The Growing Threat of Foodborne Bacterial Enteropathogens of Animal Origin

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Campylobacter and Salmonella species and Shiga toxin–producing Escherichia coli (STEC; the majority of which are type O157:H7) efficiently enter the human food chain from infected or colonized animals. Poultry contamination with Campylobacter and/or Salmonella species and produce contamination with STEC have become major public health challenges. The global food supply, which allows us to purchase desired items throughout the year, a growing interest in consuming fresh vegetables and fruits, and an increasing number of persons who consume foods at restaurants all assure that the health threats associated with these pathogens will continue. Antibiotic use by humans and food animals selects for the development of resistance among Campylobacter and Salmonella strains, promoting invasive forms of infection and complicating therapy of illness. A comprehensive public health approach is needed that focuses on disease surveillance and infection control in the food industry continuum, from harvesting and processing, to distribution, to later preparation in public eating establishments and in homes. Good Agricultural Practices, including the Hazard Analysis and Critical Control Point Program and validation of critical infection-control points at all stages of the food industry cycle, coupled with other food safety interventions, including irradiation for certain higher-risk foods, should help us improve the quality of food with regard to microbials and reduce human disease.

Each year, an estimated 76 million cases of foodborne illness occur, resulting in 325,000 hospitalizations and 5000 deaths [1]. The annual cost associated with infection due to the 4 most common bacterial enteropathogens acquired from contaminated food is ~$7 billion [2]. The collateral damage adds importantly to the cost, with lost productivity and litigation secondary to resultant illnesses. Three of the 4 common enteropathogens (Campylobacter and nontyphoid Salmonella species and Shiga toxin–producing Escherichia coli [STEC]) have an animal reservoir, can be associated with fatal complications, and are presently threatening our food supply.

The following topics are covered in this review: (1) the changing pattern of food consumption; (2) surveillance of foodborne infectious diseases and disease-control methods; (3) emerging public health threats associated with Campylobacter and Salmonella species and STEC, including the emergence of antibiotic-resistant strains of Campylobacter and Salmonella species; and (4) the future and improved safety of the food supply.

CHANGING PATTERN OF FOOD CONSUMPTION

The general public became increasingly interested in consuming fresh fruits and vegetables after the release of health claims regarding the practice. Healthy People 2010 is a US government program aimed at increasing the amount of fruits and vegetables in the diet, with the objective of increasing the percentage of persons aged ≥2 years who eat at least 2 daily servings of fruit and at least 3 daily servings of vegetables to 75% and 50%, respectively [3]. The last survey obtained (in 2005) by the Behavioral Risk Factor Surveillance System found rates of 33% and 27%, respectively [3]. During the 1950s, grocery stores in the United States stocked an average of 300 food items, whereas this number grew >80-fold in the 1990s, to 25,000–50,000 different food items [4]. Increased availability of fresh foods increases the risk of human illness associated with foodborne pathogens [5]. More and more people are eating at commercial food service establishments [6]. The risk of foodborne illness is greater when food is eaten in public restaurants rather than in homes [7, 8].
SURVEILLANCE OF FOODBORNE INFECTIOUS DISEASES AND CURRENT DISEASE-CONTROL METHODS

In 1996, the Food Safety and Inspection Service of the US Department of Agriculture adapted the Pathogen Reduction, Hazard Analysis and Critical Control Point Program (HACCP) to the food industry. HACCP is a 7-point, science-based infection-control strategy aimed at disease prevention involving identification of controllable hazards, monitoring, verification, and record keeping [9]. That year, the Emerging Infections Program of the Centers for Disease Control and Prevention (CDC), the US Department of Agriculture (via the Food Safety and Inspection Service), and the US Food and Drug Administration (FDA), together with selected state health departments, established the FoodNet program of active national surveillance for 7 bacterial and 2 parasitic agents that are known to be causes of foodborne illness. Also in 1996, the CDC, in collaboration with cooperating state health departments, established PulseNet, the national molecular subtyping network for foodborne disease surveillance; PFGE was adopted as the standard approach to subtyping. Now active in 50 states, the PulseNet network has been replicated in Canada, Europe, Latin America, and the Asia Pacific region to provide an international approach to identify and respond to multinational outbreaks of foodborne disease [10].

EMERGING PUBLIC HEALTH THREATS ASSOCIATED WITH CAMPYLOBACTER AND SALMONELLA SPECIES AND STEC

The estimated burden and clinical outcome of disease due to the 3 zoonoses are provided in table 1. Identified risk factors for pathogen-specific infection are discussed.

