The Occurrence and Prevention of Foodborne Disease in Vulnerable People

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Abstract

In developed countries, such as the United Kingdom and the United States, between 15% and 20% of the population show greater susceptibility than the general population to foodborne disease. This proportion includes people with primary immunodeficiency, patients treated with radiation or with immunosuppressive drugs for cancer and diseases of the immune system, those with acquired immune-deficiency syndrome and diabetics, people suffering from liver or kidney disease or with excessive iron in the blood, pregnant women, infants, and the elderly. Malnutrition and use of antacids, particularly proton-pump inhibitors, also increase susceptibility. We review the occurrence of infection by foodborne pathogens in these groups of people and measures to prevent infection. The nature and use of low microbial diets to reduce the risk of foodborne disease in immunocompromised patients are very variable. Diets for vulnerable people in care should exclude higher-risk foods, and vulnerable people in the community should receive clear advice about food safety, in particular avoidance of higher-risk foods and substitution of safer, nutritious foods.

Introduction

SOME GROUPS OF PEOPLE are particularly susceptible to foodborne pathogens. Indeed, there are numerous examples of problems arising from the supply of contaminated foods to vulnerable patients in hospitals (Lund and O'Brien, 2009). Several host factors, including age, contribute to increased susceptibility (Table 1). In the United States, vulnerable groups were estimated to represent almost 20% of the population (Gerba *et al.*, 1996). In the United Kingdom, people aged over 65 comprise 16% of the population; people with other conditions increasing susceptibility to infection will include elderly people and additional younger people (Table 2). Vulnerability arises often because of immune suppression, through either disease processes or the medications used to manage them, and at the extremes of age or in pregnancy. This vulnerability results in reduction in the number of organisms, in particular foodborne/waterborne pathogens, needed to cause disease and increased severity of the illness. In this article we describe some of the people who are particularly vulnerable to the major foodborne pathogens and review the recommendations for reducing their risk of foodborne disease.

Which Groups of People Are Particularly Vulnerable to Foodborne Infection?

People with pathological or iatrogenic immunosuppression

People with primary immunodeficiencies. People with primary immunodeficiencies are prone to foodborne infections (Dropulic and Lederman, 2009). For example, recurrent or chronic diarrhoea was reported in 118/252 patients (47%) with common variable immunodeficiency with hypogammaglobulinemia in France; the pathogens detected most frequently were *Giardia*, *Campylobacter*, and *Salmonella* (Oksenhendler *et al.*, 2008). In the United States, nontyphoidal salmonellas were the main cause of bacteraemia in a group of patients with chronic granulomatous disease (cited in Gordon, 2008).

Transplant recipients and cancer patients. The risk of infection in transplant recipients arises from the immunosuppressive treatment to prevent tissue or organ rejection, and prophylactic antimicrobial treatment is given (Rubin *et al.*, 1999). In cancer patients chemotherapy and radiotherapy affect bone marrow cells and the gastrointestinal mucosa,

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TABLE 1. FACTORS THAT INCREASE THE RISK OF FOODBORNE INFECTION OR THE SEVERITY OF THE DISEASE

<i>Host factors</i>	<i>Reasons</i>
Primary immunodeficiencies	Immune system inadequate to combat infection
Immunocompromised persons, including those treated with chemotherapy or radiation therapy, recipients of transplants taking immunosuppressive drugs, persons with leukemia, persons with diseases of the immune system, AIDS patients	Immune system inadequate to combat infection
Excessive iron in blood	High levels of iron increase growth of certain pathogens
Cirrhosis and other liver disease, kidney function (alcoholism)	Iron overload, immune system dysfunction
Stress, e.g., as a result of surgery	Changes in metabolism reduce resistance to infection
Pregnancy	Altered immunity
Age <5 years	Lack of developed immune system, smaller infective dose required for infection
Age 60–65 years	Immune system deteriorating, also affected by chronic ailments
Nutritional deficiency, e.g., through poor absorption of food, poor nutrition, or starvation	Inadequate immune system
Consumption of antacids, particularly proton pump inhibitors	Increase pH in stomach, increasing survival of pathogens
Consumption of large volumes of liquids, including water	Dilution of acids in the stomach, rapid transit through stomach
Ingestion of fatty foods (e.g., chocolate, cheese, hamburger) containing pathogens	Fat protects pathogens from acid in stomach

Modified from CAST (1994).

AIDS, acquired immune-deficiency syndrome.

