Foodborne Illnesses and Nutritional Status: A Statement from an American Society for Nutritional Sciences Working Group

Janet C. King, Robert E. Black, Michael P. Doyle, Kevin L. Fritsche, Brenda H. Halbrook, Orville A. Levander, Simin N. Meydani, W. Allan Walker and Catherine E. Woteki

Western Human Nutrition Research Center, University of California, Davis, CA 95616

Foodborne illness is a major public health problem in the United States and globally. Both the developed and developing countries suffer the consequences of foodborne illness, but to varying degrees.

Recent U.S. estimates indicate that some 76 million illnesses and 5,000 deaths are attributed annually to foodborne illness. Among all illnesses attributed to foodborne causes, 30% are caused by bacteria, 3% by parasites, and 67% by viruses (Mead et al. 1999). The incidence of foodborne illness in developing countries is well-understood than in the U.S. Estimates issued by the World Health Organization (WHO) that diarrheal disease caused by the consumption of contaminated food or water is the third leading cause of death in the developing countries. Estimates for 1998 indicate that 2.2 million deaths are attributable to diarrheal disease, of which 1.8 million occur in children less than 5 y of age. Overall, it is estimated that 1.5 billion cases of diarrheal disease occur annually in children under 5 y of age (WHO 1999).

The rates of foodborne illness and their causative agents vary between the developed and developing countries. Although many of the bacterial pathogens responsible for foodborne illness in the U.S. are also common in developing countries, there is a major difference in the relative importance of the bacterial pathogens in different locations (Table 1).

The risk of contracting foodborne illness depends upon many factors. In the developed countries, the risk is increased by type of food consumed; cross-contamination of foods before consumption; increased consumption of raw products, such as fruits and vegetables; and whether one is chronically ill, elderly, immunocompromised, pregnant, or very young (Bender et al. 1999). In developing countries, factors such as poverty, undereducation, poor hygiene practices, contaminated food, water, and eating utensils, and contact with animals and flies that transmit pathogens all play a role in exposing individuals to foodborne disease (Black and Lanata 1995, WHO 1999).

In both developed and developing countries, many host factors influence the development of diarrheal illness. In developing countries, nutritional deficiencies in vitamin A and zinc are recognized contributors to diarrheal disease (Barreto et al. 1994, Bloem et al. 1990, Sommer et al. 1984, Zinc Investigator’s Collaborative Group 1999). The role of nutritional status, however, in the development and severity of foodborne infection has not been fully explored or elucidated. This paper reviews the potential role of nutritional status in reducing the risk of foodborne disease. Earlier investigations have related nutritional status to the risk of chronic diseases, such as cancer, cardiovascular disease and hypertension. In this summary, host nutritional status is discussed in terms of gut-mediated immunity, the effect of nutrition on immunity and pathogen virulence and age- or health-related factors that affect the host’s ability to resist or diminish the onslaught of foodborne pathogens. New prevention and intervention strategies, particularly in the area of host susceptibility factors, are needed to reduce the risk for foodborne disease.

Research in the developing world

Studies in international settings have provided useful evidence regarding the role of nutritional factors in foodborne disease. Researchers demonstrated that moderately malnourished children have a 30 to 70% greater rate of diarrhea than better nourished children in the same settings (Baqui et al. 1993a, Baqui et al. 1993b, Black et al. 1984, Black et al. 1989, Chowdhury et al. 1990, Mathur et al. 1985, Samani et al. 1988, Schorling et al. 1990, Sepulveda et al. 1998, Tompkins et al. 1989). Undernutrition seems to have an even greater effect on the severity of diarrhea. Moderately malnourished children have a two- to three-fold increase in the duration of their diarrheal episodes in comparison to the duration in better nourished children in those communities.

The relationship between undernutrition and risk of child mortality has been well-demonstrated (Pelletier et al. 1993). With worsening nutritional status, the risk of death increases logarithmically. The WHO estimates that ~50% of childhood deaths from infectious diseases in developing countries could be due to malnutrition because of the additional risk that this deficit imparts. Two micronutrient deficiencies, vitamin A and zinc, have been particularly noted to increase the risk of diarrheal diseases. Supplementation with vitamin A in settings with a likely deficiency has reduced diarrhea-associated mortality by 20 to 55% (Beaton et al. 1993). Although there was little effect on the overall incidence of the disease, it appears from these studies that vitamin A supplementation reduces the severity of disease and the case fatality rate. Zinc deficiency has also been associated with the occurrence of diarrhea. Recent studies with zinc supplementation at one to two times

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2 To whom correspondence should be addressed.
3 Abbreviations used: IL-12, interleukin-12; PUFA, polyunsaturated fatty acids; SE, selenium; WHO, World Health Organization.
TABLE 1

