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Significance and Sources of Antimicrobial-Resistant Nontyphoidal *Salmonella* Infections in Humans in the United States: the Need for Prudent Use of Antimicrobial Agents, Including Restricted Use of Fluoroquinolones, in Food Animals

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Abstract

Human *Salmonella* infections are common; most infections are self-limiting but severe disease may occur. Antimicrobial agents, while not essential for the treatment of *Salmonella* gastroenteritis, are essential for the treatment of thousands of patients each year with invasive infections. Fluoroquinolones and third-generation cephalosporins are the drugs-of-choice for invasive *Salmonella* infections in humans; alternative antimicrobial choices are limited by increasing antimicrobial resistance and less desirable pharmacodynamic properties. Little correlation is noted between the antimicrobial resistance patterns of isolates collected from persons with *Salmonella* infections and antimicrobial agents used for the treatment of *Salmonella* infections in humans. Direct evidence is available which demonstrates that antimicrobial resistant *Salmonella* result from the use of antimicrobial agents in food animals and these antimicrobial resistant *Salmonella* are subsequently transmitted to humans, usually through the food supply. Because of the adverse health consequences in humans and animals associated with the increasing prevalence of antimicrobial resistant *Salmonella*, there is an urgent need to emphasize non-antimicrobial strategies, such as improved sanitation and hygiene, to develop guidelines for the prudent usage of antimicrobial agents, and to restrict the use of fluoroquinolones in food animals to minimize the development of antimicrobial resistance and dissemination of antimicrobial resistant pathogens.

Introduction

Much of the discussion about the adverse human health effects associated with the veterinary use of antimicrobial agents has been clouded by confusion surrounding the clinical significance and sources of antimicrobial-resistant nontyphoidal[a] *Salmonella* infections in humans.[1,2] This issue needs to be revisited in the light of the recent discussions concerning the public health implications of veterinary use of fluoroquinolones,[3,4] a class of antimicrobials essential for the treatment of several life-threatening infections in humans. [5,6] Because of these public health concerns, the Food and Drug Administration prohibited the extra-label use of fluoroquinolones in food animals in the United States in August, 1997.[b] Two fluoroquinolones, enrofloxacin and sarafloxacin, are approved, however, for use in poultry in the United States. To address the human health implications of the veterinary use of fluoroquinolones, we reviewed the medical literature and data available at the Centers for Disease Control and Prevention (CDC) about the epidemiology of human *Salmonella* infections. In this report, we discuss the clinical significance of antimicrobial-resistant *Salmonella* infections in humans, the epidemiology of antimicrobial-resistant pathogens including *Salmonella*, the sources of *Salmonella* (including antimicrobial-resistant *Salmonella*) infections in humans, the causes and consequences of development of antimicrobial-resistant *Salmonella,* and suggest necessary actions to protect the public's health.

Clinical significance of antimicrobial-resistant salmonellae

Salmonellosis results in considerable human morbidity in the United States. Although most human *Salmonella* infections result in a mild, self-limiting gastrointestinal illness characterized by diarrhea, fever and abdominal cramps, the infection can spread to the bloodstream, meningeal linings of the brain, or other deep tissue sites, leading to a severe and occasionally fatal illness. Each year, there are an estimated two to four million human *Salmonella* infections in the United States,[7,8] causing an estimated 80,000 to 160,000 persons to seek medical attention. Clinical specimens collected from some of the persons who have sought medical attention result in approximately 40,000 culture-confirmed cases a year reported to CDC.[9,10] Each year in the United States, an estimated 8,000 to 18,000 persons are hospitalized and 500 persons die of *Salmonella* infections.[11]

