Zoonosis Update

Animal sources of salmonellosis in humans

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Nontyphoidal salmonellosis is one of the leading causes of acute bacterial gastroenteritis in the United States, responsible for an estimated 1.4 million cases of illness annually.[1] Many animals, both domestic and wild, are colonized by *Salmonella* spp, usually harboring the bacteria in their gastrointestinal tracts with no apparent signs of illness. Hence, salmonellae are often present in feces excreted by healthy animals and frequently contaminate raw foods of animal origin through fecal contact during production and slaughter.

Although the genus *Salmonella* consists of more than 2,400 serovars, most human cases of salmonellosis in the United States are caused by 4 serovars. For example, in 1995 the US **Centers for Disease Control and Prevention (CDC)** reported that approximately 60% of human cases were caused by *Salmonella enterica* ser Enteritidis (24.7%), *S* ser Typhimurium (23.5%), *S* ser Newport (6.2%), and *S* ser Heidelberg (5.1%).[2] These same 4 serovars represented 46.4% of the isolates from nonhuman sources that year.

Two major changes occurred in the United States during the past 2 decades in the epidemiologic characteristics of nontyphoidal salmonellosis. These were the evolution of 2 pandemic serovars, *S* ser Enteritidis and *S* ser Typhimurium DT104, that have caused marked increases in the percentage of foodborne human *Salmonella* infections. *Salmonella* ser Enteritidis infections are largely associated with fresh shell eggs and egg products, in which the bacteria contaminate the interior contents of the egg through transovarian transmission. *Salmonella* ser Enteritidis infects the ova or oviduct of the hen's reproductive tract, which leads to contamination of the vitelline membrane, albumen, and possibly the yolk. Internal contamination of the egg's content renders egg-sanitizing practices, which focus on reducing pathogen contamination on the eggshell surface, ineffective.

Salmonella ser Typhimurium definitive phage type DT104 emerged in the early 1990s as the dominant type of *Salmonella* spp. Most isolates possess chromosomally encoded resistance to 5 antimicrobials, specifically ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (R-type ACSSuT). There is evidence that some penta-resistant DT104 strains are also acquiring resistance to quinolones and trimethoprim.[3] Evidence in Europe suggests that the emergence of DT104 in cattle was the precursor to its spread to other animals used for food production.[4] Although DT104 is presently the dominant penta-resistant clone of *S* ser Typhimurium, many other phage types (DT29, DT204, DT193, and DT204C) of this serovar have also been associated with multidrug resistance.[5] Understanding the factors that influence the emergence of these dominant serovars of *Salmonella* spp and the factors contributing to the spread and persistence of *Salmonella* spp in animal populations is useful for the development of effective intervention strategies to reduce human exposure to salmonellae.

Public Health Concerns

Salmonella spp are one of the major bacterial causes of foodborne gastroenteritis. The CDC report approximately 40,000 confirmed cases of salmonellosis annually.[1] Poultry, meat products, and eggs are most commonly identified as food sources responsible for outbreaks of salmonellosis; however, many other foodstuffs such as ice cream, vegetables and fruits, breakfast cereal, milk, juices, herbs, and spices have also been vehicles of large outbreaks. Primary vehicles can vary greatly by state. For instance, the State of Georgia Department of Human Resources reported recently that barbecue was the most common source of outbreaks for 2001, whereas the California Department of Health Services reported that alfalfa sprouts were among the most commonly implicated vehicles of salmonellosis outbreaks in California from 1996 through 1998.[6] The CDC in 1996 implemented the FoodNet surveillance network, which is an active surveillance system designed to better estimate the frequency of foodborne diseases. In 1997, FoodNet data from 7 sites in the United States, including Connecticut, Georgia, Minnesota, Oregon, California, Maryland, and New

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Supported by the American Meat Institute Foundation, Arlington, Va; International Food Protection, Bayport, NY (Project No. 2, 3, and 4); Kraft Foods, Chicago, Ill; USDA, Washington, DC (CSREES 202-34352-11932; GEOV-X145; CSREES 00-52102-9634); and the US Poultry & Egg Association, Tucker, Ga (Project No. 279 and 555).

