The Effect of Diarrhea on Appetite in Children Ages One to Five

Amy L. Beck

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THE EFFECT OF DIARRHEA ON APPETITE IN CHILDREN AGES ONE TO FIVE

Amy Laura Beck

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THE EFFECT OF DIARRHEA ON APPETITE IN CHILDRENS AGES ONE TO FIVE

Presented by

Amy Laura Beck, B.A.

Major Advisor

Judy Lewis

Associate Advisor

Juan Carlos Salazar

Associate Advisor

Stephen Schensul

University of Connecticut

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Introduction

One of the greatest health inequities between rich and poor countries is the disparate burden of childhood disease. Children born to poor families in the developing world are significantly less likely to survive to adulthood than children in developed countries and much more likely to suffer permanent sequelae as a result of childhood illness. Malnutrition is common among poor children in underdeveloped countries and is a major factor contributing to both morbidity and mortality. Numerous factors contribute to malnutrition among children in the developing world including an inadequate availability of calories and specific nutrients, dietary monotony, and illnesses such as diarrhea. There is strong evidence which demonstrates that diarrhea contributes to malnutrition. In addition, some researchers believe that being malnourished increases children’s risk of diarrhea incidence and contributes to the duration of diarrheal episodes thereby setting up a vicious cycle resulting in more diarrhea and consequently worsening malnutrition.

While the causal relationship between diarrhea and malnutrition is well established, there is currently very little specific information about the mechanisms by which diarrhea contributes to poor nutritional status. Most of the literature on this topic suggests that three factors contribute to worsening nutrition during diarrheal episodes: decreased absorption of nutrients in the gastrointestinal tract, increased metabolic demand as a result of infection, and decreased intake caused by a drop in appetite. This thesis examines the hypothesis that diarrhea leads to decreased appetite in children.

The thesis is organized in the following sections. The background section provides an overview of child mortality, childhood malnutrition, and diarrheal disease.
in the developing world. These sections are followed by a literature review of the existing research on the interactions among diarrhea and malnutrition and the effect of diarrhea on appetite. The final section of the background addresses some possible molecular mechanisms by which diarrheal illness could lead to decreased appetite in children.

Following the background, the author presents an original case control study on the effects of diarrhea on appetite in children ages one through five living in a low-income peri-urban community outside of Lima, Peru. The objective of this study was to test the hypothesis that diarrhea leads to decreased appetite in children. An observed feeding trial was used to compare the intake of children with diarrhea to that of healthy controls and of the same children when healthy. The purpose of undertaking this study was to further elucidate how diarrhea may contribute to malnutrition. Understanding the interaction between diarrhea and malnutrition will contribute to the design of interventions to improve the health status of children in the developing world.

**Background**

**Childhood mortality**

A child’s chance of survival to adulthood is largely dependent on the country in which he or she is born. A World Health Organization (WHO) report on child death from 2000-2003 determined that approximately 10.6 million children younger than five die each year, most in low-income countries and low-income areas of middle-income countries. This report estimated that 28% of all child deaths occur in the neonatal
period and are caused by neonatal sepsis (10%), pre-term birth (10%) and birth asphyxia (8%).

Outside of the neonatal period, the top three causes of death to children under age 5 are pneumonia (19%), diarrhea (18%) and malaria (8%).

The risk factors for childhood death are numerous, incompletely understood and often synergistic. One of the most significant risk factors is malnutrition, as determined by underweight, which by WHO estimates is implicated in 53% of all child deaths.

Several meta-analyses have shown that even moderate malnutrition is a major risk factor for child death and that the risk of dying increases according to the severity of the malnutrition. Caulfield et al. looked specifically at the association between malnutrition and deaths from pneumonia, diarrhea, malaria, and measles, extracting data from 10 cohort studies. The relative risk of death from all four causes examined was significantly higher in children with moderate malnutrition and increased with the severity of the malnutrition. For children with severe malnutrition, the overall relative risk of death from one of the studied causes was 4.24, while for those with very severe malnutrition, it was 8.72. Thus, understanding and addressing the causes of malnutrition is crucial to improving child survival.

**Childhood Malnutrition**

*Definitions*

Malnutrition has been defined by the WHO as "the cellular imbalance between supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific functions." This broad definition encompasses deficiencies in overall calories, protein, and specific micronutrients. The sequelae of malnutrition
in children include poor growth, decreased cognition, impaired immune function, and increased risk of death from childhood illnesses.\textsuperscript{5}

The assessment of a child’s nutritional status is based on a combination of anthropometric values, physical signs, and laboratory values.\textsuperscript{5} Measurements of height and weight are the most frequently used method of determining nutritional status.\textsuperscript{6} These values are compared to international reference standards for children of the same age and gender.\textsuperscript{6} Anthropometric measurements are frequently expressed as a Z-score which denotes the number of standard deviations that the value falls from the mean for that particular age and gender.\textsuperscript{6} Current international reference standards published by the WHO include Z-scores for weight-for-age (WAZ), height-for-age (HAZ) and weight-for-height (WHZ).\textsuperscript{6} Thus, for example, a child with a WAZ of -2 has a weight for his or her age that is two standard deviations below the expected mean, while a child with a WAZ of 1.5 has a weight for his or her age that is one and a half standard deviations above the mean.\textsuperscript{6}

\textit{Protein Calorie Malnutrition}

While poor growth can be due to a variety of nutritional deficiencies and underlying diseases, an insufficient intake of protein is thought to be the most important cause.\textsuperscript{6} Children with any of the three anthropometric Z-scores (WAZ, HAZ, WHZ) below -2 are considered to have protein calorie malnutrition while those with a Z-score below -3 are considered to have severe protein calorie malnutrition.\textsuperscript{6} \textit{Stunting} is a term which describes children who have a low height-for-age (HAZ $\leq -2$).\textsuperscript{6} The term \textit{wasting} refers to children with low weight-for-height (WHZ $\leq -2$).\textsuperscript{6} Finally \textit{underweight} refers
to children with low weight-for-age (WAZ <-2). Stunting is generally considered to reflect chronic malnutrition, while wasting is thought to indicate a more acute nutritional insult. Underweight can occur due to acute or chronic malnutrition and thus the WAZ is seen as an overall indicator of the child’s current state of health.

Data from the WHO Database on Child Growth from 1980 to 1992 indicated that greater than one-third of all children meet an anthropometric criterion for protein calorie malnutrition. Looking across the entire developing world, 43% of children were found to be stunted, 36% were underweight and 9% were wasted. However, more recent data suggests a steady decline in levels of malnutrition in all regions of the world except for Eastern Africa. A paper published in 2000 using updated information from the WHO Database on Child Growth estimated that 32.8% of all children around the world were stunted with a prediction that by 2005, this value would drop to 29%. The predicted prevalence of stunting for 2005 was much higher in Africa (33.8%) and Asia (29.9%) than Latin America and the Caribbean (9.3%). The sub-regions found to have the highest degree of stunting were East Africa and South Asia with a prevalence of 48.5% and 39.4% respectively.

The most life threatening form of malnutrition is severe protein calorie malnutrition which is further broken down into three categories—kwashiorkor, marasmus and marasmic kwashiorkor. Kwashiorkor is defined as protein calorie malnutrition with the presence of edema. Affected children frequently have flaky skin and hair that is dry and easy to pull out. They are irritable, apathetic, and have a poor appetite when offered food. In contrast, marasmus is severe protein calorie malnutrition not accompanied by edema. Children with marasmus have a thin, wasted
appearance with minimal body fat and a WHZ below -3 and tend to have a good appetite when offered food. Malnourished children with both wasting and edema, are described as having marasmic kwashiorkor. It was classically thought that kwashiorkor was caused by a deficiency in intake of protein with adequate overall caloric intake while marasmus was caused by a deficiency in both protein and total calories. However, more recent work on this topic suggests that dietary protein content alone does not determine whether a child progresses to kwashiorkor or marasmus. Some researchers feel that progression to kwashiorkor is more likely due to a deficiency in an antioxidant nutrient while others have suggested that the presence of aflatoxins in food is the main culprit.

Children with all forms of protein calorie malnutrition exhibit a decrease in their metabolic rate, a decreased level of activity and poor growth. In extreme cases, severe protein calorie malnutrition can be fatal. More commonly, however, protein calorie malnutrition is an insidious process affecting all areas of a child’s functioning, including physical growth, immune functioning, and brain development. Several studies have documented that protein calorie malnutrition in the pre-school years is associated with long term deficits in cognition.

**Micronutrient deficiencies**

In addition to protein calorie deficiencies, many children in the developing world are missing vital micronutrients. The micronutrients that are most commonly deficient in children include iron, zinc, iodide, and vitamin A. Iron deficiency most frequently manifests as anemia and is usually due to a diet poor in iron. While some
vegetable foods contain iron, the richest and most readily absorbed sources of iron are in animal foods such as red meat. Thus, poor populations which cannot afford animal foods are at high risk of anemia. In addition, certain parasitic diseases such as hookworm contribute to iron deficiency anemia in endemic areas. Iron deficiency is also very common in women of child bearing age in the developing world causing them to give birth to children with insufficient iron stores. The WHO estimates that 40% of pre-school children and 50% of pregnant women in the developing world suffer from iron deficiency anemia. This is of concern because there is strong evidence that iron deficiency in childhood is associated with long term cognitive deficits.

