Microbiology Spectrum
American Society for Microbiology Press

Antimicrobial Resistance in Nontyphoidal *Salmonella*

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ABSTRACT Non-typhoidal *Salmonella* is the most common foodborne bacterial pathogen in most countries. It is widely present in food animal species, and therefore blocking its transmission through the food supply is a prominent focus of food safety activities worldwide. Antibiotic resistance in non-typhoidal *Salmonella* arises in large part because of antibiotic use in animal husbandry. Tracking resistance in *Salmonella* is required to design targeted interventions to contain or diminish resistance and refine use practices in production. Many countries have established systems to monitor antibiotic resistance in *Salmonella* and other bacteria, the earliest ones appearing the Europe and the US. In this chapter, we compare recent *Salmonella* antibiotic susceptibility data from Europe and the US. In addition, we summarize the state of known resistance genes that have been identified in the genus. The advent of routine whole genome sequencing has made it possible to conduct genomic surveillance of resistance based on DNA sequences alone. This points to a new model of surveillance in the future that will provide more definitive information on the sources of resistant *Salmonella*, the specific types of resistance genes involved, and information on how resistance spreads.

BACKGROUND

Nontyphoidal *Salmonella enterica* (NTS) is a ubiquitous, motile, Gram-negative bacillus that is one of the most common bacterial causes of gastrointestinal disease worldwide. Salmonellae colonize the intestinal tract of a wide range of animal hosts, including pigs, cattle, poultry (1), and wildlife, as well as companion animals such as dogs, cats, birds, and reptiles (2). Humans acquire infection from the ingestion of contaminated foods. In the United States, most illnesses are associated with seeded vegetables, eggs, poultry, beef, and pork. Other sources include dairy, fruits, sprouts, and fish (3). Its ubiquity in nature and the variety of vectors mediating fecal-oral spread have made salmonellosis the most important foodborne bacterial zoonosis. For many decades, the cornerstone of *Salmonella* epidemiology has been the Kaufmann-White serotyping scheme (4). Based on antibodies to the three major surface antigens (somatic O, flagellar H, and capsular Vi antigens), over 2,500 distinct serovars are currently recognized. A comprehensive body of scientific information on *Salmonella* developed over the years makes it one of the best-understood bacterial pathogens. A great deal is known about *Salmonella* epidemiology and genetics, the various virulence factors, interaction of the bacterium with host cells, the host range of serovars, and the causes of antibiotic resistance.

Most human cases of acute NTS diarrhea are self-limiting and do not require treatment with antibiotics unless they are severe, invasive, or occur in the elderly, children, or those with underlying comorbidities (5). Cases that become invasive may result in life-threatening bloodstream infections. Antimicrobial resistance is especially problematic in these systemic infections, where antibiotic therapy can be life-saving. Efforts to limit the public health burden of salmonellosis, and the pressures leading to antibiotic resistance, have focused on farm practices, interventions in processing facilities, and consumer education on safe food handling practices.

Received: 6 March 2017, **Accepted:** 7 February 2018, **Published:** 19 July 2018

Editors: Frank Møller Aarestrup, Technical University of Denmark, Lyngby, Denmark; Stefan Schwarz, Freie Universität Berlin, Berlin, Germany; Jianzhong Shen, China Agricultural University, Beijing, China, and Lina Cavaco, Statens Serum Institute, Copenhagen, Denmark

Citation: McDermott PF, Zhao S, Tate H. 2018. Antimicrobial resistance in nontyphoidal *Salmonella*. *Microbiol Spectrum* 6(4): ARBA-0014-2017. doi:10.1128/microbiolspec.ARBA-0014-2017.

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In animals, *Salmonella* may cause overt signs of disease or may be carried asymptomatically and be shed into the environment (6). In food-producing animals, *Salmonella* is a continuous threat to animal health, especially in cattle, where infection typically presents as diarrhea with fever, anorexia, and dehydration (2). Less commonly, infection results in respiratory disease and death. *Salmonella* infections in dairy herds, where they may become endemic (7), result in decreased milk production and increased production costs, including the use of antibiotics. In addition to overt salmonellosis, a chronic asymptomatic carrier state may exist in food-producing animals. In both the carrier state and in cases of overt infection, exposure to antimicrobials promotes the evolution of resistant serovars that may be transmitted to humans. In the case of foodborne zoonotic bacteria, resistance spreads from food-producing animals to humans via the consumption of meat products derived either from treated animals or from foods cross-contaminated at processing or retail (8). Resistance also can spread by direct animal contact (as with pets) or environmental routes such as water or wildlife. The U.S. Centers for Disease Control and Prevention (CDC) classifies antibiotic-resistant *Salmonella* as a serious public health threat (9).