TABLE 2. NUMBERS OF PEOPLE AFFECTED BY CONDITIONS LEADING TO INCREASED SUSCEPTIBILITY TO FOODBORNE AND WATERBORNE DISEASE

<i>Condition</i>	<i>Region</i>	<i>Estimated number of people affected</i>	<i>Source of information</i>
Primary immunodeficiency	UK	5000	Primary Immunodeficiency Association (2010)
Hematopoietic stem cell transplant	UK and Ireland	2700 per annum	Lee <i>et al.</i> (2010)
Organ transplant	UK	3709 (April 1, 2009–March 31, 2010)	NHS Blood and Transplant (2010)
Cancer	UK	298,000 diagnosed 2007	Cancer Research UK (2010)
Rheumatoid arthritis	UK	~400,000, ~20,000 new cases/year	Arthritis Research UK (2008)
Systemic lupus erythematosus	UK	50,000	Lupus UK, pers. comm. (2010)
Diabetes	UK	2,800,000	Diabetes UK (2010)
Multiple sclerosis	UK	~100,000 (2009)	Multiple Sclerosis Society UK (2009)
HIV/AIDS	UK	65,319 (2009)	HPA (2010)
Crohn's disease	UK	60,000–80,000 ~6000 new cases/year (2004)	National Association for Colitis and Crohn's Disease (2011)
Ulcerative colitis	UK	120,000–160,000 ~12,000 new cases/year (2004)	
Cirrhosis	UK	>4000 deaths/year	British Liver Trust (2011)
Pregnant/neonates	England and Wales	706,248 Live births (2009)	Office of National Statistics (2010a)
Age over 65 years	UK	10,105,800 (2009) (16% of population)	Office of National Statistics (2010b)
Prescribed proton pump inhibitors	England	~30,000 prescriptions (2007)	Gillespie <i>et al.</i> (2009a)

causing myelosuppression and mucositis (Khan and Wingard, 2001; Dropulic and Lederman, 2009). Neutropenia and concomitant steroid treatment also increase susceptibility to infection.

Although transplant patients are susceptible to *Listeria monocytogenes* (Table 3), the reported incidence of listeriosis and other foodborne pathogens is low, but they can cause high mortality (Safdar *et al.*, 2002; Rivero *et al.*, 2003; del Pozo, 2008; Fernandez-Sabe *et al.*, 2009). This low incidence may be due, in part, to the prophylactic use of trimethoprim-sulphamethoxazole (TMP-SMX) against *Pneumocystis jiroveci* pneumonia, but which also inhibits *L. monocytogenes* and *Toxoplasma gondii*. Cancer patients also show increased susceptibility to *L. monocytogenes* (Table 3). In England and Wales in 1999–2009 cancer patients accounted for more than one-third of non-pregnancy-associated listeriosis cases (Mook *et al.*, 2011). Two patients with oral cancer developed listeriosis after eating large quantities of soft cheese to counteract severe mouth soreness (Morritt *et al.*, 2002).

Salmonella gastroenteritis is rare in transplant patients, but leads to bacteraemia in 20%–30% of cases, compared with 3%–4% in nontransplant recipients. Subsequent metastatic infection is common (Rubin, 2001), and in patients aged over 50 years, cardiovascular sites tend to be affected. *Salmonella* and *Campylobacter* gastroenteritis are more common in patients with hematological malignancies than those without a malignancy (Gradel *et al.*, 2009).

Cryptosporidium and *Giardia* are the most common parasitic infections in transplant patients, particularly in endemic regions (Kotton *et al.*, 2009). *Cryptosporidium* causes prolonged watery diarrhoea, malabsorption, nausea, and vomiting in transplant recipients, which may be life-threatening, and the organism is difficult to eradicate (Rubin 2001; Stark *et al.*, 2009; Muñoz *et al.*, 2010). Patients with leukemia and other hematological malignancies also seem to be at increased risk of cryptosporidiosis (Hunter and Nicolls, 2002). *Giardia* infection, which causes bloating and diarrhea, can be treated with metronidazole or other agents (Stark *et al.*, 2009).

Toxoplasma is a rare infection that can occur after heart, heart/lung, hematopoietic stem cell (HST), and solid organ transplants (SOT), causing high mortality (Campbell *et al.*, 2006; Edvinsson *et al.*, 2009; Weiss and Dubey, 2009). Cases are often reported when prophylactic treatment with TMP-SMX is discontinued because of ill-effects. Toxoplasmosis is also a risk for cancer patients in general (Edvinsson *et al.*, 2009; Herold *et al.*, 2009). In the United Kingdom in 1990–1992 an estimated 5–10 million people were infected with *T. gondii*, and in people aged over 60 seroprevalence was 55% (Guy, 2008). In the Netherlands in 2004 overall seroprevalence was 40.5% and in the 60–64 age group >70% (Kemmeren *et al.*, 2006). Sources of infection are consumption of undercooked meat, raw sheep or goat milk, contaminated vegetables or raw oysters, clams, or mussels, contact with contaminated cat feces, or environmental contamination (EFSA, 2007; Kijlstra and Jongert, 2008; Jones *et al.*, 2009). Toxoplasmosis can arise from allograft infection, reactivation that commonly results in encephalitis or disseminated infection, or primary infection (Campbell *et al.*, 2006). Reactivation of latent infection with *T. gondii* in immunocompromised people emphasizes the need for primary prevention.