Zinc is an essential nutrient that is necessary for proper immune function and growth. Zinc is present in animal and vegetable sources but is best absorbed from animal foods. Because the body has no way to store zinc, a constant dietary supply is necessary to prevent deficiency. Thus, children with monotonous diets that are primarily vegetarian are at high risk of zinc deficiency. The manifestations of severe zinc deficiency include characteristic skin changes, intermittent diarrhea, recurrent infections and growth retardation. However, even mild zinc deficiency leads to a decrease in immune function and increased susceptibility to infection. A meta-analysis of studies on zinc supplementation in children in the developing world demonstrated that it reduces morbidity from both diarrhea and pneumonia. Two studies have also shown that zinc supplementation leads to an overall reduction in childhood mortality.

Iodine deficiency is a problem in countries where salt is not iodized and inhabitants do not consume fish and seafood. The WHO estimates that 54 countries
are still iodine deficient and that approximately 33% of all households worldwide do not yet have access to iodized salt.\textsuperscript{14} The major consequence of iodine deficiency in children is mental retardation.\textsuperscript{14} Pregnant women with iodine deficiency have a high likelihood of spontaneous abortion, stillbirth, and giving birth to children with congenital anomalies.\textsuperscript{14}

Vitamin A deficiency leads to blindness in children and also increases a child’s risk of severe illness and death from measles infection.\textsuperscript{14} According to WHO estimates, 250 million preschool children are vitamin A deficient and 250-500,000 children become blind every year from vitamin A deficiency.\textsuperscript{14} Vitamin A deficiency can be prevented through a variety of strategies including breast feeding in the first year of life, periodic high dose supplementation, food supplementation, and encouraging the cultivation of foods with high vitamin A content.\textsuperscript{14}

\textit{Causes}

The proximate causes of malnutrition in children in the developing world include an inadequate intake of calories and essential nutrients\textsuperscript{5} as well as infectious diseases such as diarrhea (discussed later in this thesis). The most important underlying socio-economic cause of malnutrition is poverty.\textsuperscript{21} A UNICEF analysis of underweight prevalence by household asset quintile in 68 countries found that children living in the poorest households are twice as likely to be underweight as children living in the wealthiest households.\textsuperscript{21} The greatest disparities were found in Latin American and Caribbean countries where children in the poorest households were 3.6 times more likely to be underweight than children in the wealthiest households.\textsuperscript{21} Finally, in the
setting of both natural disasters and war, children are at greatly increased risk of malnutrition and those with poor nutritional status at the start of the disaster are the most vulnerable.21

**Childhood Diarrhea**

*Definition*

The WHO defines diarrhea as the “passage of loose or watery stools at least three times in a 24 hour period.”22 This is the definition most frequently used in research studies on diarrhea, although there is some variability.22 Some researchers emphasize that the change in consistency in stool from the child’s pattern is more important than frequency while others use the parental judgment that the child is having diarrhea as the most important criteria.22 Diarrhea can result from a wide variety of disease states including infection, allergic and immunological disease, and neoplastic conditions.22 Globally, however, infectious etiologies are the most frequent cause of diarrhea and the biggest concern from a public health perspective.22

*Scope of the problem*

In the early 1980s, an estimated 4.6 million children in the world died each year from diarrhea.22 Diarrheal deaths are largely due to dehydration and are almost always preventable with appropriate medical intervention.22 The number of deaths from diarrhea has decreased significantly since then, with data from 2000-2003 revealing approximately two million deaths annually.1 This decrease in mortality from diarrhea is in part attributed to the implementation of oral rehydration therapy for acute
dehydration diarrhea. Other factors that are thought to play a role are an increase in breast-feeding, the decrease in levels of malnutrition and improved sanitation. Nonetheless, diarrhea remains the second biggest killer of children outside of the newborn period. Furthermore, while childhood mortality from diarrhea has decreased, morbidity has largely stayed the same. A study published in 1992 which included data from 1980 to 1992 found a worldwide incidence of 2.6 episodes of diarrhea per child per year. In a meta-analysis of 27 studies on diarrhea morbidity carried out between 1992 and 2000, the authors determined that the median incidence for all children under age 5 living in developing countries was 3.2 episodes of diarrhea per year. This apparent increase is most likely due to improved methodology in many of the studies included in the later analysis, such as increased frequency of surveillance of the study population as well as more sophisticated statistical modeling.

Pathogens

The pathogens responsible for infectious diarrhea in children include viruses, bacteria, and parasites. Rotavirus is the most common cause of diarrhea in children worldwide infecting virtually all children by age 3 and accounting for 40% of all diarrheal cases in the developing world and 60% of cases in developed countries. Rotavirus diarrhea is thought to be responsible for 600,000-875,000 child deaths annually. Rotaviral epidemics strike most frequently in the cooler months in temperate regions but occur year round in the tropics. Rotavirus is thought to be spread via the fecal-oral route. Other viral families that cause diarrhea in children include the caliciviruses, astroviruses, and enteric adenoviruses.
The main bacterial species that cause diarrhea in children include *E. Coli*, *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia enterocolitica*, and *Vibrio cholerae*. Two strains of *E. Coli*, enteropathogenic *E. Coli* (EPEC) and enterotoxigenic *E. Coli* (ETEC) are frequently implicated in watery infantile diarrhea in developing countries. *E. Coli* is found in both human and animal reservoirs and most commonly spread by contact with contaminated food. The principal reservoirs for both *Campylobacter* and *Salmonella* are farm animals. Thus, people are most often infected through direct contact with animals or the consumption of contaminated meat and dairy products. In the case of *Shigella*, humans are the natural host and spread is generally via the fecal-oral route. *Yersinia enterocolitica* is a relatively uncommon pathogen in the developing world that is usually acquired via undercooked pork or unpasteurized milk products. *Vibrio cholerae* is a waterborne bacteria which causes cholera, a disease characterized by persistent watery diarrhea which appears both sporadically and in epidemics.

The intestinal parasites *giardia* and *cryptosporidium* are all associated with watery diarrhea in children in developing countries. However, many children who are infected with these parasites are asymptomatic. *Entamoeba histolytica* is an intestinal parasite that causes bloody diarrhea and may migrate to other areas of the body, most notably the liver. Among parasitic diseases, it is the third most deadly after malaria and schistosomiasis, resulting in approximately 100,000 deaths per year.

*Classifications*
Two severe manifestations of diarrheal illness are persistent diarrhea and dysentery. Persistent diarrhea is defined as any diarrheal episode beginning acutely and lasting longer than 14 days. An analysis of eight studies in Asia and Latin America found rates of persistent diarrhea ranging from 3 to 23% of all episodes. Various researchers have attempted to pinpoint which pathogens are responsible for persistent diarrhea with wide variation in results. For example, Enteroadherent E. Coli (EAEC) was found more frequently in persistent episodes in studies in India, Bangladesh, and Mexico. However, in a different study in Bangladesh as well as studies in Peru and Cambodia, no such association was found. Similarly, cryptosporidium was found more commonly than other pathogens in persistent diarrheal episodes in Bangladesh while in Peru it was found more often in acute episodes. In his paper on persistent diarrhea, Black suggests that many persistent diarrheal episodes may in fact be caused by a series of infections with different pathogens and that host specific characteristics such as malnutrition may be the most important determinants of diarrheal duration.

Dysentery is formally defined as “frequent, small bowel movements accompanied by blood and mucus with tenesmus, or pain on defecation.” For the purposes of case definitions in most research and treatment programs, however, the presence of gross blood in the stool of a patient in a developing world country is classified as dysentery. The two most common forms of dysentery are amebic dysentery, caused by Entamoeba histolytica and bacillary dysentery which is most often caused by Shigella species but may be caused by other bacterial pathogens such as Campylobacter.
Treatment

In general, the mainstay of treatment for infectious diarrhea is rehydration with early re-feeding.\textsuperscript{22} In almost all cases, rehydration can be achieved via the oral route with an appropriate oral rehydration solution (ORS) containing sugar and electrolytes.\textsuperscript{28} Recipes exist for home preparation of ORS using simple table sugar and salt to be administered in the early stages of an illness.\textsuperscript{28} However, if a child becomes clinically dehydrated, the use of a pre-formulated ORS supplied by a health facility is recommended.\textsuperscript{28} In 2003, the WHO and UNICEF modified its ORS formulation with the result that the new solution not only hydrates effectively but also decreases stool volume.\textsuperscript{28}

Refeeding should begin soon after initial rehydration.\textsuperscript{22} It was formerly thought that a period of “gut-rest” was beneficial in acute diarrhea, but this has been disproved.\textsuperscript{22} Breastmilk is the ideal food for children with diarrhea and mothers who are still nursing should be actively encouraged to breastfeed their children during diarrheal episodes.\textsuperscript{22} Numerous studies have shown that children who are breastfed during diarrhea have a lower risk of death and reduced requirements for oral rehydration.\textsuperscript{22} There is some evidence that cow’s milk can exacerbate diarrhea due to acquired lactose intolerance, although this is more rare than previously thought.\textsuperscript{29} However, fermented milk products such as yogurt are well tolerated because they contain an enzyme that pre-digests lactose.\textsuperscript{29} In general, children with diarrhea should resume a normal diet as soon as they will take foods.\textsuperscript{22}