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York, revealed there were an estimated 1,400,000 *Salmonella* infections leading to 113,000 physician office visits, 8,500 hospitalizations, and 300 deaths (0.02% of total cases).[7] During 1997 there were 37,200 culture-confirmed cases of salmonellosis with 92% of the positive cultures resulting from stool samples and 7% from blood. FoodNet data for 1998 and 1999 revealed that *Salmonella* infections were responsible for approximately one-third of the reported deaths attributable to all foodborne disease. Mortality rates are highest in outbreaks that affect high numbers of children or the elderly; the incidence of invasive disease is approximately 10%, but is higher in the elderly (18%), and men are slightly more likely (59%) to have invasive disease than women (41%). In 1998, the overall incidence of *Salmonella* infections in the United States population was 17.4 cases/100,000 persons. Forty percent of *Salmonella* infections occur in the summer months (June through August) and are largely food-associated. Children under the age of 1 year are most susceptible to infection with > 175 cases/100,000 persons; infections in ages 1 through 9 occur at an incidence of 50/100,000. After the age of 9, the incidence decreases to approximately 25/100,000 and remains constant for the other age groups.

Contact with animals and animal products is also a risk factor for *Salmonella* infections in humans. Contact with sick livestock is not an uncommon method of exposure for farm workers. A dairy cattle-associated outbreak caused by *S* ser Typhimurium DT104 was reported as the cover story of *US News and World Report* in 1997. This strain infected several members of a family that resulted in 1 person hospitalized with invasive disease. Reptiles also have long been recognized as sources of *Salmonella* spp for humans. The FDA banned the sale of pet turtles in 1975 because of the associated risk of infections in children. During the 1990s, the CDC reported several cases of salmonellosis in children attributable to contact with pet iguanas and snakes, and an outbreak occurred in 1996 in persons who attended a lizard exhibit at the Denver zoo.[8,9] Since that time several cases have been reported that were attributable to contact with sick kittens, Easter chicks and ducks, and dogs.[10,11] Although these sources are not usually responsible for large outbreaks, they may be responsible for sporadic cases that occur in families that have contact with the animals or contaminated items. Recently, the CDC reported several outbreaks of multidrug-resistant *S* ser Typhimurium infection associated with veterinary facilities.[10] Staff members, visitors to an animal shelter, and pet owners were affected with diarrhea, and several persons sought medical care. In each facility, *S* ser Typhimurium was isolated from sick cats and humans; molecular subtyping confirmed that the isolates were indistinguishable. In 1999, the FDA issued a public health advisory regarding *Salmonella* contamination of dog chews made from pig ears, rawhide, and cow hooves.[12] Although no human cases were identified in the United States, Canadian epidemiologists traced approximately 30 cases to the contaminated dog chews.

Current Issues Associated with Animals

The intestinal carriage of *Salmonella* by dogs and cats is more common than the prevalence of clinical disease, with numerous serovars being isolated from each animal species. Prevalence of isolation of *Salmonella* spp from feces of healthy dogs is reported to be between 1 and 36%, and from healthy cats between 1 and 18%. The actual prevalence of infection is probably higher than estimates that are based on results of fecal swab specimen culture and routine isolation procedures. Within a given serovar, different strains of *Salmonella* spp vary in their virulence. Virulence is partially determined by the ability of *Salmonella* spp to invade nonphagocytic host cells. The location and persistence of this bacterium in the intestinal epithelium, as well as the lymph nodes, accounts for protracted shedding, which occurs for 3 to 6 weeks in most cases. Fecal shedding is continuous for the first week but then becomes intermittent. Phagocytic cells in the intestinal lymph nodes, liver, or spleen may harbor organisms persistently, even in the absence of fecal shedding. Reactivation of shedding or clinical illness may occur after stress, immunosuppression, concurrent systemic viral infections, and crowding. Clinical signs of salmonellosis vary according to the number of infecting organisms, the immune status of the host, concomitant diseases, or other complicating factors. Salmonellosis can be manifested as bacteremia, with or without endotoxemia; organ localized abscesses; pyothorax; meningitis; osteomyelitis; cellulitis; abortions; stillbirths and birth of weak puppies or kittens resulting from in utero infection; and a persistent, asymptomatic carrier state. Few animals infected with *Salmonella* organisms die during the acute phase of the infection. Dogs and cats that have normal immune systems or that are infected with only a few organisms will have transitory or no clinical illness. Cats may have a chronic febrile illness characterized by anorexia and lethargy, but without diarrhea. Animals that have acute diarrhea recover within 3 to 4 weeks. Although not common, diarrhea of longer duration is possible. Animals that have recovered from infection normally continue to shed salmonellae for an additional 3 to 6 weeks; in some instances fecal shedding can be as long as 12 weeks. Sources of *Salmonella* spp for cats and dogs are numerous. The environment, contaminated foodstuffs, fomites, and animal handlers can be sources of *Salmonella spp*. Seasonal bird migrations in the United States have been associated with *S* ser Typhimurium-associated acute febrile illness in cats that usually lasts for 2 to 7 days. Affected cats live primarily outdoors and linger around bird feeders or frequently feed on birds. We have identified a case of *S* ser Typhimurium DT104 infection in 2 psittacine companion birds, indicating the potential risk of disease for humans and other pets in the household.[13]