Bacterial resistance to antibiotics is a naturally occurring phenomenon that can be accelerated by selection pressures exerted through the use of antibiotics in medical and veterinary practice (10). Resistance is mediated by a limited number of mechanisms common to other pathogens. These include enzymatic modification, target protection, energy-dependent efflux, and permeability changes in the cell wall. The use and misuse of antimicrobials in both humans and animals result in antimicrobial resistance in both pathogenic and commensal bacteria within the treated host. Many classes of antimicrobial agents used in food-producing and companion animals are the same as those used in human medicine (11). Therefore, resistance developing in one drug use environment can compromise the efficacy of drugs used in other settings. For this reason, many countries are attempting to implement antimicrobial drug use monitoring.

The relationship between resistances in food animal bacteria and antibiotic use in animal agriculture is poorly defined. Very few countries can collect detailed information on the amounts and indications of antimicrobial compounds in different animal species over time. Only in Denmark is it mandatory for veterinarians to report (via VetStat) medicines used in their own practices. Like most countries, the United States and Japan collect data on total annual sales (in kilograms of active ingredient) by drug class. Japan collects sales data only for drugs used therapeutically (12). Most European Union countries also mandate collection of sales data (13). While usually the only practicable approach, bulk annual amounts of active ingredient sold is of limited utility and is not a reliable surrogate for actual drug use in the production environment (14). In July 2016, the U.S. FDA mandated that pharmaceutical companies report antimicrobial sales by the four major animal species: cattle, chickens, turkey, and swine, along with a combined "other" category (15). The goal of this provision is to better monitor drug use and better understand the drivers of antimicrobial resistance in *Salmonella* and other foodborne microorganisms.

While there are numerous small targeted surveys in the scientific literature describing antimicrobial resistance in *Salmonella* from different places and sources, an ongoing integrated national surveillance system is necessary to combat antibiotic resistance (16). The WHO defines integrated surveillance as "the coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans; and the subsequent evaluation of antimicrobial resistance trends throughout the food production and supply chain using harmonized methods" (1). It provides necessary data to identify emerging hazards, assess risks, monitor trends, measure interventions, and inform mitigation policies. The generation of robust and consistent data is important to the development and assessment of response measures used to combat antimicrobial resistance. In the United States, this work is conducted by the National Antimicrobial Resistance Monitoring System (NARMS). Similar systems are in place across the European Union, in Canada, across Latin America, and in some Asian and African countries. Most of these programs are focused on susceptibility surveillance of human clinical isolates. Active surveillance of animal and retail meat isolates operates to varying degrees in different countries (1). This article will review the latest available information on resistance in *Salmonella* (through test year 2014), with an emphasis on the situation in the United States and Europe.

THE BURDEN OF SALMONELLOSIS

NTS is recognized as one of the most common bacterial causes of foodborne diarrheal disease worldwide. Foodborne NTS is estimated to cause over 93 million cases of gastroenteritis annually and 155,000 deaths globally (8), resulting in about 4 million disability-adjusted life years (17). At-risk populations include children <1 year of age

and adults ≥60, who are most vulnerable to infection and tend to have more severe disease (18). Extraintestinal or invasive NTS infections, often associated with certain serovars or phylogenetic clades, add to the global burden of illness, especially in resource-poor countries and immunocompromised patients (19). An estimated 3.4 million invasive infections occur annually, resulting in 681,000 deaths, with the young and old in Africa being most affected (20). The relatively high prevalence of highly invasive strain subtypes, such as those that have been identified among *S. enterica* serovars Enteritidis (21), Typhimurium (22), and Kentucky (23) may be expected to drive different antibiotic use practices to control disease in countries where invasive subtypes are endemic (24).