Norovirus (NoV) infection, which is often foodborne or waterborne, poses a higher risk of severe consequences in

TABLE 3. RELATIVE SUSCEPTIBILITIES OF DIFFERENT SUBPOPULATIONS TO LISTERIOSIS, BASED ON THE INCIDENCE OF LISTERIOSIS CASES (OUTBREAK AND SPORADIC) IN THESE GROUPS IN FRANCE IN 1992 (WHO/FAO, 2004)

Condition	Relative susceptibility
Transplant	2584
Cancer—blood	1364
AIDS	865
Dialysis	476
Cancer—pulmonary	229
Cancer—gastrointestinal and liver	211
Noncancer liver disease	143
Cancer—bladder and prostate	112
Cancer—gynecological	66
Diabetes, insulin-dependent	30
Diabetes, non-insulin-dependent	25
Alcoholism	18
Over 65 years old	7.5
Less than 65 years old, no other condition (reference population)	1

immunosuppressed patients, causing chronic gastroenteritis (Mattner *et al.*, 2006; Roddie *et al.*, 2009). Hepatitis E infection in immunocompromised organ transplant patients, which can result from consumption of insufficiently cooked game or pork meat, can lead to chronic hepatitis (Gérolami *et al.*, 2009; Colson *et al.*, 2010).

Aspergillus and *Candida* cause important invasive infections in transplant patients (Person *et al.*, 2010). *Aspergillus* infection is probably acquired mainly by inhalation, but the mould occurs commonly in spices; some foods, particularly pepper and some fruits, provided in hematology wards were highly contaminated with *Aspergillus* spp. (Bouakline *et al.*, 2000). Food or drinks may also be a source of *Candida* spp. (Costa *et al.*, 2010). *Saccharomyces cerevisiae* can cause invasive disease, particularly in transplant and cancer patients (Clemons *et al.*, 2010). It is ingested frequently in foods and beverages (de Llanos *et al.*, 2006), and it is not clear whether it is a persistent commensal in the digestive tract or is only present transiently after ingestion of food (Enache-Angoulvant and Hennequin, 2005). There are reports of serious infection of immunocompromised patients with *S. boulardii*, a subtype of *S. cerevisiae* used as a probiotic (Venugopalan *et al.*, 2010).

People with diseases of the immune system. Rheumatoid arthritis, systemic lupus erythematosus: Anti-inflammatory and immunosuppressive corticosteroids are used to treat several autoimmune diseases and have many dose-dependent effects on innate and acquired immunity (Dropulic and Lederman, 2009). Chronic use of steroids to treat rheumatoid arthritis (RA) increases the risk of infection by *L. monocytogenes*, *Salmonella* spp., and other Enterobacteriaceae, *Brucella* spp. *Cryptosporidium* and *T. gondii* (Klein *et al.*, 2001). Listeriosis is often associated with older age and concomitant use of immunosuppressants such as methotrexate (MTX), a corticosteroid and a biological agent (Slifman *et al.*, 2003; Raychaudhuri *et al.*, 2009). *Listeria* endocarditis occurred in a psoriatic arthritis patient treated with the biological agent infliximab who admitted eating soft cheeses (Kelesidis *et al.*, 2010). Consumption of soft cheese

made with unpasteurized milk resulted in *L. monocytogenes* bacteremia in an ankylosing spondylitis patient treated with infliximab, whereas eating partly cooked eggs from a local farm was followed by *Salmonella* joint infection in an RA patient treated with infliximab, prednisolone, and MTX (Makkuni *et al.*, 2006). A patient with RA treated with MTX, prednisolone, and infliximab, who traveled to India and consumed raw vegetables, experienced acute *S. paratyphi* gastroenteritis followed by bacteremia and soft tissue infection (Bassetti *et al.*, 2010).

The risk of infection and death in systemic lupus erythematosus (SLE) patients is increased by treatment with corticosteroids and other immunosuppressive agents (Dropulic and Ledermann, 2009; Goldblatt *et al.*, 2009). Bacteria, particularly *Salmonella*, are important causes of infections (Chen *et al.*, 1998; Bouza *et al.*, 2001; Chen *et al.*, 2008). *L. monocytogenes* infection is rare but causes severe symptoms, often mistaken for SLE flares (Tobón *et al.*, 2010). Tobón *et al.* (2010) reported that 2.87% of their SLE patients in Colombia contracted listeriosis, and linked this to the use of unpasteurized milk. *T. gondii* infection is rare but causes severe symptoms (Zamir *et al.*, 1999; Yamamoto *et al.*, 2003). In 83 SLE patients with major infections, the most frequently identified pathogens (43/83 cases) were *Escherichia coli*, *Staphylococcus aureus*, *M. tuberculosis*, and *Streptococcus pneumoniae*, followed by *Salmonella* (Ruiz-Irastorza *et al.*, 2009). Treatment with prednisone increased the risk of infection, whereas antimalarials had a protective effect.

Diabetes: Diabetes can increase the risk of infection (Shah and Hux, 2003). Poor glycaemic control is associated with impaired neutrophil function (Dropulic and Lederman, 2009). Controlling blood glucose appears to rectify some immune defects. During a nosocomial *Salmonella* Enteritidis outbreak, in which raw eggs were used in a hospital-prepared mayonnaise, patients with diabetes who required insulin or oral hypoglycaemics were at increased risk (Telzak *et al.*, 1991), perhaps through a combination of reduced gastric acidity and impaired intestinal motility due to autonomic neuropathy. Salmonellosis and campylobacteriosis are three and four times more common, respectively, in patients with diabetes than in the general population (Calvet and Yoshikawa, 2001), and patients with diabetes are about 25 times more likely to develop listeriosis than healthy, nondiabetics (Goulet and Marchetti, 1996) (Table 3).