Antimicrobial agents are not essential for the treatment of most *Salmonella* infections which manifest as uncomplicated gastroenteritis because such infections usually are self-limiting. Treatment may prolong the carrier state, and may result in the emergence of a resistant infection in the treated person.[5,6] Antimicrobial agents are, however, commonly prescribed for persons with *Salmonella* infections who seek medical attention. In surveys conducted by CDC in 1990[12] and 1995, 40% of persons with *Salmonella* infections who sought medical attention were treated with antimicrobial agents. Ciprofloxacin, a fluoroquinolone antimicrobial agent, was the most commonly prescribed antimicrobial agent for *Salmonella* infections. Ciprofloxacin, which became available for oral use in humans in the United States in 1988, was used by approximately 25% of persons who received antimicrobial agents in the 1990 survey and 33% in the 1995 survey, suggesting that >100,000 persons with *Salmonella* infections have been treated with ciprofloxacin in the past 10 years in the United States (between 2-3 million prescriptions of ciprofloxacin are dispensed annually, for a variety of conditions, in the United States).

In contrast to patients with uncomplicated gastroenteritis, effective antimicrobial agents are essential for the treatment of patients with bacteremia, meningitis, or other extra-intestinal *Salmonella* infections.[5,6] In approximately six percent of the culture-confirmed cases reported to CDC, *Salmonella* is isolated from specimens collected from extra-intestinal sites - usually from blood.[9,10] Since approximately 40,000 culture-confirmed cases are reported to CDC each year, effective antimicrobial agents are critical and may be life-saving for at least 2,400 persons a year in the United States. Unfortunately, the selection of antimicrobial agents for the treatment of invasive infections has become increasingly restricted due to increasing antimicrobial resistance among *Salmonella* isolates. In the past, chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were used to treat *Salmonella* infections.[12-14] However, among 1,272 randomly selected *Salmonella* isolates from humans tested at CDC in the National Antimicrobial Resistance Monitoring System in 1996, 21% were resistant to ampicillin, 10% to chloramphenicol, and 4% to trimethoprim-sulfamethoxazole.[15] In contrast, almost all of the *Salmonella* isolates tested at CDC have been susceptible to fluoroquinolones and third-generation cephalosporins.[15-17] For this reason, and because of the favorable pharmacodynamic properties of these antimicrobial agents, fluoroquinolones and third-generation cephalosporins are the drugs-of-choice for the treatment of invasive *Salmonella* infections in adults and children, respectively. Should *Salmonella* develop antimicrobial resistance to these two antimicrobial agents, suitable alternative antimicrobial agents are not currently available and adverse human health consequences, including prolonged hospitalizations and increased frequency of treatment failures, which may result in deaths, are expected.

While reviewing the clinical significance of antimicrobial-resistant *Salmonella* infections, it is useful to evaluate the correlation between the antimicrobial agents used to treat persons with *Salmonella* infections and antimicrobial-resistance among human *Salmonella* isolates. Information provided from surveys conducted by CDC within selected counties in the United States in 1985,[14] 1990 [12] and 1995 indicates that the proportion of persons with a *Salmonella* infection receiving an antimicrobial agent who were treated with ampicillin declined from 60% in 1985 to 5% in 1995, while the proportion of isolates resistant to ampicillin steadily increased. The proportion of persons treated with trimethoprim-sulfamethozone, in contrast, remained constant while trimethoprim-sulfamethozone resistance increased slightly. Most significantly, the proportion of patients with salmonellosis treated with ciprofloxacin or extended-spectrum cephalosporins markedly increased without an emergence of resistance to either of these antimicrobial agents among human *Salmonella* isolates. The continued susceptibility of human *Salmonella* isolates to fluoroquinolones and extended-spectrum cephalosporins was confirmed in over 4,000 isolates in 1995[16,17] and 1,200 isolates in 1996.[15] Taken together, these data suggest there is little correlation between the antimicrobial agents used in persons with *Salmonella* infections and development of antimicrobial resistance among human *Salmonella* isolates. If human antimicrobial use is not associated with the increasing antimicrobial resistance seen among *Salmonella* isolates, what is causing the increasing prevalence of antimicrobial-resistance observed among *Salmonella* isolates? Prior to addressing that question, it is useful to review the epidemiology of antimicrobial-resistant pathogens.