Despite sustained efforts to control NTS in animals and to educate the public on safe food-handling practices, the incidence of human salmonellosis has not changed significantly in the United States (25). The latest data from the CDC on microbial causes of zoonotic foodborne diseases ranked *Salmonella* first in incidence, at 15.5 cases per 100,000 inhabitants, resulting in over 2,100 hospitalizations and 32 deaths (18). In the European Union in 2014, the incidence of *Salmonella* infections (23 per 100,000) ranked well behind *Campylobacter* (71 per 100,000). In 2014, a total of 88,715 confirmed cases of salmonellosis were reported by 28 European Union member states and 4 nonmember states (26). In both the United States and the European Union (and in many other countries), *S. enterica* serovars Typhimurium and Enteritidis are consistently the most frequently isolated among confirmed human cases of disease (18, 26). In the United States and the European Union, poultry meat is the most commonly contaminated animal-derived food commodity (26, 27).

TREATMENT OF SALMONELLOSIS

The extent of antibiotic resistance in *Salmonella* varies by country and is influenced by antimicrobial use practices in humans and animals, as well as geographical differences in the epidemiology of *Salmonella* and regional serovar differences. In developed countries, drug resistance in *Salmonella* is driven largely by the use of antimicrobials in food-producing animals (28). In general, resistance profiles reflect the length of time an agent has been in use. Thus, irrespective of isolation source (humans, foods, food animals), the most frequent types of resistances are usually for older antimicrobials such as tetracycline, sulfamethoxazole, and streptomycin (26, 27, 29, 30).

Antimicrobial therapy is usually not indicated for uncomplicated infection. Therapy should be considered for populations at increased risk for invasive infection such as people >50 years of age with atherosclerosis, the immunocompromised, and those with cardiac disease. In these patients, the recommended antimicrobials include a fluoroquinolone such as ciprofloxacin, a third-generation cephalosporin such as ceftriaxone, trimethoprim/sulfamethoxazole, or amoxicillin. The recommended empiric antimicrobial therapy for bloody diarrhea in immunocompetent adults is either a fluoroquinolone or azithromycin, both of which show potent *in vitro* activity against *Salmonella* in the United States and the European Union. Additionally, most highly resistant strains of *Salmonella* are susceptible to carbapenem drugs (31, 32), making it a drug of last resort. Recommended empiric therapy for children includes a third-generation cephalosporin for those <3 months of age or azithromycin. Because fluoroquinolones, extended-spectrum cephalosporins, azithromycin, and carbapenems are critically important antibiotics for the management of salmonellosis, emerging resistance to these drug classes is a paramount concern (33).

ANTIMICROBIAL RESISTANCE IN *SALMONELLA* FROM THE UNITED STATES

The United States has extensive data back to 1996 on antimicrobial resistance in *Salmonella*, which is collected through NARMS (34). The NARMS program generates susceptibility data on *Salmonella* representing 5% of the nationally reported human clinical cases. These results are compared with data on *Salmonella* from 13 other sources that include (i) samples of retail chicken, turkey, pork, and beef collected in 14 states; (ii) cecal specimens from chickens, turkeys, cattle (dairy and beef), and pigs (hogs and sows) at slaughter; and (iii) carcass swabs, carcass rinses, and ground product from chickens, turkeys, cattle, and pigs at slaughter. A line listing of these data is freely available online (35), where information on nearly 160,000 isolates dating back to the start of NARMS can be downloaded and analyzed using standard spreadsheet and database software programs.

Few data are available from before 1996 to document the historical trends in *Salmonella* resistance. To address this gap, Tadesse et al. (36) conducted a retrospective study of 2,149 banked human clinical *Salmonella* strains and documented changing resistance patterns in strains dating back to 1948. Comparing data from pre-1960 with those from post-1989 for *S.* Typhimurium (which constituted most of the banked isolates) showed that

resistance rose from 0% to 33% for ampicillin, 0% to 26% for chloramphenicol, 0% to 43% for streptomycin, 20% to 43% for tetracycline, and 0% to 37% for sulfamethoxazole. While recognizing the inherent limitations in directly comparing two disparate data sets, it is striking how the historical and modern data in juxtaposition show a monotonic increasing trend in resistance to older antimicrobial compounds (ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline) from pre-1960s up until the 1990s, followed by a decline to current levels approximating those of the 1970s (Fig. 1). This study examined just over 2,100 human clinical isolates collected over 6 decades, a number now tested annually in NARMS.