Salmonella enterica infection in cattle can be serious and continues to be an important disease in areas where infection is caused by serovars such as Dublin. However, where disease is caused by *S* ser Typhimurium, the disease is sporadic and, although it may be fatal to individual animals, it is not a serious threat to the herd. Because salmonellae are facultative intracellular organisms that survive in the

phagolysosome of macrophages, they can evade the bactericidal effects of antibody and complement. Persistence of infection is an important epidemiologic feature of salmonellosis. When a large animal is infected with some serovars, such as Dublin, it may become clinically ill or an active carrier, passing organisms constantly or intermittently in the feces. Persistent excretors can shed organisms at a rate of 10^5 salmonellae/g of feces. A latent carrier condition can also occur with infection persisting in lymph nodes or tonsils but with no salmonellae shed in the feces. A passive carrier state is possible whereby the animal is constantly acquiring salmonellae from pasture or the pen floor, without invasion, so that when the pathogen is removed from the environment the infection disappears. Salmonellae probably multiply within the animals' gastrointestinal tract without them becoming permanent carriers. The importance of latent carriers is that they can become active carriers or even clinical cases under stress, especially at calving time. Adults may become carriers of *S* ser Typhimurium, but only for a short time, and calves rarely become carriers. The carrier state in sheep and cattle may persist for as long as 10 weeks. Experimental infection in pigs at 7 to 8 weeks of age with a single dose of *S* ser Typhimurium revealed that *Salmonella* infection can persist until market age. Long-term persistence is limited generally to the palatine tonsils, intestinal tract caudal to the midjejunum, and the lymph nodes. A major survey of the 12 leading cattle feeding states in the United States for *Salmonella* spp in beef in feed lots revealed that 6.3% of 10,417 fecal samples were positive for the pathogen, with the highest incidence (11.4%) occurring during the months of July through September.[14]

Clinical salmonellosis in horses occurs most commonly after incurring stress by transport. Animals that have been overfed before shipment and have water withheld for the duration of the journey are predisposed to clinical disease. Most outbreaks of salmonellosis in horses are attributed to a carrier animal within the group. The prevalence of healthy shedders can be as low as 2% or as high as 20%. The carrier state may persist for up to 14 months after infection.

Birds other than poultry and ducks may be infected with *Salmonella* spp. Passerines, raptors, psttacines, pigeons, and gulls fecally excrete salmonellae. The most common serovar is Typhimurium. Captive exotic birds, such as psittacines, can be sources of *S* ser Typhimurium DT104. [13] Gulls that feed in polluted estuaries may excrete serovars Typhi and Paratyphi, which are usually associated with humans.[14]

It is well documented that many reptiles in captivity carry *Salmonella* spp as part of their normal intestinal flora.[15] Although there are no serovars specific to reptiles, Java, Stanley, Marina, Poona, Pomona and subspecies Arizonae are commonly cultured from these animals.[16] Multiple serovars can be isolated from the same animal, but serovars associated with human infection, such as Typhimurium and Enteritidis, are seldom found in reptiles.[16]

Serovars of Recent Concern and Antibiotic Resistance

Prior to the 1970s, *S* ser Typhimurium was the most common *Salmonella* serotype associated with foodborne outbreaks in the United States.[17] More recently, however, *S* ser Enteritidis supplanted *S* ser Typhimurium as the dominant serotype associated with outbreaks of salmonellosis.[17] Outbreaks of *S* ser Enteritidis infection were first reported in the northeastern United States and subsequently spread to other parts of the country. Early investigations of these outbreaks revealed that grade A eggs were the source. **Phage type (PT)** 8 of *S* ser Enteritidis is most commonly associated with outbreaks in the US, whereas PT4 is the dominant phage type in Europe. However, PT4 has now appeared in the United States.