Epidemiology of antimicrobial-resistant pathogens, including *Salmonella*

Antimicrobial agents are used to treat microbial infections in humans, plants and animals; they are given prophylactically to healthy humans, plants and animals to prevent infections, and they are given in low doses to food animals to improve their growth rate and feed conversion. There is a preponderance of evidence that the use of antimicrobial agents, at subtherapuetic or therapeutic concentrations, results in antimicrobial resistance. However, in order for an antimicrobial-resistant pathogen to have a public health consequence, there must be both usage of the antimicrobial agent and dissemination of the resistant pathogen. The role of dissemination can be illustrated by observing the consequences of using fluoroquinolones for the treatment of three different infections: methicillin-resistant *Staphylococcus aureus* (MRSA) in humans, *Salmonella* in humans, and *Salmonella* in food animals. Fluoroquinolones have been widely used in the United States for the treatment of human MRSA and *Salmonella* infections, but since they have not been widely used for the treatment of *Salmonella* infections in food animals in this country, this latter instance will be described using events which have occurred in the United Kingdom (it is reasonable to assume such events would occur in the United States under similar conditions of fluoroquinolone usage).

The emergence of human MRSA infections in hospitals in the United States is a major public health concern.[18] When the first fluoroquinolone (ciprofloxacin) was approved in the United States for human use there was optimism that ciprofloxacin, which was highly effective against MRSA, might lessen the public health impact of MRSA infections. Shortly after the approval of ciprofloxacin, it became widely used for the treatment of human MRSA infections. With the widespread usage, human infections with ciprofloxacin-resistant MRSA rapidly emerged in the United States; by 1991-1992, 85% of MRSA isolates from hospitals in the National Nosocomial Infection Surveillance System were resistant to ciprofloxacin.[19] The rapid emergence of ciprofloxacin-resistance MRSA is clearly related to both the increased use of ciprofloxacin in humans and the efficiency of dissemination, via person-to-person transmission, of ciprofloxacin-resistant MRSA in hospitals.

As indicated earlier, ciprofloxacin has also been widely used for the treatment of *Salmonella* infections in humans. Because antimicrobial-resistance follows antimicrobial usage, *Salmonella* with decreased susceptibility to ciprofloxacin may have developed in persons with salmonellosis who were treated with ciprofloxacin, however, because person-to-person transmission of *Salmonella* is rare, *Salmonella* with decreased susceptibility to ciprofloxacin has not been disseminated in the United States. This is in sharp contrast to the situation in the United Kingdom, where a fluoroquinolone (enrofloxacin) has been widely used in food animals following its approval for veterinary use in 1993. Following the approval of enrofloxacin for veterinary use in the United Kingdom, decreased susceptibility to fluoroquinolones (Minimum Inhibitor Concentration [MIC] $\geq$0.25) rapidly emerged among human *Salmonella* isolates, particularly among isolates of multiple-resistant *S.* serotype Typhimurium DT104 which were resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (R-type ACSSuT). DT014 R-type ACSSuT has emerged as the second most common strain of *Salmonella* isolated from humans. In 1993, none of the DT104 R-type ACSSuT isolates had a decreased susceptibility to fluoroquinolones; by 1996, 14% had a decreased susceptibility.[20] A parallel rapid emergence of decreased susceptibility to fluoroquinolones, as indicated by antimicrobial resistance to nalidixic acid (resistance nalidixic acid, an quinolone, indicates decreased susceptibility to fluoroquinolones) has been observed among animal *S.* Typhimurium DT104 R-type ACSSuT isolates at the Central Veterinary Diagnositic Laboratory in the United Kingdom.

Sources of antimicrobial-resistant *Salmonella* infections

Salmonella live in the intestines of mammals, birds and reptiles. Once shed into the environment in the feces of infected animals, *Salmonella* may survive for long periods in water, soil, and on or within foods. Although *Salmonella* infections occur commonly in humans, person-to-person transmission of *Salmonella* is uncommon in the United States. In less developed countries, in contrast, person-to-person transmission may be the source for a greater proportion of human *Salmonella* infections and nosocomial sources of antimicrobial-resistant *Salmonella* have been identified.[21] Historically, before the development of hospital infection control procedures in the United States, nosocomial outbreak of salmonellosis with person-to-person transmission, particularly in newborn nurseries, were not infrequent.[22]

Most human *Salmonella* infections in the United States occur from the ingestion of contaminated food and many of these foods are of animal origin. Direct fecal-oral transmission following contact with animal feces is another, less common, source of human salmonellosis. At least six lines of evidence can be presented which, taken together, demonstrate that foods of animal origin are the dominant source of human salmonellosis, and suggest that person-to-person transmission is an uncommon source of human salmonellosis in the United States.