In NARMS, antimicrobial susceptibility testing is centralized at government laboratories of the FDA, the CDC, and the U.S. Department of Agriculture. All three laboratories employ identical media, methods, quality control parameters, and repeat testing criteria, along with a common drug panel from a single manufacturer. The compounds tested have many commonalities with the European Union testing design (see below) except that ceftriaxone is used in the United States as a class representative for extended-spectrum cephalosporins (Table 1), while in Europe either ceftazidime or cefotaxime is used. The United States currently also includes amoxicillin-clavulanate, cefoxitin, streptomycin, and trimethoprim/sulfamethoxazole, while the European Union member states test trimethoprim alone. Some European Union countries report resistance data for tigecycline and colistin.

Different breakpoints are used that result in more conservative interpretations in the European Union compared with the United States (Table 1). The European Union uses EUCAST epidemiological cutoff values (ECOFFs) as breakpoints where available (37), which are based on the highest MIC of the wild-type population. In contrast, the United States currently interprets susceptibility results in *Salmonella* based on the Clinical and Laboratory Standards Institute (CLSI) clinical breakpoints (for all agents except streptomycin). Clinical breakpoints also rely on data from MIC distributions, which are combined with pharmacological information and clinical outcome trials to set clinical breakpoints. In accord with WHO recommendations (1), NARMS MIC data are also presented as MIC distributions so that other interpretive criteria can be applied to allow direct comparisons (27). The presentation of MIC data also allows for increased power in detecting slight shifts in bacterial susceptibility to some antibiotics, giving users of the data increased ability to create predictive models of resistance based on policy interventions (38).

The latest U.S. surveillance data (test year 2014) from NARMS comprised antimicrobial susceptibility results for 5,043 NTS isolates, including 2,127 from humans, 262 from retail meats, 1,579 from hazard analysis and critical control point samples (39), and 1,075 from animal cecal samples (27). The prevalence of *Salmonella* in U.S. retail meats in 2014 was 9.1% in chicken, 5.5% in ground turkey, 1.3% in pork, and 0.8% in beef.

A general overview of key antibiotic resistance trends in U.S. clinical isolates of *Salmonella* is shown in Fig. 2. Approximately 82% of *Salmonella* isolated from humans in 2014 had no resistance to any of the antimicrobial drugs tested, a trend that has improved since NARMS testing began in 1996. Multidrug resistance

FIGURE 1 Temporal changes in resistance of clinical nontyphoidal *Salmonella* from the 1940s to 2014. AMP, ampicillin; CHL, chloramphenicol; STR, streptomycin; SUL, sulfonamides; TET, tetracycline; NAL, nalidixic acid; AXO, ceftriaxone.

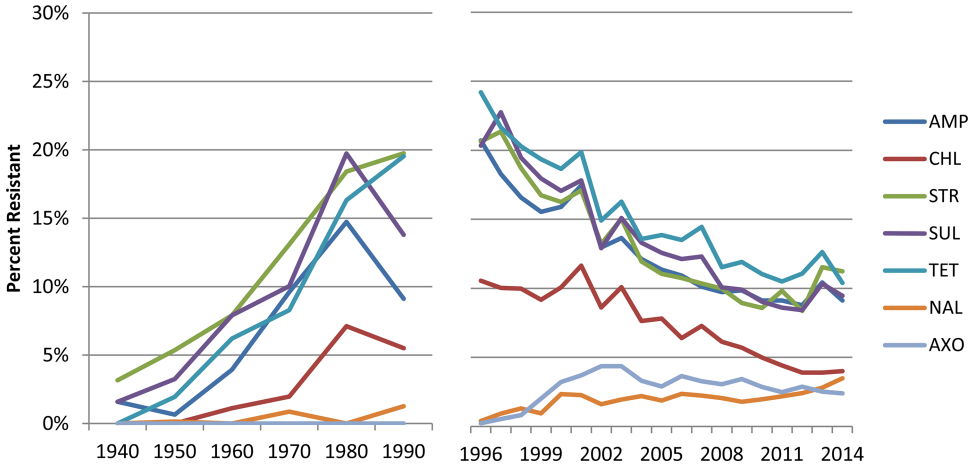


TABLE 1 Antimicrobials tested in the European Union and United States and criteria used to interpret microbiological and clinical resistance