Development of quality assurance programs to identify commercial laying hens contaminated with *S* ser Enteritidis has been effective in diverting contaminated table eggs to pasteurization processing and eradicating *S* ser Enteritidis from positive poultry farms through aggressive depopulation and monitoring programs. This quality assurance program for table eggs may account for the recent decrease in *S* ser Enteritidis-related outbreaks in the United States.[17]

Salmonella ser Typhimurium PT DT104 has become an important food safety concern because of the increased incidence in both human and animal infections in the United States, as well as its resistance to multiple antimicrobials. In fact, *Salmonella* infection with the classic penta-resistance pattern associated with DT104 accounted for 32% of human *S* ser Typhimurium-associated outbreaks in the United States in 1995.[18] The increase in reported cases of salmonellosis caused by DT104 helps to explain the displacement of *S* ser Enteritidis as the dominant serotype associated with foodborne outbreaks in the United States.[17] The first documented cases of DT104 were reported in the United Kingdom, but since those early reports, *S* ser Typhimurium DT104 has appeared in many other countries, including the United States.[18]

Salmonella ser Typhimurium DT104 has caused serious illnesses in many species, including food animals, companion animals, and wildlife. There are several reported cases of transmission of DT104 to humans from infected animals.[10] Although usually asymptomatic, many food animal species may serve as reservoirs or carriers of DT104. Contaminated dairy products and beef have served as vehicles of several outbreaks of *S* ser Typhimurium DT104 infections.

DT104 isolates are typically resistant to 5 antimicrobials, including chloramphenicol. Chloramphenicol resistance in *Salmonella* spp is rather unusual, especially since this antibiotic is no longer prescribed in the United States because of the potential risk of patients developing aplastic anemia. In fact, the FDA banned the use of chloramphenicol in food animals in the 1980s. *Salmonella* ser Typhimurium DT104 is resistant to chloramphenicol and its veterinary analog florfenicol.[19] Resistance is caused by *flo*, a putative drug efflux pump that was first described in the fish pathogen *Photobacterium damselae* and has since been found in other bacterial species. In most *Escherichia coli* iso-

lates, *flo* resides on plasmids,[20] whereas in DT104, *flo* resides on the chromosome next to the tetracycline resistance genes, efflux pump *tetG*. Both genes are further flanked in the chromosome by integrons, which are genetic elements that capture and link multiple drug resistance genes together into a single locus.[19] The integrons in DT104 encode for resistance to streptomycin, sulfonamides, and ampicillin.[19] Arrangement of these drug resistance genes within the bacterial chromosome was once considered unique to DT104, but a similar multidrug resistance locus has been identified in *S* ser Agona.[19] It appears unlikely that emergence of DT104 in the United States was caused by florfenicol usage in veterinary medicine, because its increasing prevalence in the United States predates approval of this veterinary drug.[21] Emergence of DT104 in this country and others may be more reflective of the displacement of endemic *Salmonella* clones within a population with a new, virulent clone.[21]

Many cases of ceftriaxone-resistant *Salmonella* infections have been reported from numerous countries.[22] Most ceftriaxone-resistant *Salmonella* infections are acquired outside the United States; however, the first case of a domestically acquired ceftriaxone-resistant *Salmonella* infection was recently reported in a child.[22] In that study, molecular typing techniques revealed isolates with similar typing profiles from cattle, suggesting zoonotic transmission. In a recent retrospective study,[23] the CDC determined that between 1996 and 1998, 0.1 to 0.5% of *Salmonella* isolates were ceftriaxone-resistant. Sources of the salmonellae were not identified in most patients, but 18% of the affected individuals had visited a farm within 5 days of the onset of their illness suggesting that these infections may have been associated with animal contact. Recently, *S* ser Newport has emerged as the most prevalent ceftriaxone-resistant *Salmonella* isolated from humans and animals. Some authorities regard food animals as the primary source of antibiotic resistance in human pathogens, whereas others regard imprudent use of antimicrobials in humans as the major source of the problem. The antimicrobials of choice for treating bacterial gastroenteritis are generally fluoroquinolone-ciprofloxacin for adults and cephalosporin-ceftriaxone for children. At issue today is whether the veterinary analogs of these drugs are responsible for emergence of antimicrobial resistance in foodborne pathogens like *Salmonella* spp.[21] Does the half-life of the antimicrobial in the gastrointestinal tract and immediate farm environment (litter, manure, etc) factor into the emergence of bacterial resistance? Does use of ceftiofur correlate with the emergence of ceftriaxone-resistant *Salmonella* spp in the species exposed to the antimicrobial? Further work is needed in this area to determine whether there is a connection between veterinary usage of ceftiofur and the emergence of ceftriaxone resistance in *Salmonella* spp.