In most cases, even if a diarrheal illness is of bacterial origin, antibiotics do not alter the course of the illness.\textsuperscript{25} Two exceptions to this rule in are dysentery and
cholera. Most cases of dysentery in developing countries are caused by *Shigella* and studies have confirmed a decrease in illness duration and severity with antibiotic treatment.\textsuperscript{25} Thus, the WHO recommends treating all cases of bloody diarrhea in the developing world with antibiotics to which *Shigella* is sensitive (ciprofloxacin, ceftriaxone or pivmecillinam).\textsuperscript{30} Similarly, in epidemic situations, treatment of cholera patients with antibiotics has been shown to decrease both the duration of diarrhea and the volume of stool, resulting in decreased hospitalization time.\textsuperscript{26} For children over age 7, doxycycline is most commonly used; for those under 7, erythromycin or trimethoprim-sulfamethoxazole are alternatives.\textsuperscript{26,30} In situations where a parasitology lab is available, confirmed giardia and entamoeba histolytica can be treated with metronidazole and cryptosporidium with nitazoxanide.\textsuperscript{26}

**Diarrhea as a risk factor for malnutrition**

Beginning in the late 1960’s, researchers began to explore the relationship between diarrheal incidence and malnutrition among children in developing countries. In this section, seven studies on this topic are presented. These studies were chosen as a representative sample from the existing literature on this topic based on location, study design, age group and type of analysis. In presenting these papers in chronological order, one can appreciate an increasing sophistication in study design and analysis. In each study, a cohort of children was followed over time, surveyed for diarrheal incidence and periodically weighed and measured. While the broad outlines of all of the studies are similar, they differ in the frequency and methods of surveillance, the age range of participants and the extent to which confounding variables were considered.
While the strength of effect varies, on the whole they demonstrate the link between diarrhea and growth deficits (see Table A for summary characteristics of each study).

One of the first studies on this topic was published in 1977. This study by Martorell et al. documented an association between diarrhea and growth in a population of 716 Guatemalan children aged 15 days to 7 years who were followed over a two-year period. For this study, health workers visited all subjects every two weeks to ascertain morbidity of diarrhea, respiratory infections and fever. Participants were weighed and measured every 6 months. In the analysis, children were divided into two categories—low and high frequency of diarrhea. The high frequency category included children who were reported to have diarrhea on more than 5% of days during the study period. Those in the low-frequency category grew 6.3 percent more in length and 11 percent more in height than those in the high frequency category with mean accumulated differences of 3.5 cm and 1.5 kg over the two years between the two groups. This study did not have a clear case definition for diarrhea, nor did it control for socioeconomic and environmental confounders.

In the mid 1970’s, Rowland et al. studied the effect of various infectious diseases—including diarrhea, respiratory tract infections, infectious fevers, malaria, and giardiasis—on the growth of 152 children ages 6 months to 3 years in the Gambia. The study was based in a clinic serving three rural villages and followed the participants for three years. All study participants came to the clinic monthly where they were weighed and measured and parents were interviewed about symptoms over the previous month. In addition, parents were encouraged to bring their children to the clinic for any symptoms to capture intercurrent illnesses. Similarly to Martorell et al., they
found that diarrhea in the previous month had a significant effect on weight gain (25 g
deficit per day of illness) and height gain (0.14 mm deficit per day of illness).\textsuperscript{32} The
only other disease to have a significant effect on growth in this study was malaria which
adversely effected weight gain (35 g deficit per day of illness).\textsuperscript{32} An occurrence of
diarrhea was determined by study personnel but no case definition was provided in the
paper.\textsuperscript{32} As in Martorell et al.’s work, confounding variables were not taken into
consideration.\textsuperscript{32}

In the same year that Martorell et al. published their study, Condon-Paoloni et
al. published the results of their study of 276 Mexican children who were followed from
birth to age three to ascertain the association between infection and growth.\textsuperscript{33}
Pediatricians examined the children twice a month and took an illness history focusing
on diarrhea and respiratory infections.\textsuperscript{33} The children were weighed at each visit and
measured once a month.\textsuperscript{33} In the analysis, the percentage of time ill in each one year
period was calculated for each child and each age and gender group was divided into
four quartiles with upper quartile was designated as “high frequency of diarrhea.”\textsuperscript{33} The
children in the high frequency diarrhea group had an average weight deficit of 0.59 kg
per year as compared to the rest of the group.\textsuperscript{33} No association was found between
frequency of diarrhea and linear growth or between respiratory infection and either
weight gain or linear growth.\textsuperscript{33}

In the late 1970’s, Black et al. conducted a one-year community based cohort
study of 157 children ages 6 to 48 months to ascertain the effect of diarrhea on weight
and height at the International Center for Diarrhoeal Diseases Research in Bangladesh.\textsuperscript{34}
This study was different from those discussed previously in that it also looked at the
effects of different diarrheal pathogens.\(^\text{34}\) A major improvement of this study was that surveillance was conducted every other day, increasing the likelihood that the diarrheal incidence data was accurate.\(^\text{34}\) When a child with diarrhea was encountered, a rectal swab was taken for culture and rotavirus testing.\(^\text{34}\) In this study, diarrhea was defined as four or more liquid stools in one day.\(^\text{34}\) Using reference curves established for growth patterns in the same population, the authors determined that weight gain was only 66\% of expected in two month periods in which a child had diarrhea more than 30\% of the time and that diarrhea caused by enterotoxigenic \textit{E. coli} had a greater effect on weight gain than \textit{Shigella} or rotavirus diarrhea.\(^\text{34}\) Analyzing the data over a period of one year, diarrhea prevalence was not found to affect weight gain; however, it did affect linear growth.\(^\text{34}\) A child with no diarrhea was found to gain 0.42 cm more each year than a child who experienced the mean number of days of diarrhea (approximately 46 days per year).\(^\text{34}\) \textit{Shigella} diarrhea in particular had a greater effect on linear growth than the other pathogens in a stepwise regression analysis.\(^\text{34}\)

Alam et al. conducted a study in Bangladesh published in 2000 which followed 512 children ages 6-48 months for one year to determine whether clinical type of diarrhea (dysentery vs. non-dysentery) had an effect on growth.\(^\text{35}\) Study participants were visited at home every fourth day by study workers who asked parents about diarrhea symptoms.\(^\text{35}\) Diarrhea was defined as greater than 3 loose or liquid stools in 24 hours and was classified as dysentery if stool contained blood in any day during the episode.\(^\text{35}\) For each time interval studied, participants were designated as having no diarrhea, having diarrhea but no episodes of dysentery, or having at least one episode of dysentery.\(^\text{35}\) Over a three-month period the mean weight gain by children was
significantly higher among children who had not had diarrhea than those who had although no differences were noted according to the type of diarrhea. However, the clinical type of diarrhea was correlated with three month height gain. Children with dysentery had an average adjusted height gain of 2.19 cm over three months while those with non-dysentery diarrhea had an average adjusted height gain of 2.42 cm. In an analysis of annual height gain, the no diarrhea group grew the most (6.51 cm), followed by the non-dysentery group (5.87 cm). The dysentery group grew the least (5.27 cm). The average annual weight gain was 1350 g for the dysentery group, 1500 g for the non-dysentery group, and 1866 g for the no diarrhea group. All differences in annual height and weight gain among the three groups were statistically significant. The results of this study were controlled for age, sex, parental education, household income, landownership and baseline nutritional status.

From 1995 to 1998, Checkley et al. followed a birth cohort of 230 Peruvian children to determine the longitudinal effects of diarrhea on linear growth and ascertain the timing of growth delays following diarrheal episodes. This study involved the most intensive surveillance of any presented here; subjects were visited every single day by health workers. Diarrhea was defined as having three or more liquid or semi-liquid stools in a 24 hour period. The results demonstrated that diarrhea occurring 2-4 months prior to the height measurement had a significant effect on linear growth and that the height deficit increased with increasing diarrhea days. Children with diarrhea 10% of the time in the first 2 years of life were 1.5 cm shorter than children with no diarrhea. Height deficits attributable to diarrhea in the first six months of life were likely to be permanent, while height deficits associated with diarrheal episodes after six
months were transient. In the analysis the authors controlled for the following potential confounders: water source, water storage type, sanitary facilities, maternal stature, and breast-feeding status.

The last study discussed in this section was by Assis et al. This one-year cohort study in Brazil published in 2005 demonstrated an association between diarrhea and linear growth in the subsequent three month interval. This study followed a total of 487 children ages 6 to 48 months. Participants were visited three times a week for surveillance of diarrhea and acute lower respiratory infection and were weighed and measured every three months. It was found that having seven or more days with diarrhea in a three months surveillance period was associated with a statistically significant decrease in the height-for-age Z-score. No association was found between the number of days of diarrhea and weight-for-age Z-score. The following socioeconomic and environmental variables were controlled for: water source, toilet facility, garbage disposal, and maternal education.

Of the seven studies described, six found a negative association between diarrhea and long term height gain. Three of the studies also found an effect on long term weight gain, although included in those three are the Martorell et al. and Rowland et al. studies which were the earliest and least methodologically rigorous. Some of the variation in results may be attributable to the different settings in which the studies were carried out. For example, the severity of diarrhea experienced by children in Bangladesh may have been greater than that in Peru and Brazil resulting in Alam et al. and Becker et al. seeing acute weight deficits while Assis et al. and Checkley et al. did not. Length of follow up is another factor that could have contributed to disparate
results. A major strength of the Checkley study is the three year follow up period which allowed for enough time to witness catch up growth in children who had more diarrhea after 6 months of age. Taken as a group, however, these papers strongly suggest that diarrhea is a factor which contributes to poor growth among children in the developing world and underscore the importance of diarrhea control as part of a comprehensive approach to decreasing childhood malnutrition.