Most frequent foodborne (>50% of Cases) pathogens associated with diarrheal disease in the United States and developing countries

<table>
<thead>
<tr>
<th>United States</th>
<th>Developing countries</th>
</tr>
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<tbody>
<tr>
<td>Campylobacter sp.</td>
<td>Escherichia coli-enterotoxigenic</td>
</tr>
<tr>
<td>Salmonella sp.</td>
<td>Campylobacter sp.</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Salmonella sp.</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>E. coli-enteroaggregative and enteroadherent</td>
</tr>
<tr>
<td>Shigella</td>
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</table>

the RDA have shown that the incidence of diarrhea was reduced by about 20%, as was the duration of diarrheal episodes (Sazawal et al. 1995, Zinc Investigator’s Group 1999).

In summary, the evidence from international settings indicates very clearly that nutritional factors contribute to the risk of foodborne diseases. Addressing these underlying nutritional factors would likely have a substantial effect on reducing the morbidity and mortality from these infectious diseases. Studies in the developing countries suggest that clinical or subclinical nutritional deficiencies in the developed countries also could lead to greater susceptibility to foodborne pathogens.

Nutritional status: Its role in host susceptibility and pathogen virulence

As in the developing countries, developed countries have segments of the population that are more susceptible to foodborne illness and its sequelae. In the U.S., more than 30 million people are likely to be particularly susceptible to foodborne disease (Mead et al. 1999). At particular risk are infants, pregnant women, and the elderly, chronically ill, or immunocompromised. Certain stages of the life cycle are marked by changes in the ability of the intestine to resist foodborne infection.

Infants. The gut provides some 60% of the body’s immune response (Insoft et al. 1996). From birth, the gut plays an important role in defending the host from invasion by foodborne pathogens. Epithelial and immunologic luminal and mucosal factors within the intestinal mucosal barrier work in concert to control the penetration of noxious substances and modulate self-limited inflammation and stimulate appropriate immunologic reactions to foreign antigens and microbial flora and their toxins. Colonizing bacteria participate in each step in the expression of barriers to invasion by foreign substances. Nutrition may play an important role in the development of the mucosal barrier by influencing the membrane receptors that either inhibit or promote the attachment of pathogens (Chu and Walker 1989).

How the gut is colonized after birth has a significant impact on the developing, but immature, immune system. What is known about the initial bacterial colonization of the newborn gut comes from studies of breast- and bottle-fed infants, whose intestinal flora are acidic and alkaline, respectively, which may affect the infant’s ability to avoid colonization by pathogens. There is evidence that the composition of breast milk confers a certain degree of immunity on both full- and pre-term infants and that the respective maternal milk is especially suited to these two types of infants (Dai and Walker 1999). Some published clinical studies indicate that supplemental pre- and probiotics may prevent or minimize neonatal infections with pathogenic bacteria and viruses (Holmgren et al. 1983, Kunz and Rudloff 1993, Newburg et al. 1990, Newburg 1997, Otnaes et al. 1983). Although very little is known at this point about the specific molecular mechanisms by which indigenous flora activate host intestinal defense, it will be important to investigate this area in years to come.

Elderly. The elderly have higher morbidity and mortality rates due to foodborne pathogens, such as Salmonella, Escherichia coli, Campylobacter, Cryptosporidium, and Norwalk-like viruses (Bennett and Greenough 1993). The Center for Disease Control reports that from 1979 to 1987 death occurred in 51% of the elderly aged 74 y and older affected with diarrheal disease (Lew et al. 1991). Furthermore, individuals aged 60 y and older represented 85% of diarrheal deaths in hospitals (Gangarosa et al. 1992). Several factors contribute to the increased vulnerability of the elderly to morbidity and mortality from foodborne pathogens: e.g., reduced gastric acid secretion due to aging and the use of certain drugs and antacids. The infective dose of pathogens is much lower for individuals with hypochlorhydria than for those with normal levels of gastric acidity. Other factors, such as decreased motility of the gastrointestinal tract, reduced immune response in nursing homes, retirement communities and hospitals with crowded conditions and a possible increased mucosal sensitivity to toxins, all carry greater risk to the elderly when confronted with foodborne pathogens.