Campylobacter infection. Risk factors for human Campylobacter infection, including infection due to ciprofloxacin-resistant strains, include recent foreign travel and consumption of chicken or turkey at a commercial establishment [13] (table 2).

Salmonella infection. The highest age-specific incidence of salmonellosis is seen for infants aged <12 months [27]. Identified risk factors for sporadic infection in infants include not having been breast fed, increased exposure to reptiles, riding a shopping cart next to meat or poultry, and consumption of concentrated liquid infant formula during the 5 days before exposure [28]. Breast-feeding appears to be protective in sporadic infantile salmonellosis [29].

Although the various Salmonella serotypes are found in many foods, making it difficult to pinpoint the source and vehicles of infection, identified risk factors for the more common serotypes are identified and referenced in table 3.

Salmonella enterica serotype Typhimurium, which characteristically demonstrates multidrug resistance, is responsible for 10%–30% of human Salmonella infections in the United States [30]. The major vehicles of transmission of this serotype are beef and dairy products, including eggs [30, 37]. A case-control study using 5 FoodNet surveillance sites found that prior receipt of an antimicrobial agent was an important risk factor for sporadically occurring multidrug-resistant S. Typhimurium infection [31]. In case-control studies, independent risk factors for sporadic S. Typhimurium DT 104 gastroenteritis include prior antibiotic use, residence on a livestock farm, previous international travel [32], consumption of raw eggs or undercooked meat, previous use of antibiotics, use of proton pump inhibitors or H2 antagonists, and playing in a sandbox [33].

For S. enterica Enteritidis, the first or second most common cause of Salmonella infection in the United States, important host risk factors for sporadic infection include egg consumption [38], chicken consumption outside the home [39], and international travel [40].

Between 1998 and 2002, the prevalence of multidrug-resistant S. enterica Newport increased 5-fold, becoming the third or fourth most common Salmonella serotype in the United States [58]. This serotype and S. Typhimurium DT 104 are typically resistant to the same drugs, including ampicillin, chloramphenicol, sulfamethoxazole, streptomycin, and tetracycline, as well as the extended-spectrum cephalosporins (e.g., ceftriaxone) [59], the treatment of choice for systemic pediatric salmonellosis. Risk factors for acquisition of multidrug-resistant S. Newport infection include receipt of an antibiotic to which

Table 1. Estimates of annual disease burden for selected foodborne bacterial enteropathogens of animal origin.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of cases per year</th>
<th>Complications of illness</th>
<th>Estimated no. of hospitalizations per year</th>
<th>Estimated no. of deaths per year</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter species</td>
<td>1.4–2.5 million</td>
<td>Reactive arthritis, Guillain-Barré syndrome</td>
<td>13,000</td>
<td>100</td>
<td>[1]</td>
</tr>
<tr>
<td>Nontyphoid Salmonella species</td>
<td>1.4 million</td>
<td>Sepsis, meningitis, reactive arthritis, urinary tract infection</td>
<td>&gt;15,000</td>
<td>400–600</td>
<td>[1, 11]</td>
</tr>
<tr>
<td>STEC</td>
<td>100,000</td>
<td>Hemorrhagic colitis, “ischemic colitis” in elderly persons, HUS</td>
<td>2000</td>
<td>91</td>
<td>[1, 12]</td>
</tr>
</tbody>
</table>

NOTE. HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing Escherichia coli.
Table 2. Risk factors for acquisition of diarrhea due to Campylobacter species and fluoroquinolone-resistant Campylobacter species.

<table>
<thead>
<tr>
<th>Infection, identified risk factors</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection due to any Campylobacter strain</td>
<td></td>
</tr>
<tr>
<td>Consumption of undercooked poultry</td>
<td>[14]</td>
</tr>
<tr>
<td>Consumption of chicken prepared by a commercial food establishment</td>
<td>[15, 16]</td>
</tr>
<tr>
<td>Consumption of nonpoultry meat at a restaurant</td>
<td>[16]</td>
</tr>
<tr>
<td>Consumption of unpasteurized milk</td>
<td>[17]</td>
</tr>
<tr>
<td>Consumption of improperly treated surface water</td>
<td>[18]</td>
</tr>
<tr>
<td>Receipt of antibiotics before exposure</td>
<td>[15]</td>
</tr>
<tr>
<td>Contact with home pets</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Exposure to farm animals</td>
<td>[21]</td>
</tr>
<tr>
<td>Recent international travel</td>
<td>[16, 19]</td>
</tr>
<tr>
<td>Infection due to fluoroquinolone-resistant Campylobacter strains</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use in animals</td>
<td>[22, 23]</td>
</tr>
<tr>
<td>Recent foreign travel</td>
<td>[13, 22, 24, 25]</td>
</tr>
<tr>
<td>Receipt of a fluoroquinolone or other antibiotic before exposure</td>
<td>[22, 26]</td>
</tr>
<tr>
<td>Consumption of chicken or turkey at a commercial establishment</td>
<td>[13]</td>
</tr>
</tbody>
</table>