Once the correlation between diarrhea and malnutrition was established, many researchers began to suggest that perhaps the relationship was reciprocal, with diarrhea leading to malnutrition and malnutrition in turn predisposing children to more diarrheal episodes and to episodes of longer duration. The assumption is that children who are malnourished have weaker immune systems rendering them less able to fight off infection including diarrheal pathogens. This bidirectional relationship between diarrhea and malnutrition is difficult to study because of numerous confounders and the challenge of establishing which of the two phenomena occurs first. At this time, there is no consensus in the literature as to whether malnutrition, as defined by height and weight status, increases the rate of diarrheal incidence. However, studies on this topic have consistently shown that malnutrition is associated with longer duration of diarrheal episodes. Additionally, two studies in Bangladesh found an association between cellular immune deficiency and an increased risk of diarrhea ranging from 40-80%. In these studies, cellular immune deficiency was determined by a lack of response to skin antigen testing. Cellular immune deficiency is in part attributed to deficits in micronutrients including zinc.
The prevailing conclusion from the literature on diarrhea and malnutrition is that diarrhea is associated with decreased growth in general. It also appears that malnutrition, as determined by height and weight status, predisposes children to longer duration of diarrheal illness and that micronutrient deficiencies manifesting as cellular immune deficiencies may predispose to diarrheal incidence. These observations substantiate the claim that the relationship between diarrhea and malnutrition is reciprocal and underscore the importance of addressing diarrhea and malnutrition as interrelated entities.

**Diarrhea and anorexia**

While the precise interactions between malnutrition and diarrhea are a cause for debate, it is clear that children in the developing world are nutritionally vulnerable during episodes of diarrhea. Therefore, careful attention must be paid to feeding during and after diarrhea to mitigate the effects of diarrhea on children’s nutritional status. Most authors believe that three factors are responsible for the effects of diarrhea on children’s nutritional status: decreased absorption of nutrients, increased metabolic demand, and decreased intake as a result of anorexia. Because continued feeding during diarrhea is thought to mitigate the effects of diarrhea on nutritional status, anorexia is a serious concern that deserves thorough investigation. The hypothesis that diarrhea induces anorexia has been examined in several published field studies conducted in Guatemala, Nigeria, Bangladesh, India and Peru and in three hospital based studies conducted in Bangladesh. These studies have varied greatly in their methodologies and their results; some demonstrated a large decrease in intake during
diarrhea, others a minor decrease, one study showed no significant difference, and two studies showed different effects from different pathogens (see Table B for summary characteristics of each study).

One of the earliest studies of the interaction between infection and nutrition was conducted by Mata et al. in rural Guatemala from 1964 to 1972 and included a sub-study on the effect of infections on dietary intake.43 As part of this sub-study, 30 fully weaned children ages 24-48 months were visited weekly to record the incidence of all infections and to record dietary intake via parental report.43 Intake, as determined by the percent of recommended caloric intake, was found to decrease significantly during periods of infectious disease; however the actual degree of decrease in intake was not specified.43 The authors concluded that an inadequacy of calories was the major cause of malnutrition in children in the study population and that this inadequacy was largely due to frequent infectious diseases.43

Martorell et al. followed up the work of Mata et al. with another study in rural Guatemala looking at the effect of various illnesses on appetite in children.44 The data for this study was extracted from a longitudinal study on malnutrition and mental development that enrolled 477 children for a period of 7 years.44 Parents were interviewed every two weeks and asked to recall days on which their child had displayed symptoms of respiratory illness, diarrhea (defined as any report of loose stool), or “apathy” (defined as the child not being his or her usual self).44 Every three months parents were also interviewed in depth about the child’s food intake in the prior 24 hours.44 Days on which the intake survey coincided with a report of symptoms were included in the analysis and compared to days in which no symptoms were reported.44
The data revealed that consumption on days when children were reported to have diarrhea or “apathy” was approximately 20 percent less than consumption on days when children were reported to be healthy. In their discussion, the authors pointed out that the results of this study did not support Mata’s conclusion that infections account for most of the energy deficits in children in developing countries, but that decreased food intake during periods of infection was nonetheless a significant contributing factor to malnutrition.

While the results of these two early studies are interesting, there were several major weaknesses in their design. Intake was based entirely on parental report with no direct observation or measurement of what the child actually consumed. Furthermore, both diarrhea and “apathy” were very loosely defined. Finally, the intake of sick children was not compared directly to the intake of the same children when healthy, rather aggregated child-days of observation marked by illness were compared to child-days with no illness. This leaves open the possibility that the children who generally ate less were also those with a greater tendency to have infections and to thus contribute more “sick” child-days to the analysis.

Brown et al. conducted a longitudinal assessment of dietary intake and morbidity from fever and diarrhea among 70 breast-feeding children ages 5-30 months in Matlab, Bangladesh. In this study, dietary intake was determined via 12-hour in home observations. Observations were conducted monthly at times when the children were healthy. In addition, health workers visiting the homes of participants identified children with fever, diarrhea, upper respiratory infections, otitis media and skin infections and scheduled an observation for the following day. A total of 1014 full day
observations were completed of which 632 were on healthy days. This study found that overall intake was decreased by approximately 10% on days when children had fever compared to healthy days but found no significant decrease on days with diarrhea.

In contrast to Brown et al. in Bangladesh, Dickins et al. conducted a study with a very similar design in Nigeria that revealed a small but statistically significant decrease in intake on days with diarrhea. This study included 45 children ages 6 to 28 months and evaluated their intake over a two day period on three separate occasions: while ill with diarrhea, during convalescence (within 1 week after recovery) and when healthy. Observers spent 12 hours in the homes of children where they weighed and recorded all foods consumed. The overall energy intake of children with diarrhea was 11 percent lower than when they were healthy. These differences were entirely due to decreased consumption of solid food; the consumption of breast milk and liquid pap (a common weaning food in Nigeria) was unchanged. Only five children in the study were fully weaned; these children showed a difference in intake of 35 percent versus only seven percent for the breastfed children. Thus, the authors concluded that the effect of diarrhea on intake may be more significant in older children, who are mostly consuming solid foods, than in younger breastfed children. In this study, no differences in the results were noted among children who were reported to have had fever.

Two groups of researchers working in Peru obtained similar results to Dickins et al. Brown et al. conducted research in a periurban community near Lima; 131 infants ages 1-11 months were observed longitudinally and surveyed three times per week for the presence of diarrhea, fever, upper respiratory symptoms and other infections. In
addition, dietary studies were conducted during 1615 full day observations in which all foods consumed by the infant were measured and the number and duration of nursing episodes were recorded. This study demonstrated a five to six percent decrease in overall intake on days with diarrhea and fever. These differences were entirely due to intake of non breast-milk foods which decreased by 20 to 30 percent; there were no differences in breast-milk intake.

Bentley et al. working in a rural area of Peru followed the dietary intake of 40 children ages 4 to 36 months via in-home observations during two to four days each of diarrhea, convalescence and health. This study found a decrease in intake of 11 percent during diarrhea as compared to healthy periods. Through the use of observational scales measuring maternal encouragement of eating and child acceptance of food, it was discovered that mothers’ encouragement of eating was higher during episodes of diarrhea and that child’s acceptance of food was lower. The authors suggested that this was due to anorexia induced by the diarrheal episode.

Three hospital based studies on the effects of diarrhea on appetite were performed at the diarrheal treatment center of the International Centre for Diarrhoeal Disease Research (ICDDR) in Bangladesh. Hoyle et al. conducted a study evaluating the intake of hospitalized children with diarrhea compared to healthy controls. The study enrolled 41 children ages 6 to 35 months, 30 who had acute diarrhea and 11 healthy controls. The children with diarrhea were divided into two groups; mothers of one group received intensive education about the importance of continuing to feed and breastfeed children during diarrheal episodes while the other group received no specific advice on feeding. All cases and controls were allowed to breastfeed ad
libitum and to eat other foods that their parents chose to offer them. In addition, they were offered a special weanling food five times a day made of local ingredients. All feeding episodes were observed by staff and the amount of food consumed was measured. Intake of breast milk was determined by weighing children before and after breastfeeding. Healthy controls consumed an average of 129.9 kcal per kg over the 24 hour study period. Those in the diarrhea group which did not receive additional dietary education consumed an average of 75 kcal per kilogram while those in the group that did receive dietary education consumed 60.9 kcal per kilogram. The reduction in caloric intake in the diarrhea group was entirely attributable to decreased consumption of solid food; breast milk intake was the same in all groups. Thus, as in several of the community based studies, diarrhea appeared to significantly depress children’s appetite for solid food but not breast milk. Furthermore, the fact that parental education on the importance of feeding did not improve intake suggests that the children’s appetites were significantly depressed.