Inflammatory bowel disease: Immunosuppressants, including MTX, azathioprine/6-mecaptopurine, cyclosporine, steroids, and biological therapies such as infliximab, used to treat inflammatory bowel disease (IBD), increase susceptibility to infection, particularly when two or more drugs are used (Viget *et al.*, 2008). Foodborne infections associated with immunosuppressant therapy in IBD patients include *Salmonella*, *L. monocytogenes*, and *T. gondii* (Williams *et al.*, 2005; Viget *et al.*, 2008; Epple, 2009; Rim and Tenorio, 2010). For example, a man with Crohn's disease receiving infliximab treatment died from listeriosis after eating a contaminated chicken salad from a retail store (Marcus *et al.*, 2009).

Multiple sclerosis: The treatments for multiple sclerosis, including steroids and immunosuppressive drugs, might be expected to increase susceptibility to foodborne infection. There appear to be few reports of such infection, but a case of central nervous system toxoplasmosis and a case of ocular toxoplasmosis have been reported in patients treated with the

monoclonal antibody natalizumab (cited in Berger and Houff, 2009; Zecca *et al.*, 2009).

Immunosuppressant therapies that increase the risk of foodborne disease

Several therapies, developed to cure or control some of the diseases described above, can also increase patients' foodborne disease risks. Chronic use of steroids increases the risk of infection. Purine analogs such as fludarabine, used in the treatment of cancer, increase the risk of *Listeria* and mycobacteria infections (Hequet *et al.*, 1997; Levidiotou *et al.*, 2004; Wadha and Morrison, 2006). Treating chronic myeloid leukemia patients with the tyrosine kinase inhibitor imatinib mesylate has caused monocytopenia, leading to *L. monocytogenes* meningitis (Ferrand *et al.*, 2005).

Alemtuzumab is a monoclonal antibody directed against the CD52 antigen on the surface of a range of cells, including T and B lymphocytes. It is used to treat patients with lymphoid malignancies and transplant patients, many of whom are at increased risk because of prior treatment with other agents. A range of infections has been reported after alemtuzumab treatment, including toxoplasmosis and listeriosis, and the use of *P. jiroveci* prophylaxis is advised (Martin *et al.*, 2006; Koo *et al.*, 2010).

Tumor necrosis factor- α (TNF- α) is an essential component of the host immune response. Treatment of RA or IBD patients with TNF- α inhibitors, particularly infliximab (often combined with other immunosuppressant agents), is associated with an increased risk of infection by a range of microorganisms, including *Mycobacterium tuberculosis*, *L. monocytogenes*, *Salmonella*, *Toxoplasma*, and *Brucella* (Slifman *et al.*, 2003; Crum *et al.*, 2005; Hamilton, 2005; Dixon *et al.*, 2006; Dixon *et al.*, 2007; Kesteman *et al.*, 2007; Pena-Sagredo *et al.*, 2008; Salvana and Salata, 2009; Greenberg *et al.*, 2010; Kelesidis *et al.*, 2010). Treatment may cause reactivation of latent infection with *M. tuberculosis*, *M. bovis*, *T. gondii*, and *Brucella* spp. (Wallis *et al.*, 2004; Young and McGwire, 2005; Lassoued *et al.*, 2007; Raychaudhuri *et al.*, 2009). Tuberculosis occurred in two patients (one with RA and one with Crohn's disease) treated with infliximab, because of reactivation of *M. bovis* (Larsen *et al.*, 2008; Nager *et al.*, 2009). In each patient a tuberculin test before treatment was negative; both patients probably drank unpasteurized milk many years previously.

People with acquired immune-deficiency syndrome

Human immunodeficiency virus type 1 (HIV-1) infection causes chronic progressive immunodeficiency through reducing CD4⁺ T-cell lymphocytes (Dropulic and Lederman, 2009). Foodborne organisms causing diarrhea in people with HIV include nontyphoidal *Salmonella* and *Giardia* and, less commonly, *Shigella*, *Campylobacter*, *Microsporidium*, *Cryptosporidium*, *Isospora*, and *Cyclospora* (Sax, 2001). Patients with acquired immune-deficiency syndrome (AIDS) are also at greater risk of invasive listeriosis than the general population, although widespread TMP-SMX prophylaxis and dietary recommendations probably decreased listeriosis in parts of the United States (Tappero *et al.*, 1995). CD4 counts below 200/ μ L are associated with toxoplasmosis encephalitis (Weiss and Dubey, 2009), and diarrhea caused by *Cryptosporidium*, which can be severe (Hunter and Nicholls, 2002; Stark *et al.*, 2009). Where antiretroviral treatment is available, with the

attendant recovery of CD4 count, dramatic reductions in toxoplasmosis have been seen. People with advanced HIV are particularly susceptible to recurrent, invasive salmonellosis (Gordon, 2008) and occasionally to *Salmonella* meningitis (Leonard *et al.*, 2002).