The increased susceptibility in the elderly also can occur due to factors such as dysregulation of the immune response, which results in a higher incidence of morbidity and mortality from neoplastic, infectious, inflammatory, and autoimmune diseases (Hayek et al. 1994, Makinodan and Hirokawa 1985, Miller 1995). Age-related changes in the human peripheral immune response have been well-delineated and include a decline in T cell-mediated functions and an increased production of suppressive factors from macrophages (Beharka et al. 1997, Hayek et al. 1994, Miller 1995). In contrast, the age-associated changes in gut-associated immune response have not been well-studied (Beharka et al. 1997). The age-related changes in both peripheral and gut-associated immune response function could contribute to the increased susceptibility of older adults to foodborne pathogens. Thus, improving the peripheral and gut-associated immune response in older subjects should reduce the susceptibility to, and morbidity and mortality from, foodborne pathogens. Furthermore, studies have shown that the immune response in the elderly is influenced by the macro- and micronutrient components of the diet.

Several investigators have used single nutrient (vitamins B-6, C and E, β-carotene, selenium, zinc and lipids) interventions to improve the immune response in the elderly (Bogden et al. 1990, Delafluente et al. 1986, Kaplan et al. 1988, Kiremidjian-Schumacher and Roy 1998, Meydani et al. 1991, Meydani et al. 1993, Meydani et al. 1997, Pallast et al. 1999, Santos et al. 1996, Santos et al. 1997, Talbott et al. 1987, Wu et al. 1999). Among the nutrients tested, vitamin E seems to be most effective in improving the immune response. Furthermore, vitamin E has been shown to significantly decrease lung viral titers in old animals infected with influenza virus (Han et al. in press, Hayek et al. 1997). The enhancement of the immune response in healthy elderly was also associated with a 30% reduction in self-reported infections, although this finding was not significant (P < 0.9) (Meydani et al. 1997). Others have reported increased resistance to infection when immune response is improved by micronutrient supplementation in older subjects. Chandra (1992) reported significant improvement in cell-mediated immune response follow-
ing a year of supplementation with a mixture of micronutrients in older people. This improvement was associated with decreased number of sick days and antibiotic use due to infection. While no information on the effect of nutrient supplementation on gastric-associated immune response is available, based on the above information, it is feasible to propose that the gastric-associated immune response of the elderly would be responsive to nutrient modification. Enhancing both the gastric-associated and the peripheral immune response of the elderly could improve their resistance to gastrointestinal infections and lower their morbidity and mortality rates.

Because of the impaired immunologic and nutritional status of the elderly, studies are needed that focus both on reducing the source of food contamination and improving the nutritional quality of food consumed by the elderly. In addition to micro- and macronutrients, food components with pre- and probiotic properties need to be considered.

**Emerging concepts**

Recent research indicates that manipulation of the diet may have an effect on either the human host or the infective agent.

**(n-3) Fatty acids.** Several laboratories have explored the relationship between host nutritional status and the immune response, particularly with reference to Listeria monocytogenes, as well as the effect of nutritional status on the virulence of a coxsackievirus (Beck et al. 1994a, Beck et al. 1994b, Fritsche et al. 1997).

Fritsche et al. used a murine infectious disease model involving healthy, but nutritionally manipulated, mice that were injected with live L. monocytogenes bacteria (Fritsche et al. 1997). Experimental mice were fed diets rich in (n-3) polyunsaturated fatty acids [(n-3) PUFA] from fish oil and challenged with L. monocytogenes. Fish oil adversely affected host resistance to Listeria by reducing both bacterial clearance and the expression of interferon-γ receptors on immune cells (Fritsche et al. 1997, Fritsche and Feng 1997). Interferon-γ is an important cytokine that plays a critical role in inflammatory infectious and auto-immune diseases. The underlying immuno-modulatory mechanism of (n-3) PUFA is not fully understood.

In addition, the in vivo production of interleukin-12 (IL-12) was impaired by fish oil consumption in mice and is thought to be influenced by (n-3) PUFA (Fritsche et al. 1999). IL-12 is a potent stimulus for interferon-γ production and plays an important role in innate and adaptive immune responses. It also is critical for host defense against intracellular pathogens such as Listeria, Salmonella, Mycobacterium and Leishmania. The potential to nutritionally modulate IL-12 biosynthesis with (n-3) PUFA could have far-reaching implications for human disease prevention and treatment.

**Role of nutrition in virology.** Not only does the quality of the diet influence resistance of the host to infectious disease, but also, recent studies have offered an alternative mechanism by which nutritional state might influence the course of infection in a host organism. Apparently, the type of diet consumed by the host can affect the virulence of the pathogen itself by altering its genetic constitution.

In 1992, Beck and Levander initiated a series of experiments designed to clarify how selenium (Se) could improve a host's defense against viral infection. Initially, they explored the relationship between poor Se status and Keshan disease, a juvenile cardiomyopathy endemic in certain areas of China, and found that Se status did not fully explain the incidence of the disease. They hypothesized that a viral infection along with Se deficiency may precipitate the disease (Beck et al. 1994a).