Pathogenesis

To initiate disease in the gastrointestinal tract, salmonellae must adapt to the hypoxic, acidic, and alkaline environments that they encounter en route from the stomach to the small intestine. The bacteria must then swim through mucin overlying the enterocytes, attach themselves to the intestinal columnar epithelial or specialized M-cells overlying Peyer's patches, and invade the host epithelial cell. The host range for *Salmonella* spp varies from narrow (*S* ser Pullorum: avian species only) to broad-host adapted serovars (*S* ser Typhimurium: avian and mammalian species). Host adaptation exhibited by *Salmonella* serovars is believed to be caused, in part, by the distribution of specific adhesins among *Salmonella* serovars that are involved in the organism's colonization of the gastrointestinal tract.[24]

Salmonella organisms exist as intracellular pathogens in diseased animal hosts. *Salmonella* organisms produce hair-like projections, resembling pili, which upon contact with epithelial cells "inject" bacterial proteins into the host cell's cytoplasm.[25] This event triggers a signal transduction cascade that results in the transient, disassembly, and reorganization of the cytoskeleton and uptake of *Salmonella* organisms by enterocytes or M-cells.[26] Following internalization, salmonellae are confined to endocytic vacuoles, but these infected vacuoles move from the apical to the basal surfaces of the host cell releasing *Salmonella* organisms to the submucosal compartment. *Salmonella* invasion genes are organized into contiguous and functionally related loci in the bacterial chromosome. These genes are evolutionarily conserved among *Salmonella* spp, making them useful targets in polymerase chain reaction-based detection schemes for salmonellae.[27] Although this locus is not essential for the organism to spread systemically, it does appear to be one of several factors that mediate enteritis associated with *Salmonella* infection.[28]

For *Salmonella* organisms to cause systemic infection, the organism must resist being killed by WBC. Salmonellae do not resist phagocytosis but do adapt to the hostile milieu of the phagolysosome. It is the outcome of this interaction between phagocyte and microbe that determines whether the disease develops into a potentially fatal enteric fever.[29]

On-Farm Intervention Strategies

In 1996, the USDA Food Safety and Inspection Service issued the Pathogen Reduction: Hazard Analysis and Critical Control Point Systems regulation. This regulation was instituted to encourage the implementation of effective pathogen reduction systems in meat and poultry processing facilities. *Salmonella* spp performance standards were included as part of the regulation and were based on a *Salmonella* prevalence survey of meat and poultry from an FSIS nationwide in-plant study. These performance standards were expressed in terms of the maximum number of *Salmonella*-positive samples allowed per sample set. The results of 4 years of testing revealed that most meat and poultry processing establishments meet or exceed the established performance standards.[30] Despite the success the processing industry has had in reducing *Salmonella* spp on fresh meat and poultry, some consumer organizations call for measures to reduce the amount of *Salmonella* organisms entering processing plants through live animals. Hence, there is continuing pressure for on-farm intervention strategies to control *Salmonella* spp in food animals.

The poultry industry in the United States is a fully integrated system of animal agriculture. Vertical integration allows each company the advantage of control of their operation's aspects. Consequently, when consumers, retailers, or specific restaurant chains set food safety standards for poultry meat and eggs, the poultry company can readily adopt programs on the farm that can meet these standards. The poultry industry actually involves 3 different industries: commercial table egg layer chickens, broiler chickens, and turkeys. Each of the 3 segments has unique bird husbandry conditions that result in uniquely different food safety issues. For example, the major concern for the table egg layer industry is *S* ser Enteritidis, whereas all *Salmonella* serotypes are issues for broiler chicken and turkey producers.