People with defects of iron metabolism, cirrhosis, or other liver diseases

Conditions that increase iron availability in the body, including multiple transfusions of whole blood or erythrocytes in excess, liver dysfunction, alcohol-induced cirrhosis, hemochromatosis, and thalassemia, can stimulate growth of several foodborne pathogens, including *Bacillus*, *Clostridium*, *Listeria*, *Campylobacter*, *Salmonella*, *Shigella*, *Vibrio*, *Yersinia*, and *Toxoplasma* (Khan *et al.*, 2007; Weinberg, 2009). Bacterial infection is a major complication and an important cause of death in patients with liver cirrhosis (Brann, 2001) because of defects caused in the immune response, in bacterial translocation, and in the reticulo-endothelial system. For example, *Vibrio vulnificus* septicemia after eating raw or undercooked seafood or following wound infection occurs mainly in patients with liver diseases such as cirrhosis or hepatitis, elevated serum iron levels, or immunodeficiency (Jones and Oliver, 2009). Cirrhosis increases the risk of nontyphoidal *Salmonella* bacteraemia (Hsu and Lin, 2005), and hepatitis E virus can cause a high rate of mortality in people with chronic liver disease (Dalton *et al.*, 2008).

People with physiological impairment of the immune system

Pregnant women and neonates. Important foodborne pathogens for pregnant women are *L. monocytogenes* and *T. gondii* (Smith, 1999). *L. monocytogenes* infection in pregnant women is often mild, with fever or flu-like illness, but can cause fetal loss, stillbirth, or birth of a severely infected infant (Table 4). Transplacental infection gives rise to early-onset illness in the neonate resulting in bacteraemia, respiratory distress, fever, neurologic abnormalities, and, less frequently, disseminated granulomas in multiple internal organs. Late onset illness results from infection during passage through the birth canal or after delivery and usually presents as meningitis (Painter and Slutsker, 2007).

Congenital infection with *T. gondii* usually occurs when a pregnant woman is newly infected, but can follow infection just before pregnancy or result from reactivation of an infection acquired before pregnancy (Dubey and Jones, 2008). Infection in pregnancy is usually asymptomatic but occasionally causes lymphadenopathy. The risk of congenital infection between weeks 10 and 24 of pregnancy is low, but the symptoms can be severe, including spontaneous abortion. Infection of the fetus in weeks 26–40 of pregnancy results in subclinical disease that can cause symptoms later in life, because the organism survives in tissue cysts that persist, particularly in neural and muscle tissue and in the eye. If left untreated, children with subclinical disease can develop chorioretinitis or neurologic symptoms.

The immune system in neonates and very young infants is not fully developed (Dropulic and Lederman, 2009). Unlike most adults, infants are susceptible to infection by spores of *Clostridium botulinum*, which can germinate and colonize the infant colon producing botulinum neurotoxin and leading to

TABLE 4. RELATIVE SUSCEPTIBILITY OF DIFFERENT GROUPS BASED ON THE INCIDENCE OF LISTERIOSIS CASES (OUTBREAK AND SPORADIC) IN THESE GROUPS IN THE UNITED STATES

Condition	Relative susceptibility
Perinatal	14
Elderly (60 years and older)	2.6
Intermediate-age population (reference population)	1

Data from WHO/FAO (2004).

infant botulism. In healthy adults, the intestinal microflora stops growth from ingested *C. botulinum* spores, but in infants the microflora is unable to prevent growth. Most cases of infant botulism occur before the age of 1 year (Arnon, 2004). Honey is the source of spores in some cases of infant botulism and so warnings are issued in several countries, including the United Kingdom, United States, and Italy, that honey should not be given to infants <1 year old. Other possible sources are soil and dust, but in many cases of infant botulism the source is unknown.

Rarely, *C. botulinum* or a neurotoxin-forming strain of *C. butyricum* can become established in the adult intestine—"adult intestinal botulism." This can occur if competing bacteria in the normal intestinal microflora are suppressed by antibiotic treatment, or as a result of intestinal tract malformation (Fenicia *et al.*, 2007).

Infant formula or follow-on formula contaminated with *Cronobacter sakazakii* (*Enterobacter sakazakii*) or *Salmonella* has caused serious infection in infants (Bowen and Braden, 2008). *C. sakazakii* can be isolated from many sources, including foods, and may lead to meningitis, bacteraemia, urinary tract infections, and wound infections. There are also several reports of *C. sakazakii* infection in immunocompromised adults (Healy *et al.*, 2010).

Elderly people. Age-related deterioration of the immune system and comorbidity result in increased susceptibility to infections (Smith, 1998; Aw *et al.*, 2007; Aspinall *et al.*, 2010). In the United Kingdom 63% of cancers are diagnosed in people aged 65 and over, and 36% in those aged over 75 (Cancer Research UK, 2010). In elderly people with chronic gastritis, stomach acid production declines; gastrointestinal motility decreases, increasing the gastrointestinal transit time and leading to constipation (Smith, 1998).