Molla et al. conducted a separate study at the diarrheal treatment center of the ICDDR looking at intake and absorption of nutrients in children with known cases of diarrhea caused by cholera and rotavirus. The study enrolled 19 children with cholera and 13 children with rotavirus ages 5 years and under who were undergoing inpatient treatment. Children were provided a varied but standardized diet of local foods which they were offered at specified intervals and allowed to consume ad libitum. Their consumption of nitrogen, fat, and overall calories was measured during illness and after recovery (although the criteria for recovery were not defined in the paper). The mean caloric consumption was greater during recovery than illness for both cholera and
rotavirus patients; however, this difference was only statistically significant for cholera patients (70 kcal/kg/day versus 108 kcal/kg/day). There was no mention of breast-milk versus solid food intake in this study and there were no healthy controls.

A third hospital based study conducted in Bangladesh by Rahman et al. examined the effects of diarrhea caused by different species of *Shigella* on children’s intake. Eighty-two children between the ages of 24 and 59 months with *Shigella* diarrhea were enrolled. Children were offered food every two hours for the duration of their hospitalization. Children with fever were found to consume less in the first 48 hours of the study than afebrile children (469 kJ/k/d vs. 517 kJ/k/d). In addition, the mean energy intake of children infected with *Shigella dysenteriae* species was significantly less than children infected with other *Shigella* species (435 kJ/k/d vs. 536 kJ/kg/d). This difference was still significant after controlling for the effect of fever.

In aggregate, prior studies on the relationship between diarrhea and intake in children suggest that diarrhea significantly decreases the intake of non breast milk foods in breast-feeding children and has no effect on breast milk intake, resulting in a modest overall decrease in intake during diarrhea in breast feeding children. It also appears that certain pathogens have a greater effect on appetite than others. However, the effect of diarrhea on intake in weaned children has not been determined. Furthermore, the existing literature on diarrhea and appetite makes no mention of possible mechanisms by which diarrhea might decrease appetite.
**Diarrhea and decreased appetite: possible mechanisms**

Anorexia is a widely recognized consequence of many inflammatory disease states including infections and cancer. Pro-inflammatory cytokines that are released by activated immune cell have been demonstrated to play a role in inducing fever, anorexia, and a variety of "sickness behaviors" such as decreased motivation and decreased grooming. The family of pro-inflammatory cytokines include interleukin 1 (IL-1β, IL-1α), IL-6, tumor necrosis factor-α (TNF-α), and the interferons (IFNs). In animal models, both peripheral and central administration of IL-1β and TNFα consistently suppress feeding behaviors. The pathways by which peripheral cytokines induce a central nervous system response are under investigation and include direct diffusion of cytokines across the blood-brain barrier, the induction of local cytokine production in the brain by various immunomodulators, and a direct neural pathway from the gut to the brain that is stimulated by the presence of cytokines in the bloodstream. A study of the cytokine profile induced by rotavirus infection demonstrated elevated levels of IL-6, IL-10, and IFN-γ in the sera of children with rotavirus diarrhea compared to healthy controls demonstrating that the cytokines do play a role in the immune response to the most common diarrheal pathogen in children. Further research would be required to determine whether there is a connection between the cytokine response and appetite suppression.

Gut hormones are important physiologic mediators of appetite that could potentially be involved in appetite suppression in pathophysiologic states as well. Ghrelin is a stomach derived hormone known to stimulate appetite while glucagons like peptide-1, oxyntomodulin, cholecystokinin, pancreatic polypeptide and peptide YY
Peptide YY is secreted by the L-cells in the small intestine with peak levels occurring one hour post prandially. Once released into the bloodstream it acts at the level of the hypothalamus to suppress the release of a neurotransmitter called neuropeptide Y (NPY) which stimulates food intake. Thus, peptide YY is a potent appetite suppressant, a fact which has been confirmed by studies of peripheral administration of peptide YY in both rats and humans.

Peptide YY is a particularly interesting candidate as a possible mechanism of appetite suppression during diarrhea because it is known to be elevated in malabsorptive disorders. Adrian TE et al. compared fasting and post-prandial peptide YY levels in healthy controls to patients with a variety of malabsorptive disorders and found elevated levels in patients with the following disorders: tropical sprue, steatorrhea secondary to chronic pancreatitis, inflammatory bowel disorders, and acute infectious diarrhea. Up until this point, studies of peptide YY release have been restricted to animal models and adult humans. Thus further research would be necessary to determine whether an elevation of peptide YY is a significant factor in appetite suppression in children with diarrhea.
The Effect of Diarrhea on Appetite: A Case-Control Study

The remainder of this thesis presents an original research study conducted by the author in a low-income peri-urban community called Pampas de San Juan de Miraflores located in a desert region outside of Lima, Peru.

Introduction

As is clear from the background section of this thesis, diarrhea is a major cause of malnutrition. However, the mechanism by which diarrhea leads to malnutrition has not been established. There is some evidence that diarrhea leads to decreased intake of solid food but has no impact on breastfeeding. This suggests that anorexia during diarrheal episodes may have a significant effect on the nutritional status of toddlers who are getting most of their calories from non-breast milk sources. As small children cannot be expected to reliably indicate their degree of hunger and desire to eat, consumption of food during an observed feeding trial is a method that can be used to approximate appetite.

Aims

The specific objective of this study was to determine the effect of diarrhea on appetite in Peruvian children ages one through five. The broader aim of this study was to better understand how diarrhea contributes to malnutrition in children. Ultimately, this information will aid in the design of interventions to decrease malnutrition among children in the developing world.
Hypotheses

1. Children with diarrhea will consume less than healthy controls.

2. Children will consume less when they have diarrhea than when they are healthy.

Methods

Research Setting

Peru is a South American country with a population of approximately 28 million people. It is a relatively poor country with a gross domestic product per capita of $5,600. According to UNICEF statistics, the infant mortality rate in 2005 was 23 per 1000. Children in Peru have relatively high rates of chronic malnutrition compared to other countries in the region, with a prevalence of stunting of 25.8% in comparison to 9.8% for all children in South America. The prevalence of underweight among children under 5 is 8% and wasting is 1%. Most health indicators vary greatly between urban and rural regions. For example, while 74% of urban dwellers have adequate sanitation facilities, only 32% of rural dwellers do. An estimated 57% of children under 5 with diarrhea received oral rehydration and continued feeding.

Lima is the capital city of Peru as well as its largest city with a population of approximately 7.8 million people. San Juan de Miraflores is one of the cities in the metropolitan district of Lima, located Southeast of the city center. It has a population of 330,000 people and is a mix of working class residential areas, impoverished residential areas and industrial zones. Pampas de San Juan de Miraflores is a community within the city of San Juan de Miraflores with a population of approximately 40,000 people. Pampas is largely populated by families that emigrated
from the province of Ayacucho in northern Peru in 1980’s to escape the threat of terrorism. The community was established as a *pueblo joven*, a term which describes areas of incorporated land surrounding cities that are claimed by new arrivals. When the earliest migrants arrived, the area in which they settled had no public services or paved roads and most houses were constructed from scrap materials. Over time, the socioeconomic level of the community has risen, access to public services has increased and many inhabitants have been able to improve their homes. Data collected by the non-profit organization Asociación Benéfica PRISMA (AB PRISMA) in 1992 showed that 50% of homes had brick walls. Another survey by AB PRISMA in 1995 demonstrated that 97% of homes had electricity, 48% had toilets, and 64% had a household water connection.

Since the 1970’s, Peru has been a nexus for diarrheal research. Researchers from several different institutions have conducted numerous studies in pueblo jóvenes in Lima as well as in rural communities in the highland regions. Dr. Robert Gilman from the Johns Hopkins University School of Public Health has had a field research site in the community of Pampas de San Juan de Miraflores since 1988. Two local institutions, the Universidad Cayetano Heredia in Lima and the non-profit organization AB PRISMA also collaborate on the administration of the site and participate in studies. Numerous studies related to childhood diarrhea have been conducted at the Pampas site, including one of the most rigorous studies linking diarrhea and stunting.
Study Design

This study was a prospective case-control study. Children ages 1 to 5 with diarrhea and age matched healthy controls underwent an observed feeding trial during which their consumption of strawberry yogurt was measured. Both cases and controls repeated the trial after 10 days. Cases were healthy on the day that they repeated the trial allowing for a comparison of their intake when sick with diarrhea to their intake when healthy. Cases and controls were recruited from an ongoing cohort study at the Pampas de San Juan de Miraflores field work site on the epidemiology of the intestinal parasites *Cyclospora* and *Cryptosporidium*. The principal investigators for this ongoing cohort study are Professor Robert Gilman from the Johns Hopkins School of Public Health and Dr. Vitaliano Cama from the Centers for Disease Control. This cohort was comprised of 384 children ages 1 through 13. In the cohort, 303 children were between the ages of 1 and 5 at the start of the study. Health workers visited the homes of all children in the cohort on a daily basis to determine diarrheal incidence. Thus, recruiting participants from this cohort allowed for easy identification of potential cases as well as appropriate controls. At the outset of the trial, the goal was to recruit only cases and controls who were no longer breastfeeding. However, in the initial month of the trial, recruitment was slow and it appeared that it would not be possible to achieve the desired sample size in the time allotted for the study. Hence, the decision was made to allow the participation of children who breastfed four or fewer times per day. Approval for this study was granted by the Institutional Review Boards of the University of Connecticut Health Center, and the Johns Hopkins University School of Public Health. Approval was also granted by the ethics committee of the Universidad
Cayetano Heredia in Lima, Peru and from the organization AB PRISMA, a Peruvian based NGO which collaborates in running the research site.