	Breakpoints (μg/ml)		
	European Union[a]		U.S.[a]
Antimicrobial	Microbiological	Clinical	Clinical
Tetracycline (TET)	>8	>4[b]	>8
Sulfonamide (SUL)	>256	>256[b]	>256
Ampicillin (AMP)	>8	>8	>16
Chloramphenicol (CHL)	>16	>8	>16
Nalidixic acid (NAL)	>16	>16[b]	>16
Third-generation cephalosporin (CEP)[c]	>0.5	>1	>2
Gentamicin (GEN)	>2	>2	>8
Trimethoprim-sulfa (COT)[d]	>2	>2	>2
Ciprofloxacin (CIP)	>0.064	>0.064	>0.5
Azithromycin (AZI)	>16[e]	>16[e]	>16[f]
Colistin (COL)	>2		N/A

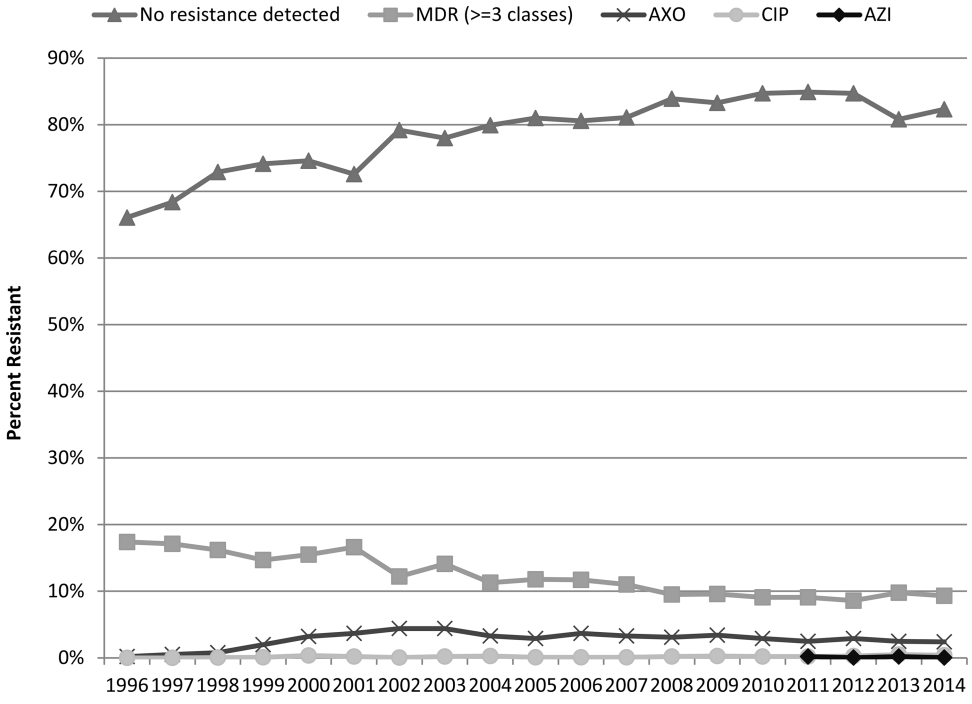
[a]European Union breakpoints are from EUCAST, and U.S. breakpoints are from CLSI unless otherwise noted.
[b]Derived from CLSI.
[c]In the European Union, isolates are tested against ceftazidime and cefotaxime.
[d]In the European Union, non-human isolates are tested against trimethoprim and sulfonamide separately. In the United States, isolates are tested against trimethoprim-sulfamethoxazole and sulfamethoxazole.
[e]Reference 150, 151.
[f]Reference 149.

(MDR, resistant to ≥3 antimicrobial classes) was present in around 10% of isolates on average, appearing in 9.3% of human isolates in 2014. In 2014, resistance in human strains was most frequent to streptomycin (11.2%), tetracycline (10.4%), sulfamethoxazole (9.4%), and ampicillin (9.1%), followed by lower levels of resistance to chloramphenicol (4.0%), nalidixic acid (3.5%), ceftriaxone (2.4%), cefoxitin (2.2%), amoxicillin-clavulanate (2.1%), gentamicin (1.4%), trimethoprim-sulfamethoxazole (1.3%), ciprofloxacin (0.4%), and azithromycin (<0.1%) (27). Resistance to the three critically important drugs ceftriaxone, azithromycin, and ciprofloxacin was below 3% (Fig. 2). These three major findings were largely unchanged from the previous 10 years. The most common *Salmonella* serovars infecting humans in the United States in 2014 were Enteritidis (21%), Typhimurium (12%), and Newport (11%), followed by Javiana (6%), I 4,[5],12:i:– (5%), and Infantis (3.4%) (27).