1. Carriage rates

Although the prevalence varies, *Salmonella* is frequently isolated from the feces of food animals, companion animals, and wild animals. In longitudinal studies, some animals may excrete *Salmonella* for long periods of time. For example, many birds, including poultry, are infected with *Salmonella* and shed the organism in their feces (an estimated 20% of retail packages of poultry are contaminated with *Salmonella*). Fecal excretion of *Salmonella* by humans, in contrast, is relatively uncommon among apparently healthy individuals and is fairly short-lived among persons with salmonellosis. A review of several surveys of stool specimens from apparently healthy persons found a median carriage rate of *Salmonella* of 0.15%.[23] A review of several outbreak investigations determined the median duration of excretion by persons with salmonellosis to be about four weeks.[24]

2. Infectious dose

Volunteer studies among healthy adults suggest that a large oral infectious dose of *Salmonella* ($\geq 10^6$ organisms) given in water usually is necessary to cause infection in a high proportion of recipients.[25] These observations are supported by the relative low frequency of secondary illness within households in which a primary culture-confirmed case is identified and the rarity of day-care center outbreaks of salmonellosis; such setting commonly result in person-to-person transmission of enteric pathogens with low infectious doses (e.g., *Shigella* and *Escherichia coli* O157). The infrequent occurrence of secondary infections of salmonellosis and day-care center associated outbreaks suggest that person-to-person transmission of *Salmonella* occurs infrequently.

3. Outbreak investigations

Although outbreaks only represent a fraction of the cases of *Salmonella* infections which occur, much insight into the epidemiology of salmonellosis has been provided through investigations of outbreaks. Most outbreak investigations are conducted by state or local health departments who report foodborne disease outbreaks to CDC as part of the Foodborne Disease Outbreak Surveillance System.[26] A small number of investigations are conducted each year by CDC in collaboration with state and local health departments.

Between 1988 and 1992, an average of 110 outbreaks of *Salmonella* were reported each year to CDC.[26] Sixty percent of these outbreaks were caused by *Salmonella* serotype Enteritidis and most of these were attributed to eating undercooked eggs. Many of these egg-associated outbreaks were traced back to their farm of origin and it was demonstrated that infected hens were the source of the outbreak. Among outbreaks caused by *Salmonella* serotypes other than Enteritidis, a variety of food items were implicated, particularly other foods of animal origin. A small number of fresh fruits and vegetables were also implicated. A few of these outbreaks were traced back to their farm of origin. Although some outbreaks involved infected food handlers, rather than being evidence of person-to-person transmission of *Salmonella*, in most cases, the food handlers probably became infected because they also ate the contaminated foods. Taken together, outbreak investigations demonstrate that foods, particularly foods of animal origin, are an important source of *Salmonella* infections in humans.

4. Sporadic case-control studies

Further evidence that foods of animal origin are associated with many human *Salmonella* infections is provided from investigations of persons with sporadic *Salmonella* infections (infections that were not recognized to be associated with an outbreak). Few such investigations have been reported, however, perhaps because investigations of sporadic infections are less likely to implicate a common source because several sources may be involved.