Inclusion and Exclusion Criteria

Inclusion criteria cases:
- Ages 1-5
- Breastfeed 4 or fewer times per day
- Have diarrhea at the time of recruitment as defined by 3 or more liquid or semi-liquid stools in a 24 hour period.

Exclusion criteria cases
- Febrile at time of feeding trial.
- Clinical evidence of dehydration at time of feeding trial
- Vomiting during the feeding trial
- Report or evidence of any other illness besides diarrhea
- History of chronic illness
- Allergy to strawberries

Inclusion criteria controls:
- Ages 1-5
- Breastfeed 4 or fewer times per day.

Exclusion criteria controls
- Diarrhea at time of recruitment or in previous 7 days.
- Evidence or report of another illness at the time of the study
- History of chronic illness.
- Allergy to strawberries

Recruitment procedure

Cases and controls were enrolled in the study over a 5 month period from January through May of 2007. When a health worker for the cohort study on *Cyclospora* and *Cryptosporidium* encountered a child with diarrhea who met the criteria for cases, parents were asked whether they would like their child to participate. If parents agreed, informed consent was obtained from the parent and assent was obtained from the child. Once a case was enrolled, an age and gender matched control was
sought and invited to participate. No records were kept of the number of refusals or the specific reasons for refusals. Anecdotally, it was noted that some parents refused to have their child participate because they attended pre-school and did not want their child to miss. Another commonly mentioned reason for a child with diarrhea to not participate was that a parent was not home to give consent at the time that the health worker was visiting.

Study procedure

Parents of cases and controls were asked not to feed their child anything before the research team arrived the next morning. The research team consisted of a nurse and either the author or a health worker from the research site. The health workers recruiting the family inquired as to the time that the child normally arose so that the research team could arrive just after the child woke up. Upon arrival, the nurse first inquired to make sure that the child hadn’t eaten or drunk anything since waking up. If the child had eaten or drunk something, the feeding trial was cancelled. The trial was rescheduled if the child continued to have diarrhea over the ensuing 24 hour period.

The nurse then took the child’s temperature and briefly examined the child for any signs of dehydration. If the child was febrile or appeared dehydrated the study was not conducted. All children found to be clinically dehydrated were immediately referred to a nearby clinic which provides free care to all participants in the *Cyclospora* and *Cryptosporidium* diarrhea cohort study through an agreement with the investigators. Parents were asked whether the child breast-fed and if so how many times in 24 hours, the number and type (solid, semi-liquid, liquid) of bowel movements in the previous 24
hours, the presence or absence of fever during the diarrheal episode, the presence or absence of blood in the stool, the presence or absence of vomiting, the number of times the child vomited, the last time that the child had eaten, and whether the child was taking any medication.

After the interview, a health worker stayed in the homes of cases and controls for 2 hours to conduct an observed feeding trial with strawberry flavored liquid yogurt. Strawberry yogurt was selected after taste testing a variety of foods by 20 children from the cohort. It was found to be universally acceptable whereas all other attempted foods were rejected by at least 25% of the taste test participants. Other foods that were attempted included oatmeal, a cereal made from quinoa, and Kiwigen, a commercialized product made from the grain kiwicha and flavored with chocolate, vanilla, or strawberry. The same commercial brand of strawberry yogurt was used for all participants and provided in 200 mL bottles so that the ingredients and nutritional information were standardized.

Prior to starting the feeding trial, health workers weighed a bottle of yogurt on a scale accurate to 1g. The health worker then provided the yogurt to the parent so that he or she could offer it to the child and the time was noted. Participants were given the option of drinking the yogurt from a straw or being fed by a parent with a spoon. Parents were asked not to pour the yogurt into another receptacle. The child was allowed to consume the yogurt ad libitum. If a child finished one bottle, another was opened and offered to the child. When the child indicated that he did not want anymore (handing the bottle to the parent, placing it down on a surface and engaging in another activity, refusing more spoonfuls), the health worker took the yogurt and replaced the
cap. After a five minute pause, the child was again offered the yogurt by the parent. If the child refused to eat more, the yogurt was again covered. If the child accepted, he/she was allowed to eat ad libitum until another refusal. This process was repeated one and two hours after the initiation of the feeding trial such that yogurt was directly offered to each child six times over a two hour period. In addition, if children requested more yogurt at any point during the study, it was provided. Health workers weighed each bottle when the child had finished it as well as the last opened bottle at the end of the trial to determine exactly how many grams of yogurt were consumed. Parents were instructed not to give their child any other food or drink during the two hour period. While not eating yogurt, the participants engaged in their normal activities (playing, helping with housework, etc.). Cases repeated the study as soon after ten days that they were found to be healthy. Being healthy was defined as not having any liquid or semi-liquid bowel movements in the previous three days or any other reported illnesses by the parent. Controls also repeated the study after 10 days.

The surveillance data from the ongoing *Cyclospora* and *Cryptosporidium* diarrhea cohort study was used to determine the total duration of each episode. This was necessary because the repeat visit to the homes was conducted 10 or more days after the initial feeding trial and by that point parental recollection of the precise day that the diarrhea had ended was poor. An episode was considered to have ended on the first day that the child was recorded to have fewer than three liquid or semi-liquid bowel movements. Socioeconomic data on cases and controls was also extracted from the data base of the diarrhea cohort study.
Statistical analysis

The power calculation was based on an assumed normal daily intake in children under 6 of approximately 1200 calories\textsuperscript{65}, with an estimated average intake of 300 calories (SD 100 calories) at the first morning meal. In order to demonstrate a difference of intake of 20% between cases and controls (confidence 95%, power 80%), it was determined that a minimum of 44 participants would be needed in each study group.

Data were entered first into Excel and then analyzed via Intercooled STATA for Windows Version 8.2. The mean intake of cases was compared to the mean intake of controls by a t-test. The results were then confirmed with the non-parametric Mann-Whitney rank sum test. The mean percent difference in intake from visit 1 to visit 2 for cases and controls as well as the mean percent difference among sub-groups of cases were also compared using a t-test and confirmed with the Mann-Whitney rank sum test. Logistic regression was used to determine the effect of various characteristics of the diarrheal episodes and percent difference in intake of cases when sick and whey healthy (dichotomized to greater than 20% difference and less than 20% difference). The anthropometric Z-scores were calculated using the WHO provided Anthro software, 2005.

Results

A total of 46 cases and 46 controls completed the study. All children who did the first feeding trial also completed the second. Eight of the cases and four of the controls were still breastfeeding. The remaining participants were fully weaned. Of
the cases, 22 participated in the feeding trial on day 2 of their diarrheal episode, 17 participated on day 3, 4 participated on day 4 and 1 each participated on days 5, 6, and 7. The main reasons for delay were a family member feeding the child in the morning before the study team arrived or the parent or guardian not being at home to provide consent for participation.

Among the cases, 25 were male and 19 were female with the same gender balance in the controls (see Table 1). The mean age of cases was 39.4 months while the mean age of the controls was 40.6 months. The mean WAZ scores of cases and controls were -0.1 and -0.37 respectively. The mean HAZ scores of cases and controls were -0.92 and -1.09. The mean WHZ scores were 0.77 for cases and 0.9 for controls. None of these differences were significant.

Among cases 71% had toilets with a sewage connection; 82% of controls had toilets. Indoor running water was present in the homes of 63% of the cases and 76% of the controls. The per person monthly household income for cases ranged from $10.00 to $117.00 with a mean of $40.00. The per person monthly household income for controls ranged from $7.00 to $106.00 with a mean of $45.00.

The diarrheal episodes were mostly mild with a mean duration of 3.07 days (see Table 2). Twelve children were reported to have had fever during the diarrheal episode. Of those, four were given acetaminophen by their parents for fever and one received ibuprofen. Twelve children were reported to have vomited, and six were reported to have both fever and vomiting. Only seven children were reported to have had blood in their stool; three were reported as having had both fever and blood in their stool.
The mean consumption of children with diarrhea was slightly less than healthy controls (24.7 kcal/kg vs. 26.5 kcal/kg), but this difference was not statistically significant (see Table 3). However, the mean consumption of cases at visit 1 (sick) was significantly less than consumption of cases at visit 2 (healthy) (24.7 kcal/kg vs. 29.5 kcal/kg p=.035). The mean consumption of controls was also less at visit 1 than visit 2 (both healthy), but this difference was not significant (26.5 kcal/kg vs. 29.1 kcal/kg).

The subgroup of cases with a reported history of fever consumed much less than cases without fever at visit 1 (17.1 kcal/kg vs. 27.4 kcal/kg p=.003) and approximately the same as all other cases at visit 2 (31 kcal/kg vs. 28.5 kcal/kg p=.45).

After examining mean intake of cases, controls and the sub-group of cases with fever and vomiting, a variable was created for the percent difference in intake from visit 1 (sick) to visit 2 (healthy). For cases, the mean percent difference in intake from visit 1 to visit 2 was 35%, while for controls it was 19% (see Table 4). However, this difference was not statistically significant. The mean percent difference in intake from visit 1 to visit 2 for cases with a report of fever during the diarrheal episode was 100% compared to 11.8% for cases without fever (p<.002).