The elderly are susceptible to various infections, including listeriosis (McLauchlin *et al.*, 2004) (Tables 3 and 4), *Campylobacter* and *Salmonella* bacteraemia (Skirrow *et al.*, 1993; Weinberger *et al.*, 2004; Gillespie *et al.*, 2009b; Nielsen *et al.*, 2010), and focal infections, such as aortic infections, secondary to salmonella gastroenteritis (Ispahani and Slack, 2000; Chen *et al.*, 2007). Recent increases in listeriosis in France, Germany, and England and Wales have mainly affected the elderly and those with malignancies (Goulet *et al.*, 2008; Gillespie *et al.*, 2009a). Elderly people are also the group most likely to die after infection with Shiga-toxin-producing *Escherichia coli* O157 (Gould *et al.*, 2009). Norovirus infection is generally considered to be mild, but there were an average of 80 deaths/

year in people aged over 65 attributable to norovirus in England and Wales in 2001–2006 (Harris, 2009).

Malnourished people. Malnutrition is a major factor increasing susceptibility to infection worldwide (Schalbe and Kaufmann, 2007). Although malnutrition often refers to macronutrients, micronutrient deficiencies are also important and common in older adults. While malnutrition is most widespread in low-income countries, it also occurs in hospital patients and homeless people in high-income countries (Smith, 1998; Moulias, 2002; Macallan, 2005).

People with impairment of physical barriers to foodborne infection

People with reduced stomach acidity. Stomach pH in fasting, healthy people is usually between pH 1.5 and pH 2 and serves as a barrier to foodborne pathogens. When food enters the stomach there is a transient rise in pH ($> \text{pH } 6.0$), which gradually declines as the stomach empties, depending on the nature of the food (R. Faulks, pers. comm.). In experiments by Giannella *et al.* (1972) gastric juice aspirates from achlorhydric, pernicious anemia patients or from normal patients, adjusted with hydrochloric acid (HCl) to pH 2.0, killed $>99.9\%$ of *Salmonella* in 30 min, but when adjusted to pH 4.0 failed to reduce the numbers in 120 min. Proton pump inhibitors are the most effective agents for suppressing acid production and can prevent the intragastric pH from falling below pH 4 for a high percentage of time (Kirchheimer *et al.*, 2009). There is evidence that patients with hypochlorhydria or achlorhydria, or who have been treated with proton pump inhibitors or H_2 receptor antagonists are more susceptible to *Campylobacter*, *E. coli* O157, *L. monocytogenes*, *Salmonella*, *Shigella*, and *Vibrio cholerae* than healthy persons (Smith, 2003; Bowen *et al.*, 2007; Leonard *et al.*, 2007; Gillespie *et al.*, 2009a; Tam *et al.*, 2009; Canani *et al.*, 2010). Proton pump inhibitors are available increasingly without prescription, so that people can self-medicate without realizing that this might mean an increased risk of foodborne disease.

People using antidiarrhoeal medication. The diarrhea caused by enteropathogens helps to eliminate organisms during intestinal infections. As well as masking dehydration, antidiarrheal agents can increase the severity of infections. For example, in an outbreak of foodborne *Clostridium perfringens* in the United States in 2001, three elderly patients developed severe bowel necrosis and two died (Bos *et al.*, 2005). The symptoms were attributed in part to drug-induced constipation and fecal impaction, resulting in prolonged exposure of colonic tissue to *C. perfringens* toxins. Similarly, antidiarrheals are not recommended in children with *E. coli* O157 infection since they appear to increase the risk of serious complications such as hemolytic uremic syndrome (Tarr *et al.*, 2005).

Preventing Foodborne Infection in Vulnerable Groups

In view of the effects of illness, medication including immunosuppressants, pregnancy, and age, on susceptibility to foodborne infections, food safety for vulnerable people is particularly important. Outbreaks of foodborne disease in vulnerable people in hospitals and other healthcare settings are avoidable (Lund and O'Brien, 2009) and can be prevented in several ways.

Food safety management systems

Suppliers of food, including water and beverages, to hospitals, nursing homes, elderly-care homes, schools, and day-care centers for children aged nine or less, and to vulnerable people in the community should have in place a food safety management system based on Hazard Analysis Critical Control Point principles (Lund and O'Brien, 2009). The U.S. Food Code (FDA, 2009) contains special requirements for food establishments serving highly susceptible populations.

A low microbial diet

Low microbial diets avoid foods that are more likely to contain pathogenic microorganisms, including certain uncooked foods with a high microbial load, and substitute safer alternative foods. Such diets are recommended by some hospitals for high-risk patients (Memorial Sloan-Kettering Cancer Center, 2011; Roswell Park Cancer Institute, 2011).

A low microbial diet is recommended for HST patients before engraftment (CDC, 2000; Tomblyn *et al.*, 2009). Autologous HST recipients are advised to remain on this diet for 3 months, whereas allogeneic recipients should remain on this diet until all immunosuppressive drugs are discontinued and the patient is able to receive live virus vaccines. These recommendations can be extrapolated to SOT patients (Avery *et al.*, 2009). After SOT opportunistic infection remains a risk throughout a patient's life, particularly if graft-versus-host disease develops, requiring increased dosage of immunosuppressant drugs, so life-long attention to safe food handling is recommended (Chen *et al.*, 2010).