the strain is resistant during the month before illness and consumption of uncooked ground beef, runny scrambled eggs, or omelets prepared in the home during the 5 days before the onset of illness [41]. Bovine sources appear to be particularly important for acquisition of multidrug-resistant S. Newport infection [42].

Outbreaks of gastroenteritis due to S. enterica Heidelberg, the third or fourth most commonly identified Salmonella serotype in the United States, are characteristically related to consumption of poultry or eggs [43, 44]. In one study of sporadic illness, egg consumption outside the home was found to be particularly important [45].

**ANTIBACTERIAL RESISTANCE OF CAMPYLOBACTER AND SALMONELLA SPECIES**

Antibiotic use in agriculture exceeds that in human populations [60–62] and is credited for producing resistance among enteric bacterial pathogens, causing illnesses in humans that are difficult to treat [22, 62–64], including campylobacteriosis [23] and salmonellosis [65]. The growth-promoting effects of antibiotics in food animals should be better quantified, with emphasis on nonantimicrobial drugs that have equivalent benefits for the food production industry [66]. Abolishment of the use of antibiotics for growth promotion will lead to reductions in the rate of drug resistance among bacterial enteropathogens [67] while increasing meat costs by only fractions of a cent per pound [60], making it cost-effective, considering both animal production and human health goals [68].

The fluoroquinolones sarafloxacin and enrofloxacin were first licensed for use in animals in 1995 and 1996, respectively; the presence of fluoroquinolone-resistant Campylobacter strains in chickens dramatically increased thereafter [69]. The removal of fluoroquinolones from use in animal populations in the European Union [70] and the United States [71] was a major public health accomplishment. Additional efforts are needed to reduce fluoroquinolone use by humans in our fight to slow the emergence of antibacterial resistance among Salmonella species [31] and Campylobacter species [22, 26].

A national registry study in Denmark demonstrated that patients with fluoroquinolone-resistant Campylobacter infection had a 6-fold (95% CI, 1.62–23.47-fold) increased risk of invasive disease or death ≤30 days after obtainment of a stool sample for culture, compared with patients whose illness was due to fluoroquinolone-susceptible strains [72]. Compared with drug-susceptible strains, multidrug-resistant Salmonella strains were shown to have greater virulence [73], resulting in more-severe infection and higher rates of hospitalization [74] and mortality [75]. In a FoodNet study, bloodstream Salmonella infection occurred more frequently among patients who were infected with an isolate that was resistant to at least 1 antibacterial drug (adjusted OR, 1.6; 95% CI, 1.2–2.1), compared with patients who were infected with drug-susceptible strains [76].

**STEC, INCLUDING E. COLI O157:H7**

In a study of 5 FoodNet sites, the following risk factors of sporadic STEC infection were identified: eating at a table-service restaurant (matched OR, 1.7; 95% CI, 1.0–2.9), eating a pink (i.e., undercooked) hamburger at home (matched OR, 5.0; 95% CI, 1.7–15) and away from home (matched OR, 5.0; 95% CI, 1.3–20), using immunosuppressive medications (matched OR, 11; 95% CI, 1.6–72), and living on or visiting a farm for persons aged ≥6 years (matched OR, 10; 95% CI,
examined mission through person-to-person contact. In a US study that 
transmission from contaminated animals or water, or trans-
in human populations: foodborne transmission, environmental 
epidemics of STEC infection, including visiting a diary farm
Other studies have revealed a variety of risk factors for or
1.8–53) or <6 years (matched OR, 5.2; 95% CI, 1.3–22) [77].
Other studies have revealed a variety of risk factors for or 
epidemics of STEC infection, including visiting a diary farm
[78] or a petting zoo [79, 80].
There are 3 general modes of transmission of STEC infection 
in human populations: foodborne transmission, environmental 
transmission from contaminated animals or water, or trans-
mission through person-to-person contact. In a US study that 
examined >8000 cases of STEC illness that occurred during 
1982–2002 as part of 350 outbreaks occurring in 49 states, 
foodborne transmission occurred in 183 cases (52%), person-
to-person transmission occurred in 50 cases (14%), waterborne 
transmission occurred in 31 cases (9%), transmission associated 
with animal contact occurred in 11 cases (3%), and transmis-
sion associated with laboratory acquisition occurred in 1 case 
(0.3%); the transmission route was uncertain in 74 cases (21%) [81]. In the reported outbreaks of foodborne infection, 75 out-
breaks (41%) were associated with ground beef, and 38 (21%) 
were associated with contaminated produce [81].