Management practices for on-farm *Salmonella* risk reduction begin with reviewing the sources of *Salmonella* entering the food animal production unit (**Fig 1**). Prevention of the introduction and reintroduction of *Salmonella* spp becomes a key strategy in *Salmonella* control.[31] The biosecurity strategies used to prevent the introduction of *Salmonella* spp can be the same as those used to prevent the introduction of many of the diseases that impact the health of livestock and poultry.[32] *Salmonella* spp can infect broilers in the hatchery or by exposure to contaminated feed, water, and rodents on the farm. Hatchery control often begins with surveillance of *Salmonella* carriage in the parental flocks, since the hatching eggs may be contaminated by feces during laying. The hatchery manager may also include egg disinfectants and hatching cabinet sanitizers to reduce aerosol contamination of uninfected eggs and chicks. In addition to biosecurity and feed and drinking water management, *Salmonella* control in breeders often includes the use of autogenous vaccines to reduce or eliminate intestinal colonization.

Salmonella infection is endemic in many food animal production units; therefore, it becomes necessary to not only prevent additional introduction and reintroduction, but also to enhance the animals' ability to resist *Salmonella* infection or colonization. Live attenuated and inactivated vaccination of poultry and cattle to increase the immunity has been successful in reducing the level of colonization and amount of reintroduction of *Salmonella* spp into the environment.[33,34] Reducing the amount of Salmonellae in the animals' environment will not only reduce the amount of Salmonellae that can contaminate the food but also reduces the amount of Salmonellae available to reinfect other animals or poultry on the farm. Therefore, control of *Salmonella* spp in food animals on the farm should include biosecurity, rodent control, and feed and drinking water management.

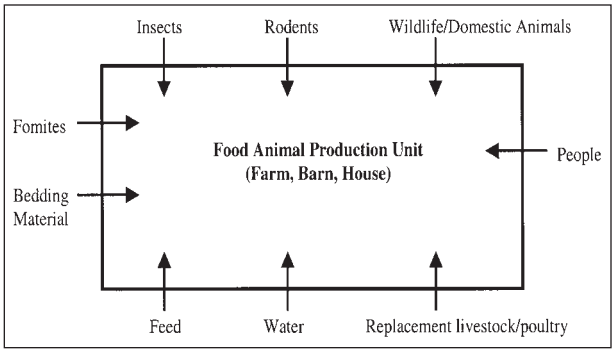

Figure 1—Sources of *Salmonella* organisms in a food animal production unit.

Another method of reducing the number of Salmonellae and other intestinal pathogens that colonize in the intestines of ruminants, swine, and poultry is via **competitive exclusion (CE)**. This method dates back to 1908 with the use of *Lactobacillus* spp cultures to prevent traveler's diarrhea in humans.[35] Competitive exclusion is the process by which normal intestinal bacterial flora from an adult animal is rapidly established in a neonate. This method has been extensively studied in poultry to reduce the amount of *Salmonella* contamination on the farm and at the processing plant.[36] The use of antimicrobial treatment to remove colonized Salmonellae followed by competitive exclusion has been a successful method for control of *S* ser Enteritidis in breeder poultry flocks.[37] The successful application of a combination of methods for controlling *Salmonella* spp in poultry breeders using CE and live *Salmonella* vaccination has been reported.[38] It was determined that CE alone reduced cecal colonization by *S* ser Typhimurium by 3 to 4 $\log_{10}$ and the vaccine alone reduced colonization by 1 to 1.5 $\log_{10}$, whereas the combination of vaccine and CE almost completely prevented a challenge of 9 $\log_{10}$ from colonization.

Public and regulatory pressure on meat processors to provide consumers with an ever "safer" food supply is likely to continue. This will eventually lead back to the farm for control and reduction of *Salmonella* spp. An on-farm intervention strategy to reduce *Salmonella* organisms from entering meat and poultry processing establishments requires identifying and stopping the sources of introduction, then using various practices such as CE, probiotics, antimicrobial therapy, or vaccination either alone or in combination to reduce the amount of farm environmental contamination.

Animals are a primary reservoir for nontyphoidal salmonellae associated with human infections, and contact with animal feces either directly through animal handling or manure or indirectly through fecal contamination of foods are principal vehicles of human infection. Veterinarians can be an important link to reducing the incidence of nontyphoidal salmonellosis in humans by assisting in the development and implementation of control strategies to reduce carriage of salmonellae by food-producing and companion animals.

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