According to the The American Cancer Society (2010) an absolute neutrophil count (ANC) of $<1000/\mu\text{L}$ means that the immune system is weak, an ANC $<500/\mu\text{L}$ for a few days results in a high risk of infection, and an ANC of $100/\mu\text{L}$ or less for more than a week means that the risk of infection is extremely high. "A low microbial diet (neutropenic diet) may be suggested if a patient's absolute neutrophil count is low" (American Cancer Society, 2010).

It has been stated that evidence of the effectiveness of low microbial diets is lacking, partly because in studies evaluating low microbial diets other interventions have also been used (Moody *et al.*, 2002). But since immunosuppressed people are susceptible to infection from many sources, it is difficult to envisage an ethical study to prevent foodborne infection that would not include other interventions alongside a low microbial diet.

In a survey of mainly European blood and marrow transplant centers, the nature and use of low microbial diets was highly variable (Mank *et al.*, 2008). It is clear, however, that certain ready-to-eat foods carry a risk of infection with foodborne pathogens (FDA/USDA, 2003; WHO/FAO, 2004; Little *et al.*, 2007, 2009; Lynch *et al.*, 2009; Pennington, 2010). In the light of this knowledge, it makes little sense to subject severely ill patients, who are receiving expensive and complex treatments, to foods that may contain pathogenic microbes, particularly when equally nutritious and safer foods are available.

Advice to avoid high-risk foods

The FSIS/USDA (2010) has published the following brochures or fact sheets, which give advice for vulnerable people:

- Food Safety for Older Adults
- Food Safety for People with Cancer
- Food Safety for People with Diabetes
- Food Safety for People with HIV/AIDS
- Food Safety for Transplant Recipients
- Protect Your Baby and Yourself from Listeriosis

Each of the food safety brochures contains guidelines on selecting lower-risk foods (Table 5) and advice on purchasing, storing, and cooking foods. Nevertheless, it seems that the advice might not always reach the right people. For example, Kirkham and Berkowitz (2010) reported that in the United States and Canada few pregnant women received adequate advice about food safety from their healthcare providers although their risks of *L. monocytogenes* and *T. gondii* infection are well known. Chen *et al.* (2010) found that transplant patients preferred to receive food safety information either verbally or in written form from the hospital, clinic, or physician's office.

Other workers have recommended that patients being treated with TNF- α inhibitors should be advised about specific high-risk foods to avoid (Slifman *et al.*, 2003; Dixon *et al.*, 2006; Makkuni *et al.*, 2006; Viçet *et al.*, 2006; Raychaudhuri *et al.*, 2009; Kelesidis *et al.*, 2010).

Safe water and ice

Hospital tap water used for drinking and ice-making can be a source of infectious organisms, including *Campylobacter*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* (Rautelin *et al.*, 1990; Anaissie *et al.*, 2002). U.K. guidelines state that persons whose T-cell function is compromised or who have specific T-cell deficiencies should boil and cool their drinking water, from whatever source, to reduce the risk of *Cryptosporidium* infection and that ice cubes should be produced from boiled and cooled water (CMO, 1999). Tomblyn *et al.* (2009) advised patients recovering from HST to boil tap water for at least 1 min. to avoid the risk of *Cryptosporidium* infection. Hall *et al.* (2004) concluded that end-line water filtration was the best way to produce drinking water for immunocompromised patients, provided that "there are robust protocols to ensure that filter cartridges are changed at appropriate times."

Bottled natural water should be free from parasites and pathogenic organisms, but noncarbonated, bottled water may contain high numbers of bacteria. It has been implicated in nosocomial infection (Eckmanns *et al.*, 2008) and should not be given to severely neutropenic patients; water dispensers should not be used by these patients (Hunter, 2008). Ice

TABLE 5. COMMON FOODS: SELECT THE LOWER-RISK OPTIONS

Type of food	Higher risk	Lower risk
Meat and poultry	Raw or undercooked meat or poultry	Meat or poultry cooked to a safe internal temperature
<i>Tip: use a food thermometer to check the internal temperature</i>		
Seafood	Any raw or undercooked fish Refrigerated, smoked fish Precooked seafood such as shrimp or crab	Smoked fish and precooked seafood heated to 165°F (74°C) Canned fish and seafood Seafood cooked to 145°F (63°C)
Milk	Unpasteurized milk	Pasteurized milk
Eggs	Foods that contain raw/undercooked eggs, such as Caesar salad dressings Homemade raw cookie dough Homemade eggnog	<i>At home:</i> Use pasteurized eggs/egg products when preparing recipes that call for raw or undercooked eggs <i>When eating out</i> Ask if pasteurized eggs were used
<i>Tip: Most premade foods from grocery stores, such as Caesar dressing, premade cookie dough, or packaged eggnog, are made with pasteurized eggs</i>		
Sprouts	Raw sprouts (alfalfa, bean or any other sprouts)	Cooked sprouts
Vegetables	Unwashed fresh vegetables, including lettuce/salads	Washed fresh vegetables, including salads
Cheese	Soft cheeses made from unpasteurized milk, such as Feta Brie Camembert Blue-veined cheese Queso fresco	Hard cheeses Processed cheeses Cream cheese Mozzarella Soft cheeses that are clearly labeled "made from pasteurized milk"
Hot dogs and deli meats	Hot dogs and luncheon meats that have not been reheated	Hot dogs, luncheon meats, and deli meats reheated to steaming hot or 165°F (74°C)
<i>Tip: Your need to reheat hot dogs, deli meats, and luncheon meats before eating them because the bacterium Listeria monocytogenes grows at refrigerated temperatures.</i>		
Pâtés	Unpasteurized, refrigerated pâtés or meat spreads	Canned pâtés or meat spreads