Case-control studies of sporadic cases of *Salmonella* Enteritidis were conducted in New York in 1989,[27] California in 1994,[28] and Utah in 1995.[29] These studies each demonstrated that eating raw or undercooked eggs was the most important risk factor for acquiring infections. Case-control studies of sporadic *Salmonella* cases involving serotypes other than Enteritidis include an investigation in Switzerland in 1996 of infections caused by a variety of serotypes which implicated eggs as the most important sources of infections,[30] California in 1984 of infections again caused by a variety of serotypes which implicated poultry,[31] California in 1985 of *Salmonella* dublin which implicated raw milk,[32] and a study of *Salmonella* typhimurium and Enteritidis infections in Minnesota in 1989 and 1990 which found eggs as the most important source for both infections.[33]

5. Molecular "fingerprinting"

After the identification of the particular *Salmonella* serotype, several procedures (e.g., phage typing, pulsed-field gel electrophoresis, plasmid profiling, ribotyping) may be used to further differentiate *Salmonella* isolates.[34] Such subtyping techniques may be useful in epidemiological investigations to support or refute the postulated source of the outbreak. For example, in the 18 outbreaks of *Salmonella* enteritidis in 1990 and 1991 in which eggs were implicated as the source, trace backs and environmental investigations on the implicated farms led to the detection of the human outbreak strain of *S.* enteritidis, as determined by phage type, from the environment (100%) and from internal organs (88%) of implicated flocks strongly suggesting that the implicated farms were the sources of the outbreaks.[35] Another example is provided from Denmark where phage-typing, and plasmid profiling of *Salmonella* typhimurium isolates from human and animal sources showed some animal strains and human strains to be indistinguishable and concluded that spread of the strains from animals to humans was the most probable explanation.[36]

6. Emergence of usual strains in humans

Monitoring of human *Salmonella* surveillance data, when supported by serotyping and perhaps additional subtyping techniques, can enable the detection of the emergence of a unusual strains of *Salmonella*. Possible sources for an increased number of an unusual strain of *Salmonella* among human isolates may sometimes be indicated by the emergence of the same unusual strain among isolates from animals, foods, and other sources. When such investigations have been conducted, often the source of the increase has been traced to foods of animal origin. For example, beginning in 1969 there was a marked increase in human isolates of *Salmonella* agona detected in the United States and several other countries. *Salmonella* agona had not been isolated in the United States before 1969, but by 1972 it was the eighth most common serotype isolated from humans in the United States.[38] Field investigations and surveillance data determined Peruvian fish meal fed to chicken to be the source of the infections. Critical to the investigation was the identification of *Salmonella* agona from Peruvian fish meal in routine surveillance sampling of fish meal in 1970.

The widespread geographic distribution of unusual strains also supports a limited role for person-to-person transmission of *Salmonella* in the developed world. For example, the almost simultaneous emergence in the United States and Europe of *Salmonella* agona, and more recently an indistinguishable clone of multidrug-resistant *Salmonella* typhimurium DT104 R-type ACSSuT,[38] suggests transmission via the contamination of a widely distributed vehicle, such as food, rather than infected persons.

Although comparisons between human and animal *Salmonella* surveillance data are useful in investigating the epidemiology of salmonellosis, such comparison should consider the specimen collection practices inherent in the submission of specimens to clinical laboratories within each surveillance system. For example, for both human and animal isolates, the specimens submitted to the clinical laboratories usually are collected from sick individuals. Since the serotypes of *Salmonella* in sick animals and in foods of animal origin, which come from apparently health animals, are likely to be different, crude comparisons of the "top ten" *Salmonella* serotypes in humans and in animals can lead to the erroneous conclusion that *Salmonella* serotypes which are common in certain animals (*e.g., Salmonella* serotype Cholerasuis in swine) and rare in humans are nonpathogenic to humans. Thus, comparisons of the most common serotypes in certain animals and humans cannot be used to conclude that food animals are not the most common sources of certain serotypes.

Sources of antimicrobial-resistant *Salmonella* infections

Since most human *Salmonella* infections in the United States are acquired from ingestion of contaminated foods, and because most stool specimens which yield *Salmonella* (including antimicrobial-resistant *Salmonella*) are obtained from patients before the patient takes antimicrobial agents (if the patient takes antimicrobial agents), it follows that most antimicrobial-resistant *Salmonella* infections are acquired from ingestion of foods contaminated with antimicrobial-resistant *Salmonella*. Another, less common, source of antimicrobial-resistant *Salmonella* is direct fecal-oral transmission following contact with animal feces. Strong supporting evidence that, in the United States, persons infected with antimicrobial-resistant *Salmonella* rarely obtain their infection from other infected persons is provided by the inability to identify fluoroquinolone-resistance among 4,000 *Salmonella* isolates in 1995 — since ciprofloxacin is widely used for the treatment of patients with salmonellosis, it is reasonable to assume the fluoroquinolone-resistant *Salmonella* emerged in the intestinal tract of some of the individuals infected with *Salmonella* who received ciprofloxacin, however, transmission to other persons must be rare because no domestically acquired resistant infections were detected.