Multidrug resistance

In general, resistance in human isolates of *Salmonella* has been fairly low and stable over the past decade in the United States. Because a substantial proportion of human infections are acquired from non-food-animal

FIGURE 2 Resistances to critically important antimicrobials in human clinical *Salmonella* isolates from the United States. MDR, multidrug resistant; AXO, ceftriaxone; AZI, azithromycin; CIP, ciprofloxacin.



sources (3), however, it is not unexpected that resistance in animal isolates tends to be higher. By animal species, resistance to any of the 14 tested compounds was most frequent in turkey sources (approximately 60% to 80% resistant to ≥1 agent), followed by broilers (about 30% to 60%), and cattle (30% to 40%). These findings are consistent with other studies that show that *Salmonella* from poultry sources tend to be more resistant than *Salmonella* from cattle sources (38) and that swine isolates tend to be more resistant than those from cattle (40).

In human clinical strains, MDR is most frequent in *S. enterica* serovars Typhimurium (28.9%), I 4,[5],12:i:– (27.9%), and Heidelberg (7.6%). While MDR is declining in *S.* Typhimurium (see below), it has risen in *S.* 4,[5],12:i:–, from 5.5% in 2007 to 50% in 2014, with 47.3% exhibiting resistance to more than four drug classes. In animals at slaughter, MDR was most frequent in isolates from turkeys (47%) and hogs (20%), followed by broilers (15%), dairy cattle (10%), beef cattle (6%), and sows (6%) (27). In 2014, MDR was detected in 36% of retail ground turkey isolates and 20% of retail chicken meat. MDR is disproportionately high in broilers among serovars Kentucky (33% hazard analysis and critical control point to 58% cecal isolates) and Typhimurium (16% to 53% among hazard analysis and critical control point and cecal isolates, respectively).

Measuring MDR by the number of resistance phenotypes without regard to the importance of the drug classes involved is of limited value. To help overcome this limitation, NARMS has published new tools online that allow the user to investigate any combination of specific MDR patterns and their changes over time (31). This permits a more refined analysis of MDR patterns in assessing risks, for identifying specific resistance trends of higher public health importance, and to better understand the specific drivers of resistance where coresistances are involved.

The percentage of *Salmonella* strains that are resistant to ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline (the ACSSuT penta-resistant phenotype) has been tracked as a hallmark of the globally disseminated *Salmonella* Typhimurium DT104 for decades. The ACSSuT resistance pattern has declined steadily in all U.S. salmonellae from 34% in 1996 to 14.5% in 2014. Declining levels of both *S.* Typhimurium (27) and MDR *S.* Typhimurium (41) are the main drivers behind overall declining levels of MDR *Salmonella* in human isolates. The ACSSuT resistance in cattle isolates of *S.* Typhimurium declined sharply from 67% in 2009 to 7% in 2014. This highlights an important feature of *Salmonella* resistance, namely, the serovar-specific nature of some resistance patterns whose ascendancy and decline may be temporally associated with the prevalence of specific strains.

In the United States in recent years, the ASSuT (ampicillin, streptomycin, sulfonamide, tetracycline) MDR pattern has increased among human isolates of *S.* I 4,[5],12:i:–, where it climbed from 1.4% in 2009 to 43% in 2014. Outbreak investigations of this strain have pointed to swine as a possible source (42), backed by findings of increased *S.* I 4,[5],12:i:– in diseased pigs in Minnesota (40), one of the top five pig-producing states in the United States.

While MDR is not common in *S.* Enteritidis, it is driven by a higher resistance to nalidixic acid compared with other serovars. MDR is common in *S.* Newport, where the MDR-AmpC phenotype on an IncA/C or IncI backbone is a common feature of resistance (43).

Quinolone Resistance

Overall, fluoroquinolone resistance has been consistently low among *Salmonella* isolated from all U.S. surveillance sources. In human isolates, it predominantly presents in serovar Enteritidis (47%) and is associated with travel (44). Since 2007, ciprofloxacin resistance has been detected in a total of only four cattle and six swine isolates in the United States. Ciprofloxacin resistance is not present (using CLSI breakpoints) in isolates from U.S. poultry *Salmonella*, where fluoroquinolones have not been used since 2005. In 2014, the first instance of ciprofloxacin-resistant *Salmonella* in meat was a single isolate from a retail pork sample which carried the *qnrS* gene. This was the first report of *qnr* genes present in retail meat *Salmonella* isolated in the United States (27).