The median percent difference in intake from visit 1 to visit 2 for all cases was 21% with a highly skewed distribution. Thus, to examine the effect of a broad number of variables on the percent difference in intake among cases, this variable was dichotomized into those who ate at least 20% more at the second visit and those who ate less than 20% more. The following variables were then analyzed in a univariate logistic regression to determine their relationship to the likelihood of a case eating at least 20% more at the second visit: history of fever, history of vomiting, presence of blood in
stool, duration of diarrhea, number of bowel movements in the 24 hour period before the feeding trial, breastfeeding status, household income, age, gender and anthropometric values. Only the history of fever and duration were significant. These remained significant in a multivariate analysis (see Table 5) with an odds ratio of 5.8 (p=.05) for fever and 1.5 (p=.042) for duration of the diarrheal episode.

**Discussion**

The first hypothesis, that children with diarrhea would consume less than age matched healthy controls, was not supported. With regard to the second hypothesis, that cases would eat less when sick than when healthy, cases did consume less on average when they had diarrhea than when they were sick (24.7 kcal/kg vs. 29.5 kcal/kg p=.035). At the same time, the mean percent difference from visit 1 to visit 2 for cases (35%) was not significantly different from that of controls (19%). While most cases ate more when healthy than when sick, most controls also ate more at the second visit perhaps because they were familiar with the feeding trial at the second visit and felt more comfortable than they had at the first visit.

The change in intake from visit 1 to visit 2 for cases with a reported history of fever during their diarrheal episode was highly significant. The mean increase for children with fever was 8 times greater than that for children without fever. Finally, fever was found to be a significant predictor of the likelihood of a child with diarrhea consuming at least 20% more at visit 2 than visit 1. The ultimate duration of the diarrheal episode was the other variable found to significantly predict cases eating at least 20% more at visit 2 than visit 1. On the whole, this study indicates that mild
diarrhea has no appreciable effect on appetite in children ages 1-5. However, more severe diarrheal episodes accompanied by fever that are of ultimately longer duration do appear to result in significant anorexia.

Both fever and anorexia are thought to be induced by the cytokine response to infection. Thus, from a mechanistic standpoint, it is reasonable that a pathogen which causes a febrile response would also cause anorexia in the same patient. Subjects in the study designated as having fever were not actually febrile at the time of the feeding trial, but rather parents reported fever at some point prior to the trial during the same diarrheal episode. This study therefore shows that anorexia persists even after the patient is no longer febrile, potentially as a result of persistent elevation of cytokines. The duration of diarrheal episodes may have been a marker of the virulence of pathogens both in terms of the immune response generated and the amount of damage to the gut mucosa. Again, the observed anorexia may have been due to a cytokine response, to factors released from the damaged gut mucosa, or to an as yet undescribed mechanism.

Dickin et al. did find a decrease in intake of 35% among weaned children with diarrhea, however, only five children were included in this study group and the characteristics of the diarrheal episodes were not described. The finding that fever decreased appetite in children with diarrhea is consistent with the work of Rahman et al. who found that among children hospitalized for diarrhea those who were febrile ate slightly less in the first 48 hours of hospitalization than afebrile children.

A major limitation to this study is the small sample size of children with severe diarrhea, making it difficult to generalize the results to other populations with a higher
prevalence of severe diarrhea. For example, it may be that dysentery is another marker of severity associated with anorexia but that there were simply too few children in this study with dysentery to detect an association. The Pampas community has served as a field site for diarrheal research for over 15 years resulting in a strong infrastructure for research. At the same time, however, the socioeconomic level of the community has risen and the number of families with running water and sewage connections has increased significantly. In addition, the presence of the non-profit organization PRISMA in the area—one of the field site collaborators—has resulted in improved health care and health knowledge for the inhabitants. All of these improvements have resulted in a drop in diarrheal incidence as well as a decrease in the severity of diarrhea.

Another limitation of the study was that the feeding trial was limited to one meal and was only carried out once during the illness; thus it may not have reflected the child’s appetite throughout the illness. Additionally, while the yogurt used had significant nutritional value, it was nonetheless in liquid form. Thus, intake of this yogurt might not accurately reflect intake of solid food.

Despite the described limitations, this study did reveal that children whose diarrhea was accompanied by fever experienced significant anorexia. Additionally, diarrheal episodes of longer duration appear to affect appetite to a greater extent than shorter episodes. These results suggest that in areas of the developing world where childhood diarrhea tends to be more severe, anorexia may in fact be a very important cause of poor intake and resultant malnutrition in children who are not primarily breastfeeding. Repeating this study in a population with a higher prevalence of severe diarrhea is necessary to confirm these results. Additionally, in future studies it would
be valuable to repeat the feeding trial on multiple days and to potentially include a variety of foods to closer simulate the subjects’ usual eating patterns.

Conclusions and Recommendations

Given that high diarrheal morbidity is likely to persist for some time in many parts of the developing world, this study suggests that specifically addressing the problem of anorexia is worthwhile. Current WHO guidelines for feeding children during diarrheal illness recommend continued feeding in small amounts as well as additional feeding after the episode has concluded to allow for catch up growth. However, if a child’s appetite is very poor during a diarrheal episode, then this recommendation becomes challenging and anorexia should be addressed directly. One potential intervention is to educate mothers to offer children food more frequently throughout the day in small amounts. In a hospital based study in Bangladesh Hoyle et al. found that intensive parental education on the importance of feeding during diarrhea did not result in increased intake for the intervention group. This was a small study, however, and it is possible that an intervention with larger numbers of children may reveal some benefit. Another interesting question is whether the administration of acetaminophen would mitigate the effects of fever on appetite. Further studies would be required to investigate this possibility.

Ultimately, the best way to uncouple diarrhea and malnutrition is through prevention of diarrheal disease. One of the simplest means of preventing morbidity and mortality from diarrhea disease is via the promotion of breast feeding. Numerous studies have shown children who are breast fed through a diarrheal episode are less
likely to die that those who are not. Breastfeeding also decreases the risk of hospitalization and decreases the incidence of severe dehydrating diarrhea. Another proven means of preventing diarrhea among children in developing world countries is through zinc supplementation and zinc supplementation during and after diarrheal episodes is now part of the WHO’s recommendations for the management of diarrheal illness. Beyond nutritional interventions, improvements in hygiene, sanitation and water supply are also proven to decrease the risk of diarrhea. A meta-analysis by Fewtrell et al. looked at all studies of the effects of water, hygiene, and sanitation interventions on rates of diarrhea. The authors found that all of the interventions studied reduced diarrheal incidence. The most effective interventions were hand washing, general hygiene education, and point of use water disinfection. Finally, the new rotavirus vaccines offer the possibility of significantly decreasing rates of rotavirus diarrhea worldwide.

While prevention should be the first priority of any public health initiative, improving the way that diarrheal illness is managed in the developing world will also help to save lives and decrease the nutritional sequelae of diarrheal disease. The WHO’s Integrated Management of Childhood Illness (IMCI) program is a comprehensive strategy for improving how health care is delivered to children in the developing world with a focus on five conditions: diarrhea, pneumonia, measles, malaria and malnutrition. The IMCI approach recognizes that most children in the developing world present to a health facility with more than one diagnosis. Furthermore, even if children have only one presenting complaint, they are at risk for multiple other conditions. The key components of the strategy are improving case
management, improving the health system and improving family and community practices. The widespread implementation of IMCI is a strategy with great potential for reducing the burden of diarrheal disease.

Preventing and properly managing diarrheal illness will decrease childhood mortality in developing countries. It will also lead to improved nutritional status for children which will in turn decrease their risk of mortality and increase their ability to grow into healthy, productive adults. Millions of the poorest children in the world are trapped in a vicious cycle of poverty and disease. A poor diet and high infectious disease burden lead to malnutrition which in turn increases the risk of both disease and death. The dual burden of malnutrition and disease puts a strain on individual and family resources decreasing the possibility that children living in poverty will be able to improve their situation as adults. Intervening to interrupt this cycle is a moral imperative with benefits for individuals, communities and society at large.
Table A: Summary of studies on the association between diarrhea and malnutrition