Modified from food safety for older adults; people with cancer; people with diabetes; people with HIV/AIDS; transplant recipients [FSIS/USDA (2010)].

prepared in ice-making machines may also be a source of infection, and appropriate maintenance is essential (Hunter, 2008)

Safe infant formula

Cordier (2008) has described the safe, commercial production of infant formula, including measures to prevent the presence of *C. sakazakii* and *Salmonella* in the finished products. However, powdered infant formula is not sterile, and, if present, *C. sakazakii* and *Salmonella* can survive for long periods in the dry powder. Several organizations have issued guidelines to ensure product safety up to consumption. For high-risk infants (preterm, low birth weight, immunocompromised) the safest option is to use ready-to-feed liquid formula, which is sterile. When reconstituting and storing powdered infant formula, special precautions and good hygiene are important. In particular, bottles should first be treated in boiling water, infant formula should be reconstituted in boiling water cooled to not less than 70°C, and reconstituted formula should be stored below 5°C in a refrigerator (EFSA, 2004; FSA/DH, 2005; WHO/FAO, 2007).

Antimicrobial prophylaxis

Antimicrobial prophylaxis is recommended during treatment of many vulnerable groups. Currently, TMP-SMX is used in many transplant centers for varying durations (3 months to as long as a lifetime) primarily to prevent *Pneumocystis pneumonia*, and this combination is also effective against *L. monocytogenes* and *T. gondii* (Marty and Rubin, 2006; Fishman 2007; del Pozo, 2008; Muñoz *et al.*, 2010). The great majority of *L. monocytogenes* isolates from clinical and food sources were susceptible to TMP-SMX, but a very few isolates were resistant (Safdar and Armstrong, 2003; Conter *et al.*, 2009; Morvan *et al.*, 2010). Alternative prophylactic agents against *Pneumocystis* may have less activity against *L. monocytogenes* (Baden *et al.*, 2001).

Prophylaxis with TMP-SMX also appears to reduce the incidence of *Salmonella* infections after transplant, but resistance has occurred in some *Salmonella* species (Baden *et al.*, 2001).

Listeria and *Pneumocystis* infections are more frequent in chronic lymphocytic leukemia patients treated concurrently with fludarabine and corticosteroids, and TMP-SMX prophylaxis should be considered for these patients (Wadhwa and Morrison, 2006).

Patients with lymphoid cancers treated with the biological agent alemtuzumab, often following other immunosuppressants, may show increased susceptibility to infections, including those by *T. gondii* and *L. monocytogenes* (Martin *et al.*, 2006). Prophylaxis with TMP-SMX and other agents was recommended routinely.

A range of antimicrobials is used in treatment of cancers, but increased rates of bacterial resistance have occurred. It has been suggested that antimicrobial prophylaxis should be limited to high-risk patients with severe neutropenia expected to last >10–14 days (Rolston, 2009).

Although adding prophylactic ampicillin or TMP-SMX to standard antibacterial regimens for patients receiving TNF- α inhibitors has been suggested (Crum *et al.*, 2005), in practice TNF- α inhibitors are often used in conjunction with MTX, which increases the risk of hematological toxicity when given with trimethoprim or cotrimoxazole (British National

Formulary, 2010). Similarly, penicillins increase the risk of toxicity when given with MTX, so using these antibacterials in patients on MTX could create problems.

The development of resistance in microorganisms, and possible changes in practice regarding the use of antimicrobials emphasize that reliance on treatment with antimicrobials is not a substitute for avoiding high-risk foods to protect vulnerable groups from foodborne illness.

Conclusion

Ensuring the microbiological safety of food for vulnerable groups and providing advice about high-risk foods and food safety are essential to minimize foodborne infections. A significant proportion of the population is more susceptible to foodborne disease, including people who are immunocompromised as a result of disease or of medication, as well as pregnant women, infants, and the elderly. In addition, more sophisticated treatments to control cancer and chronic disease are liable to increase the size of this vulnerable population. There is an urgent need for agreement on the nature and use of low microbial diets in centers treating immunosuppressed patients and for more generally available guidance on the microbiological safety of food and beverages, of the type issued by the FSIS/USDA (2010), for vulnerable people in the community.

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