While ciprofloxacin resistance is rare in U.S. salmonellae in general, decreased susceptibility to ciprofloxacin (DSC, MIC ≥ 0.125 μg/ml) has increased in humans and cattle strains as well as in swine strains. (Strains with this MIC would be considered microbiologically resistant according to EUCAST breakpoints.) Studies have reported extremely low quinolone resistance among *Salmonella* isolated from feedlot and beef cows as well as dairy cows (45, 46). However, decreased susceptibility is rarely assessed. Distribution of extrachromosomal *qnr* genes is thought to be the main reason why this phenotype is increasing in frequency. Because fluoroquinolones are widely, and often repeatedly, used to treat bovine respiratory disease, a common illness in cattle herds, there is a possibility that fluoroquinolone use may help to propagate an acquired resistance gene. Particularly concerning is the emergence of DSC in

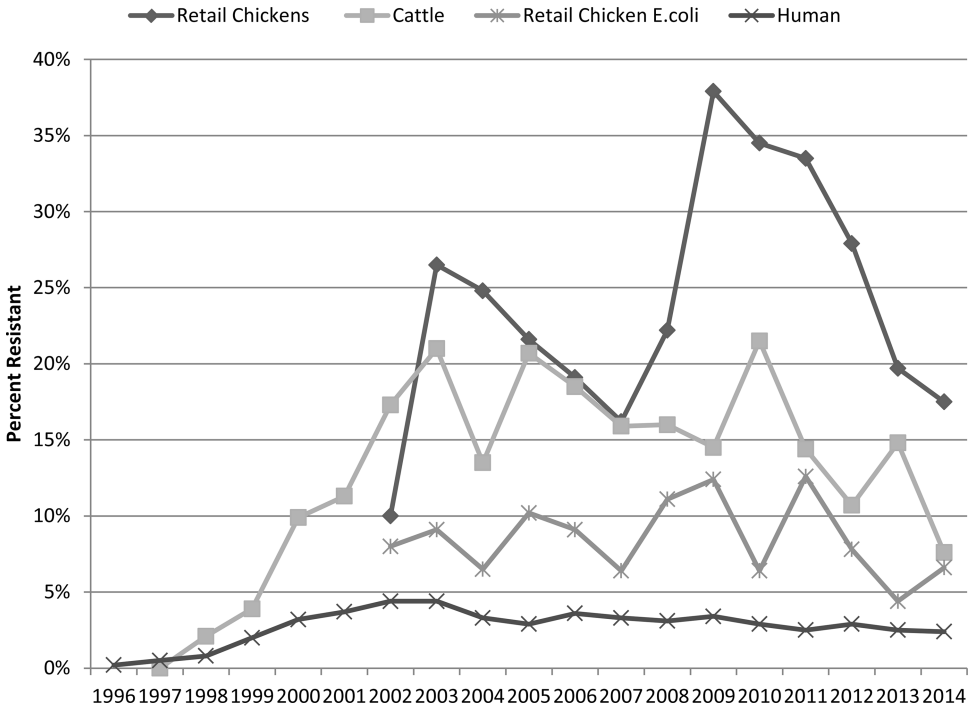
S. enterica serovar Dublin isolates from humans and cattle, where increasing cephalosporin resistance is also occurring. The incidence of human *S.* Dublin infections is relatively low, but it can cause invasive disease with more severe outcomes. *S.* Dublin also causes severe disease in cattle, mainly respiratory infections, and ranks among the top four serovars isolated from retail ground beef and cattle samples in NARMS and the top serovar among isolates derived from clinical specimens (40). As of the 2014 NARMS testing year, 57% (4/7) of DSC *S.* Dublin isolates from humans and 40% (18/42) of DSC *S.* Dublin isolates from cattle were also resistant to ceftriaxone. This combination of DSC and ceftriaxone resistance puts significant limitations on possible treatment options for human illness.