If antimicrobial-resistant *Salmonella* infections are acquired from the ingestion of foods contaminated with antimicrobial-resistant *Salmonella*, what causes the emergence and increasing prevalence of antimicrobial-resistant *Salmonella*? The emergence and increasing prevalence of antimicrobial resistance *Salmonella* is the direct result of antimicrobial agents usage. In the United States, antimicrobial agents are mostly used in humans, animals and on plants. Since, human usage in the United States has little impact on resistance among *Salmonella*, and because most persons infected with antimicrobial-resistant *Salmonella* do not have a history of recent international travel[12-14] and few antimicrobial agents are used on plants, the only likely cause for the emergence and increasing prevalence of antimicrobial-resistant *Salmonella* in the United States is the use of antimicrobial agents in animals, predominantly food animals. Four lines of evidence support the conclusion that most antimicrobial-resistance among *Salmonella* isolates in humans results from the use of antimicrobial agents in food animals.

1. Trace backs of selected foodborne disease outbreaks

Several outbreak investigations of antimicrobial-resistant *Salmonella* infections in humans have combined epidemiologic fieldwork and laboratory subtyping techniques to trace back antimicrobial-resistant *Salmonella* through the food distribution system to farms, and antimicrobial use on the farms was found to be associated with the antimicrobial resistance.[39-42] In one investigation, hamburgers contaminated with antimicrobial-resistant *Salmonella* were traced, using a unique plasmid profile, from supermarkets, through meat processing, to healthy beef cattle which had been fed subtherapuetic antimicrobial agents.[39] In another investigation, approximately 1,000 persons were infected by hamburger contaminated with antimicrobial-resistant *Salmonella* serotype Newport with an unusual marker - chloramphenicol resistance. Chloramphenicol-resistant *S.* newport was traced from sick persons, through processing, to dairy cattle on farms where chloramphenicol had been used.[40] Although such investigations provide considerable insight into the complexity of *Salmonella* transmission, they suffer from the limitations of epidemiology studies. However, when combined with other lines of evidence, such investigations illustrate the potential human health consequences of the use of antimicrobial agents on farms.

2. Emergence of Salmonella typhimurium DT104 R-type ACSSuT with decreased susceptibility to fluoroquinolones in the United Kingdom

The continued emergence of *S.* typhimurium DT104 with decreased susceptibility to fluoroquinolones in humans in the United Kingdom provides increasingly strong evidence that antimicrobial-resistance among *Salmonella* isolates in humans results from the use of antimicrobial agents in food animals. Decreased susceptibility to fluoroquinolones among human *Salmonella* isolates was rare in the United Kingdom prior to 1993, despite the widespread use of ciprofloxacin in humans since 1987. As previously mentioned, following the 1993 approval and widespread use of enrofloxacin in veterinary medicine, human *Salmonella* isolates (and animal isolates) with decreased susceptibility to ciprofloxacin rapidly emerged beginning in 1994.[20]

3. Comparison of patterns of antimicrobial resistance patterns of Salmonella isolates from humans and animals

If veterinary use of antimicrobial agents is responsible for the development of antimicrobial resistant *Salmonella* in animals which may be transmitted to humans, then the patterns of antimicrobial resistance observed among *Salmonella* isolates collected from healthy animals and humans should be similar. These similarities become most evident when focusing on a serotype of *Salmonella* in humans which are predominantly derived from a single animal source. For example, human infections with *S.* serotype Heidelberg are often associated with eating undercooked chicken. Resistance patterns of *S.* heidelberg isolates from humans and healthy chickens are similar.