To investigate that hypothesis, they studied Se-deficient mice inoculated with a benign coxsackievirus (CVB3/0), a strain that does not cause cardiopathology in normal mice. As hypothesized, hearts of the Se-adequate, infected controls appeared unaffected by CVB3/0. But, the hearts of Se-deficient mice exhibited considerable damage. That is, the benign strain had somehow converted to virulence by virtue of replicating in a Se-deficient host. Similar results were obtained with vitamin E-deficient (but Se-adequate) mice (Beck et al. 1994b).

Determination of the genomic sequence of this newly virulent virus demonstrated that its genetic composition had been altered to resemble that of other virulent CVB3 (Beck et al. 1995). This is the first report that the genome of a virus can be changed because of the nature of the diet fed to a host. The fact that deficiencies of either Se or vitamin E could result in the same outcome suggests that oxidative stress in the host may play a mechanistic role in this phenomenon. The heightened oxidative stress could precipitate genetic change in the virus either directly—by increasing oxidative damage to the genomic ribonucleotides—or less directly—by allowing the emergence of a previously suppressed virulent viral quasi-species.

At present, it is not possible to predict how many different host nutritional deficiencies will affect viral virulence similarly. Nor is it possible to predict how many different microorganisms will be affected by various nutritional deficiencies. Coxsackieviruses are RNA viruses, well-known for their genomic mutability and changeability. Whether the virulence of other microorganisms, such as foodborne bacteria or viruses, also will be influenced by the nutritional status of the host is a topic for future research.

**Research needs**

Clearly more research is needed to further develop these compelling hypotheses. The experts who attended the workshop identified the following priorities for new research.

**Population or observational studies.** Conduct large-scale clinical trials in vulnerable populations in U.S. on the effect of nutritional supplements on incidence and duration of foodborne illnesses. Identify biomarkers of nutritional risk for foodborne illnesses and of functional markers responding to the nutritional interventions; also identify biomarkers of gut-immune function.

Identify the initial vs. the long-term effects of foodborne illnesses on health. Also identify the critical periods for increased risk and the long-term effects on development. For example, what are the differences between prenatal vs. postnatal infections?

Conduct large-scale clinical trials to determine why the response to pathogens is so variable. Is it related to genetics, age, dose of pathogen, nutritional status of the host during
infection or after infection? This trial might be conducted in a nursing home. Identify appropriate animal models for studying nutritional status and susceptibility to foodborne pathogens. Determine the interaction between nutrition, host genetics and the host response. Add biomarkers of foodborne illness in ongoing studies of high-risk populations studied through the national nutrition monitoring program (i.e., NHANES/CSFII) or the U.S. Department of Agriculture Lower Mississippi Delta Project, or the European Elderly Project. Determine whether there is a threshold of nutritional status at which the risk to the elderly of foodborne pathogens increases.

**Fundamental or mechanistic questions.** What are the effects of various nutritional states on the genomic make-up of infecting viruses or other organisms? What is the mechanism by which genetic changes occur in vitamin E or Se-depleted animals infected with viruses? What nutritional influences affect a pathogen’s virulence? Is this influenced by the host and, if so, how?

How does nutritional status affect gut immunity? What is the developmental effect of poor nutrition on gut immunity? How does infection with a foodborne pathogen cause long-term effects in immunity? Are those long-term effects nutritionally mediated?

**At-risk populations.** Among low birth weight or pre-term infants, what is the role of nutrition in their susceptibility to foodborne illness? Is there any improvement with nutrient supplementation? What is the role of maternal nutrition? Among the elderly, what role does nutrition play in increasing their risk for foodborne illness? What is the impact of pre- and probiotic supplementation in infants and the elderly? What is the definition of “healthy elderly,” and why do some at-risk groups do well? Is it due to their genetic makeup, frequency of exposure, or dietary intake? Would the chronically ill and the immunocompromised, require further investigation to enhance their immune response to better resist foodborne infection and its attendant morbidity and mortality? Does obesity increase a carrier risk for foodborne illness? If so, what is the mechanism?

The role of nutritional status in preventing foodborne illness, or diminishing its effects, is not clearly understood. The special needs of populations at risk, such as infants, the elderly, and the immunocompromised, require further investigation to determine the impact of dietary manipulation on immunity, especially gut-mediated immunity. Of equal importance may be the further study of the influence of host nutritional status on the pathogenicity of an organism. A greater understanding of the interplay among nutritional status, age-related factors in immune function and foodborne pathogens could have far-reaching implications for human disease prevention and treatment of foodborne disease.

**LITERATURE CITED**


FOODBORNE ILLNESSES AND NUTRITIONAL STATUS