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>N</th>
<th>Ages</th>
<th>Duration</th>
<th>Methods</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martorell</td>
<td>1975</td>
<td>Guatemala</td>
<td>716</td>
<td>15 days – 7 yr</td>
<td>2 yr</td>
<td>Home visits every two weeks for surveillance of diarrhea, fever, respiratory infection. Weighed, measured every 6 months.</td>
<td>Annual height and weight gain greater in low frequency diarrhea group than high frequency diarrhea group.</td>
</tr>
<tr>
<td>Rowland</td>
<td>1977</td>
<td>Gambia</td>
<td>152</td>
<td>6 m – 3 yr</td>
<td>3 yr</td>
<td>Clinic visits once a month for anthropometry and surveillance of diarrhea, fever, respiratory infection, malaria, skin infection.</td>
<td>Diarrhea in previous month had a significant effect on weight gain and height gain.</td>
</tr>
<tr>
<td>Condon-Paoloni</td>
<td>1977</td>
<td>Mexico</td>
<td>276</td>
<td>0-3 yr</td>
<td>1 yr</td>
<td>Illness histories taken by pediatricians every two weeks. Weighed every two weeks, measured once monthly.</td>
<td>Children in high frequency diarrhea group had less annual weight gain than rest of group. No association between diarrhea and height gain.</td>
</tr>
<tr>
<td>Black</td>
<td>1984</td>
<td>Bangladesh</td>
<td>157</td>
<td>6m – 48m</td>
<td>1 yr</td>
<td>Home visits every other day by a field worker for surveillance of diarrhea, fever, and respiratory infection. Weekly visits by a physician. On days of diarrhea, rectal swabs were collected for culture and rotavirus testing.</td>
<td>Diarrhea incidence correlated with decreased short-term weight gain and decreased long-term height gain. Enterotoxigenic E. Coli had a greater effect on short term weight gain than rotavirus and Shigella. Shigella had a greater effect on long term linear growth.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Location</td>
<td>N</td>
<td>Ages</td>
<td>Duration</td>
<td>Methods</td>
<td>Key Results</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
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<td>-----</td>
<td>------</td>
<td>----------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alam</td>
<td>2000</td>
<td>Bangladesh</td>
<td>512</td>
<td>6-48m</td>
<td>1 yr</td>
<td>Home visits every 4th day for diarrhea surveillance. Episodic with blood in stool designated as dysentery. Weighed and measured monthly.</td>
<td>Annual height and weight gain was greatest for children with no diarrhea, intermediate for those with non-dysentery diarrhea and smallest for those with dysentery during the year.</td>
</tr>
<tr>
<td>Checkley</td>
<td>2003</td>
<td>Peru</td>
<td>224</td>
<td>0-35m</td>
<td>3 yr</td>
<td>Daily home visits for surveillance of diarrhea. Monthly anthropometry.</td>
<td>Diarrhea during the first 6 months of life resulted in long-term height deficits. Diarrhea after age 6 months had transient effects on height.</td>
</tr>
<tr>
<td>Assis</td>
<td>2005</td>
<td>Brazil</td>
<td>487</td>
<td>6-48m</td>
<td>1yr</td>
<td>Home visits three times per week for surveillance of diarrhea and respiratory infection. Weighed, measured every 3 months.</td>
<td>Diarrhea on &gt;7 days in a three month period correlated with decreased HAZ. No association between diarrhea and WAZ.</td>
</tr>
</tbody>
</table>
Table B: Summary of articles on the effects of diarrhea on appetite in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Age</th>
<th>Methods</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mata</td>
<td>1977</td>
<td>Guatemala</td>
<td>30</td>
<td>24-48m</td>
<td>Subjects visited weekly by health workers who recorded intake per parental report and any symptoms of illness.</td>
<td>Intake reported to be significantly decreased during periods of infectious disease including diarrhea</td>
</tr>
<tr>
<td>Martorell</td>
<td>1980</td>
<td>Guatemala</td>
<td>477</td>
<td>0-60m</td>
<td>Parents asked every two weeks about diarrhea and respiratory illness. Interview on intake over past 24 hours conducted every 3 months.</td>
<td>Consumption on days when children reported to have diarrhea by parents was 20% less than consumption on days when children were reported to be healthy.</td>
</tr>
<tr>
<td>Brown</td>
<td>1985</td>
<td>Bangladesh</td>
<td>70</td>
<td>5-30</td>
<td>Dietary intake determined via 12 hour in home observations on days when healthy and days when sick with diarrhea, respiratory infection, and fever.</td>
<td>There was a 10% decrease in intake on days with fever. No decrease on days with diarrhea but no fever.</td>
</tr>
<tr>
<td>Dickin</td>
<td>1990</td>
<td>Nigeria</td>
<td>45</td>
<td>6-28m</td>
<td>Dietary intake was determined via 12 hour in home observation when ill with diarrhea, during convalescence and when healthy.</td>
<td>Intake during diarrhea was 11% lower than when healthy. All differences were due to intake in solid food. Breastmilk intake was unchanged.</td>
</tr>
<tr>
<td>Brown</td>
<td>1990</td>
<td>Peru</td>
<td>131</td>
<td>1-11m</td>
<td>Dietary intake was recorded during 1615 full day in home observations during periods of health and illness with diarrhea, fever and respiratory infections</td>
<td>There was a 5-6% decrease in intake on days with diarrhea entirely attributable to a decrease in intake in solid food. Breastmilk intake was unchanged. Solid food intake decreased by 20-30%.</td>
</tr>
<tr>
<td>Bentley</td>
<td>1991</td>
<td>Peru</td>
<td>40</td>
<td>4-36m</td>
<td>Dietary intake was determined by in home observations during periods of diarrhea, convalescence and health.</td>
<td>Intake was decreased by 11 percent during diarrheal episodes.</td>
</tr>
</tbody>
</table>
Table B: Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Age</th>
<th>Methods</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoyle</td>
<td>1981</td>
<td>Bangladesh</td>
<td>41</td>
<td>6-35m</td>
<td>Intake of 30 hospitalized children with diarrhea was compared to intake of 11 healthy controls. Parents of half of the hospitalized children were educated on the importance of feeding during diarrhea.</td>
<td>Healthy controls ate 129.9 kcal/kg over 24 hours. Those with diarrhea who parents received education ate 60.9 kcal/kg. Those with diarrhea whose parents did not receive the education ate 75 kcal/kg. Breast milk intakes was the same for all groups.</td>
</tr>
<tr>
<td>Molla</td>
<td>1982</td>
<td>Bangladesh</td>
<td>32</td>
<td>0-60m</td>
<td>The dietary intake of children hospitalized with cholera and rotavirus diarrhea was recorded during illness, convalescence, and when fully recovered. No controls.</td>
<td>Children with cholera ate 70 kcal/kg/day when sick compared to 108 kcal/kg/day when healthy. The difference in intake during sickness and health was not significant for rotavirus cases.</td>
</tr>
<tr>
<td>Rahman</td>
<td>1992</td>
<td>Bangladesh</td>
<td>82</td>
<td>24-59m</td>
<td>The dietary intake of children hospitalized with <em>Shigella</em> diarrhea was recorded throughout hospitalization. No controls.</td>
<td>Children with fever consumed less in the first 48 hours than others. Those with <em>S. dysenteriae</em> consumed less than those with other species.</td>
</tr>
</tbody>
</table>
Table 1: Summary characteristics of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td># male</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Age range</td>
<td>12.8 to 68.8 months</td>
<td>12.7 to 70.5 months</td>
</tr>
<tr>
<td>mean age</td>
<td>39.4 months</td>
<td>40.6 months</td>
</tr>
<tr>
<td>mean WAZ</td>
<td>-0.1</td>
<td>-0.37</td>
</tr>
<tr>
<td>mean HAZ</td>
<td>-0.92</td>
<td>-1.09</td>
</tr>
<tr>
<td>mean WHZ</td>
<td>0.64</td>
<td>0.41</td>
</tr>
<tr>
<td># breastfeeding</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Mean per person monthly income</td>
<td>$40.00</td>
<td>$45.00</td>
</tr>
<tr>
<td>Percentage with toilets</td>
<td>71%</td>
<td>82%</td>
</tr>
<tr>
<td>Percentage with indoor running water</td>
<td>63%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Table 2: Summary characteristics of the diarrheal episodes experienced by cases

<table>
<thead>
<tr>
<th>Duration in days</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-13</td>
</tr>
<tr>
<td>Range</td>
<td>3.07</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td># bowel movements in 24 hours prior to feeding trial</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3-18</td>
</tr>
<tr>
<td>Mean</td>
<td>5.1</td>
</tr>
<tr>
<td># with fever</td>
<td>12</td>
</tr>
<tr>
<td># with vomiting</td>
<td>12</td>
</tr>
<tr>
<td># with blood in stool</td>
<td>7</td>
</tr>
<tr>
<td># with fever and vomiting</td>
<td>6</td>
</tr>
<tr>
<td># with fever and blood in stool</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3: Average intake in kcal/kg of cases, cases with fever, cases without fever and controls and visit 2

<table>
<thead>
<tr>
<th></th>
<th>cal/kg visit 1</th>
<th>cal/kg visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>24.7</td>
<td>29.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cases with fever</td>
<td>17.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31</td>
</tr>
<tr>
<td>Cases without fever</td>
<td>27.4</td>
<td>28.5</td>
</tr>
<tr>
<td>All controls</td>
<td>26.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29.1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significantly different from mean intake of cases at visit 1 (p=.035)
<sup>b</sup>Significantly different from mean intake of cases without fever at visit 1 (p=.003)
<sup>c</sup>Not significantly different from consumption of cases.
<sup>d</sup>Not significantly different from consumption of controls at visit 1.

Table 4: Mean percent change in intake from visit 1 to visit 2 for all cases, cases with fever, cases without fever and controls

<table>
<thead>
<tr>
<th></th>
<th>Mean percent difference in intake from visit 1 to visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>35%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cases with fever</td>
<td>100%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cases without fever</td>
<td>11.8%</td>
</tr>
<tr>
<td>Controls</td>
<td>19%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not significantly different from percent difference in intake of controls from visit 1 to visit 2.
<sup>b</sup>Significantly different from the percent difference in intake of cases without fever (p=.002)

Table 5: Multivariate logistical regression of the effect of the occurrence of fever during the diarrheal episode and the duration of the diarrheal episode on the likelihood that cases ate greater than or equal to 20% more at visit 2 than visit 1

|                | Odds Ratio  | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|----------------|-------------|-----------|-------|-----|----------------------|
| Fever          | 5.819814    | 5.233901  | 1.96  | 0.050 | 0.9986259            |
| Duration       | 1.512058    | .3068289  | 2.04  | 0.042 | 1.015878             |

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