackled, in terms of improving nutritional state. Then, with regard to nutrition supplementation, you are not convinced that the reported high intakes in some of the supplementation trials in the city slums in India were real, so maybe the diets were not changed substantially. If we knew that, we might know where we are going. You have also emphasized the importance of childcare and the attitudes of mothers to feeding and about how much children can eat when you have somebody who feeds the child very frequently. I would like to throw the challenge back to you and ask you to come up with an answer that is a bit more encouraging than has been the case up to now.

Dr. Bhan: For me, the primary challenge in South Asia today is the mother. The mothers don’t see their children as being undernourished. They don’t recognize the problem. They say their children are fine—what’s wrong with them? It is extremely difficult to get across the amounts of food a 9-month-old child requires. They are all on as little as 10% or 15% of their complementary food requirements between 6 and 9 months, and between 4 months and 8 months, there is a fourfold increase in the rate of stunting. I think that factor is extremely important. How can we change it? Can we do it by programs targeting the perspectives of mothers and families, or do we need a larger, more deep-seated change, dependent on 10 years of schooling for girls or other general improvements? I tend to believe that we have to change the “consumer” right from the beginning. If you change the consumer, you change the person who is looking for food and providing the care. Control of infection—at least to the extent of reducing its severity—is also a function of the mother, because she has to go and seek treatment. I don’t mean to say that we do not need urgently to reduce morbidity—I’m not questioning that at all. But did all the investments we have made into improvement in sanitation and so on ignore that other dimension? It may come down to the fact that the consumer is not ready for change.

But there is a huge problem. Many children spend one-third of the year being ill, so clearly the morbidity must be tackled. Micronutrients seem to be important here—you have seen that the effects of zinc on diarrhea and pneumonia are huge
in routine supplementation trials. In most of the slums, a clean tap water supply is already available, so the behavioral issue is that of the handling of the tap water. How do we change that? It comes back to the mother again. What we don’t have is proper excreta disposal, and there is still gross overcrowding. So, in the long term, we mustn’t get carried away by the effects of particular micronutrients. The issue is larger than that.

Dr. Ulijaszek: I would like to bring up the issue of deworming trials and the number of studies that have shown a lack of impact. Can you comment on the extent to which there may be replacement of parasites by other potential infectious agents that have an impact on growth?

Dr. Bhan: At the end of these trials, the prevalence of helminthiasis has generally been reduced by half, but never eliminated. So, a 90% infestation rate becomes a 50% rate at the end of the trial. With infection rates being so high, the intervention does not always work as it should. My straightforward way of looking at this is that in most cultures, parasitic infestation does not have a big impact on growth. The primary issue is the availability of sufficient food.

Dr. Stoltzus: We just recently completed an antihelminthic trial in rural Tanzania, where we were looking at the preschool age group because there are no policies for use of antihelminthics in preschoolers, at least from the WHO. So, we wanted to clarify the age above which antihelminthic treatment would be helpful, knowing that it takes a while for children to accumulate enough worms to affect their health and nutritional status. What we found was the exact opposite of our expectations: All the benefits of antihelminthic treatment were in the youngest children—children under 30 months of age in whom the worm burdens were low. What we saw in those children was that the relative risk of wasting malnutrition was decreased by nearly half. Small-arm circumference went down very dramatically, anorexia went down, severe anemia went down, and all in the young children. This caused us to rethink what helminthic infections might be doing and to focus on a possible inflammatory response to the initial infection rather than on the accumulated worm burden that has driven the deworming policy up to now—focused on schoolchildren because they harbor the greatest number of worms. Perhaps a 9-month-old infant who is experiencing the migration of larvae through the body is mounting an inflammatory response that has large metabolic effects. So, I was particularly interested in the reports about cryptosporidium in Peru. We know that in many of these cases, for example, malaria, the immune response to a first infection is different from subsequent infections. So, it is possible that in these early years of life, when we see such profound stunting and wasting in children, a part of it is related to their first inflammatory response to infections. These are not easy things to study.

Dr. Bhan: It’s an extremely important question, especially when you consider that the largest growth impact of cryptosporidium is in the first 9 months of life.

Dr. Brunser: I listened to your presentation with real pleasure, because I think it mirrors what we have seen in Chile. I believe that if one has to invest in something that will decrease the incidence of asymptomatic infection and diarrhea, it will involve overall development of the area or the country. If you want to deal with a single factor, I agree with you that it must be the mother. Up to 2 years of age, the mother is the most important factor in whether her child becomes infected or not or malnourished or not. Studies that we did here years ago came up with the finding that in the same environment, with the same socioeconomic conditions, with the same level
of education of the mothers, and so on, there are mothers whose infants are sick all the time with diarrheal disease (5). But there are also mothers whose children never get ill, and these are called “positive deviants.” To us, this was a sign that probably the most cost-effective means of preventing diarrhea during the first 2 years of life is maternal education.

I also agree with you that asymptomatic infection has an important impact on nutritional status. One has to bear in mind that there is no such thing as the “innocent” passage of bacteria along the gastrointestinal tract. You pay a toll for that, and one has to understand that the gut, besides being 300 m² in surface area, is the largest immune organ in the body and the second largest endocrine organ. If it is bombarded by pathogenic or even nonpathogenic bacteria in large numbers, it has to keep the immune machinery acting all the time. This is what you see when you look at the mucosa under the microscope—you see the activation of the immune system, and that has a cost. It has a cost in terms of energy, in terms of loss of nutrients, and probably in terms of interleukin action, signifying that there is active stimulation and active defense.

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