4. Comparison patterns of antimicrobial usage in humans and animals with antimicrobial resistance patterns among humans and animals

Although limited data are available on antimicrobial agent usage (subtherapuetic and therapeutic) in food animals, the available data suggest that the patterns of antimicrobial agent usage in food animals are similar to the spectrum of antimicrobial resistance observed among *Salmonella* isolates from food animals and humans. In contrast, the patterns of antimicrobial agent usage in humans are dissimilar to the spectrum of antimicrobial resistance observed in humans.

Human health risks of fluoroquinolone use in food animals

With the recognition that foods of animal origin are the source of most human *Salmonella* infections (and most antimicrobial-resistant *Salmonella* infections), and that most antimicrobial resistance among *Salmonella* isolates in the United States is caused by the use antimicrobial agents in food animals, it is possible to evaluate the potential human health consequences of unrestricted veterinary use of fluoroquinolones in the United States using the human health risks model developed by the Institute of Medicine in 1988.[1] Each year in the United States, most of the approximately 2,400 persons with life-threatening invasive *Salmonella* infections are treated with fluoroquinolones, of whom (although the isolates are susceptible to fluoroquinolones) approximately 500 die. Fluoroquinolones may therefore be life-saving for approximately 1,900 persons each year in the United States. If widespread fluoroquinolone resistance were to emerge among *Salmonella* isolates in the United States, evidence presented in this review demonstrates that this resistance would be the direct result of fluoroquinolone use in food animals. Because few persons have had fluoroquinolone-resistant *Salmonella* infections, the clinical significance of fluoroquinolone-resistance is not precisely known, however, because other antimicrobial treatment options are limited, treatment failures and serious outcomes, including deaths, would be expected. If 10% of *Salmonella* isolates in the United States were fluoroquinolone-resistant, and 10% of persons with invasive fluoroquinolone - resistant infections were to die, fluoroquinolone usage in food animals, which is currently limited to use in poultry, under such a scenario, would result in 19 deaths each year.

Need for prudent use of antimicrobial agents in food animals

The emergence and increasing prevalence of antimicrobial-resistant *Salmonella* complicates the treatment of *Salmonella* infections in humans and animals. For example, few antimicrobial agents are available for the treatment of *Salmonella* typhimurium DT104 R-type ACSSuT which becomes resistant to trimethoprim and fluoroquinolones. The increasing prevalence of antimicrobial resistance among *Salmonella* isolates, and the potential emergence of fluoroquinolone-resistant infections with adverse human health consequences, demonstrates the urgent need to develop strategies to reduce antimicrobial agent usage in food animals. Since antimicrobial agent usage can be reduced through the implementation of non-antimicrobial means of controlling infectious diseases, such as improved hygiene and sanitation, such efforts, which will minimize development of antimicrobial resistance and dissemination of antimicrobial-resistant pathogens, should be emphasized.[43]

Efforts should also be taken to ensure that antimicrobial agents are used prudently in food animals—prudent usage of antimicrobial agents maximizes the therapeutic effect of the antimicrobial agent and minimizes the development of antimicrobial resistance. Since subtherapuetic (growth promoter) uses of antimicrobial agents do not exert a therapeutic effect, such uses are non-prudent and should be replaced by non-antimicrobial methods of growth promotion. Because of the particular contribution of subtherapeutic use of penicillin and tetracycline in the development and dissemination of antimicrobial resistant *Salmonella*, the subtherapeutic use of penicillin and tetracycline should be terminated.[44] Because fluoroquinolones are a vital class of antimicrobial agents for the treatment of potentially life-threatening *Salmonella* infections in humans, and widespread usage of fluoroquinolones in food animals will lead to rapid emergence and dissemination of resistance to humans with adverse health consequences, the use of fluoroquinolones in food animals should be restricted, particularly until validated guidelines for the prudent use of antimicrobial agents in food animals have been implemented and certified.

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Footnotes

a This report pertains only to nontyphoidal *Salmonella*

b Federal Register May 22, 1997 (Volume 62, Number 99) page 27944-7.