Multiple-state outbreaks of STEC infection occurred in the 
United States in 2005 and in 2006 in association with spinach 
and lettuce purchased at retail outlets or at popular restaurant 
chains in the United States [82, 83]. These outbreaks have put 
great pressure on the growers, processors, distributors, retailers, 
consumers, and the government [84]. Most studies of produce 
contamination with STEC have focused on store-bought let-
tuce. Little is known about the attachment of STEC to growing 
plants in the field, although this appears to be the central prob-
lem in outbreak illness. One study found that fully virulent 
strains of STEC persisted in farm environments for 8 weeks
[85], whereas a second study found that the organisms survived 
on the farm for 8–12 months [86, 87]. In a third study, when 
bovine or poultry manure compost was exposed to irrigation 
water contaminated with a pathogenic strain of E. coli O157: 
H7 under natural growing conditions, STEC persisted in the 
soil for 154–217 days and was detected on lettuce and parsley 
for up to 77–177 days [88]. Recovery of viable STEC from the 
inner tissues of lettuce may occur when plants are grown in 
contaminated manure, providing evidence that STEC bacteria 
is capable of entering the lettuce plant through the root system 
with migration to the edible portion of the plant [89]. In a 
related study, the association of lettuce seedlings with STEC in 
soil was studied using experimentally contaminated irrigation 
water in a hydroponic model and a soil model [90]. The path-
ogen was found to adhere preferentially to the plant root in 
both model systems and to seed coats in the hydroponic system. 
The studies support the idea that preharvest crop contami-
nation with STEC strains can occur via irrigation water through 
the plant roots, which makes control measures designed to 
prevent STEC contamination of produce particularly challenging.

Although most diagnostic laboratories in the United States 
routinely test for Salmonella and Campylobacter species when 
stool samples obtained from patients with diarrhea are sub-
mited for bacteriologic culture, not all routinely test for E. coli 
O157:H7 strains [91]. Studies of non-O157 STEC strains that 
allow determination of their incidence and disease-producing 
capacity are lacking. Increased clinical suspicion and devel-
opment of improved methods of laboratory detection and iso-
lation are needed for this group of organisms [92].

<table>
<thead>
<tr>
<th>Table 3. Risk factors for acquiring nontyphoid Salmonella infection.</th>
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</thead>
<tbody>
<tr>
<td><strong>Salmonella enterica serotype</strong></td>
</tr>
<tr>
<td>S. Typhimurium</td>
</tr>
<tr>
<td>S. Enteritidis</td>
</tr>
<tr>
<td>S. Newport</td>
</tr>
<tr>
<td>S. Heidelberg</td>
</tr>
<tr>
<td>All <em>Salmonella</em> serotypes</td>
</tr>
<tr>
<td>Antibiotic-resistant <em>Salmonella</em> strains</td>
</tr>
</tbody>
</table>

Most strains found in foods are antibiotic resistant.
THE FUTURE AND IMPROVED SAFETY OF THE FOOD SUPPLY

General approaches needed. Validation of the effectiveness of the HACCP system should be undertaken, with identification of the most relevant critical control points through hypothesis-driven research [93, 94]. Methods for controlling contamination of produce are of greatest importance, requiring research to define routes of transmission and critical control points at all phases of the food production-consumption cycle.

Improving food safety in restaurants. Although all eating establishments are instructed by city and health departments to have an HACCP plan, the impact of these programs in preventing foodborne illness remains largely untested. In 1998, in Los Angeles County, a restaurant hygiene-grading program was implemented that used publicly posted grade cards [95]. The grading program was associated with a 13.1% decrease ($P < .01$) in the number of foodborne-disease hospitalizations in the county during the 2 subsequent years of the study.

Improving food safety in homes. With the reduction of cross-contamination and improvement in personal hygiene, an estimated 80,000 enteric infections could be prevented each year in US households, resulting in savings of $138 million [96]. In ranking behaviors in the home that would lead to reduced foodborne illness, use of a thermometer for cooking and hand washing in the kitchen were ranked as the 2 most important behavior modifications [97]. In a study of home food-handling practices, a significant association was found between inconsistent hand washing and food preparation and an increased risk of sporadic salmonellosis in adults (adjusted OR, 8.3; 95% CI, 1.1–61.8) [98]. An economic model found benefit of a disinfection program for high-risk food preparation, particularly when the household contained elderly or immunocompromised persons [96]. In-home foodborne transmission of enteric pathogens is most important when persons at the extremes of age or others with underlying medical conditions and compromised immune systems live in the household [99]. Such persons should not eat certain foods, including raw seed sprouts [100]. Persons who are receiving long-term treatment with H2 antagonists and proton pump inhibitors are at increased risk for foodborne illness [33]. The CDC has recommended that all consumers avoid consumption of unpasteurized milk and milk products and certain raw or undercooked foods. In food irradiation, the energy from the rays is transferred to water and other microbial molecules, creating transient, reactive chemicals that cause defective microbial DNA, making organisms unable to propagate. Microbes differ in their susceptibility to irradiation and the rate at which they can repair damaged DNA. The larger the pathogen (and the more DNA), the more susceptible they are to the lethal effects of irradiation. The methodologies are safe, and the World Health Organization has endorsed food irradiation, as have the CDC, the US Department of Agriculture, and the FDA.

There are ~60 commercial irradiation facilities available in the United States. In 1997, the FDA approved the use of ionizing radiation to inactivate pathogenic bacteria in red meat. The principal arguments against pursuing food irradiation are 2-fold. First, the technology has not been adequately studied for harmful effects caused when altered chemical bonds and potentially toxic ions or free radicals react with constituents in food to form “radiolytic products” [103]. Second, the specific foods for which the approach should be used and the specific methodology for decontamination have not been fully developed. A major issue in moving this concept forward is consumer acceptance of irradiated foods in the absence of public health laws and requirements [104]. With efforts to educate the public about irradiation of food at the grocery store level, consumer acceptability is likely to improve [105]. This year, the FDA proposed letting companies use the term “pasteurized” to describe irradiated foods [106], which could help with public acceptance. Irradiation will be useful for certain foods, such as poultry.

CONCLUSIONS

Although the pathogen load of food animals has improved in response to good hygiene and sanitation practices on farms and during transportation, there remain obstacles to disease prevention. Expanded surveillance of pathogen-specific foodborne disease will allow more rapid implementation of control measures. Methods of reduction of pathogen load present in animals when slaughtered and in produce at time of harvest are needed.

There remains a disconnect between government monitoring and disease-control measures and the complex chain of food production and preparation, from farms where butchering or harvesting take place to retail stores, restaurants, and commercial caterers to homes. Focusing on major local and interstate outbreaks has helped to implement important control
measures, yet we are missing many crucial outbreaks [107], underscoring the need for enhanced capacity for surveillance of foodborne disease. The capacity of state health departments to respond to foodborne disease outbreaks will require addressing shortages in epidemiology and laboratory support for outbreak investigation [108]. Although efforts are underway to deal with this issue, there remains a limited worldwide public health infrastructure to adequately detect outbreaks of foodborne disease [109], limiting the speed and completeness of disease-control measures [110].

Food is being increasingly imported from developing countries [111] where production and surveillance standards are lower than are those for growers in the United States. Although good agricultural practices are essential for control of foodborne disease, we need sensitive, field-tested molecular methods to detect specific pathogens in foods during production and distribution [112]. This is difficult, considering sampling problems and the many pathogens that can potentially cause foodborne disease. Newer molecular methods, which more actively fingerprint bacterial enteropathogens, may provide a more accurate approach for molecular typing in outbreak investigations [113].

We need to move faster with regard to methods of pathogen reduction in slaughtered animals and harvested produce. Irradiation methods should be used for certain higher-risk foods, such as poultry. Decontamination of produce remains a challenge and studies are needed to determine the optimal method to reduce pathogen loads at harvest, including use of chemicals, such as peracetic acid [114], ozone [115], and irradiation [116].

Acknowledgments

Potential conflicts of interest. H.L.D.: no conflicts.

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