Cephalosporin Resistance

Among critically important human antibiotics, the temporal association of ceftiofur use in food animals and the emergence of ceftriaxone resistance in both animals and humans has been an area of concern in the United States, the European Union, and elsewhere. In the United States, ceftriaxone resistance was not detected in *Salmonella* prior to the approval of ceftiofur (36) and rose following its approval for use in the United States in livestock and poultry (Fig. 3). From 1996 through 2009, the percentage of NTS human isolates resistant to ceftriaxone increased from 0.2% to 3.4% (41). These rising trends have caused several countries, including the United States, to limit certain uses of cephalosporins in animal agriculture, with positive effects. A well-known example occurred in Canada when voluntary restrictions on ceftiofur use were followed by a rapid and significant decline in ceftriaxone-resistant *S.* Heidelberg (and *Escherichia coli*) in chickens, retail chicken meats, and human clinical isolates (47). In the United States, the FDA announced plans in 2008 to restrict the use of some cephalosporins, which went into effect in 2012 (48). As of 2014, it appears that the restrictions may be producing the desired effect of reducing cephalosporin resistance in humans and select animal species. Ceftriaxone resistance has declined since 2009 in human (3.4% to 2.4%) and retail chicken (38% to 18%) *Salmonella* isolates (Fig. 3).

Changes in ceftriaxone resistance were most notable for *S.* Heidelberg, where resistance in human isolates declined to 8.5% in 2014, down from a peak of 24% in 2010 (27). Ceftriaxone resistance in retail chicken *S.* Heidelberg remained at 0% from 2011 to 2013 (down from a peak of 32% in 2009), but reappeared in 3/24 isolates in 2014. In retail ground turkey isolates in 2014, resistance continued to decline to 7% after peaking

FIGURE 3 Trends in third-generation cephalosporin resistance in *Salmonella* from the United States.



at 22% in 2011. In cattle *Salmonella* isolates in 2014, ceftriaxone resistance reached its lowest level (7.6%) since 1999 (31). Studies of diagnostic cattle isolates show varied results. While some studies show demonstrable decreases in cephalosporin resistance among dairy cattle since 2012 (46), others show continued increases (40) or even no resistance at all among healthy feedlot cattle (49). Many of these disparities are due to regionalization of serovar frequencies, as well as the types of samples analyzed (diseased versus healthy animals).

Ceftriaxone resistance in human strains is most common in the same serovars in which MDR prevails, namely, Typhimurium, Newport, Heidelberg, and I 4, [5],12:i:–, with the addition of Dublin, 11.5% of which were ceftriaxone resistant. Ceftriaxone resistance was also high in *S.* Dublin from cattle (34.6%) and ground beef (60%). In other nonhuman sources, ceftriaxone was disproportionately high in serovars Newport from cattle (66.7%), Kentucky from broilers (66%), Typhimurium from broiler meat (72%), and Heidelberg from fattening turkeys (60%).

NARMS data show that extended-spectrum cephalosporin resistance among U.S. isolates of *Salmonella* (and *E. coli*) is usually mediated by bla_{CMY} genes, whereas extended-spectrum beta-lactamases (ESBLs) have been rare (50). This appears to be changing. Examining NARMS strains from 2012 to 2014, 26 instances of ESBLs occurred, mainly conferred by members of the CTX-M family, along with 3 instances of $bla_{\text{SHV-12}}$ and one case of $bla_{\text{SHV-30}}$. Finding $bla_{\text{CTX-M-65}}$ in a 2014 retail chicken sample led to an expanded examination of U.S. human and animal strains and revealed that the gene had become widespread in a strain of serovar Infantis previously identified in Europe and South America (51).

ANTIMICROBIAL RESISTANCE IN EUROPE

Denmark established the world's first integrated antimicrobial resistance surveillance program in 1995, and other members of the European Union have followed with their own national programs. In the European Union, antimicrobial resistance in *Salmonella* is tracked in data submitted by European Union member states and Norway and is reported jointly by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC).

The latest European Union data are from 2014 (26), when for the first time, all 28 member states along with Iceland and Norway submitted isolate-level data on poultry and poultry meat products. Therefore, the European Union report focuses on resistance in human and poultry sources of isolates. Countries submit both MIC data, which is interpreted using published ECOFFS, and susceptibility categories interpreted from disk diffusion. In 2014, 21 member states and Norway provided data on human *Salmonella* isolates. Twelve countries (Austria, Denmark, Estonia, Finland, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, and Romania) reported isolate-level results in the form of inhibition zone diameters or MICs, which allows for improved comparability between human and animal/food isolates. Ten countries reported categorical interpretations of susceptible (S), intermediate (I), or resistant (R) according to the clinical breakpoints. The number and types of antimicrobials reported varied by country, from 2 countries testing only three antimicrobials to 13 countries testing all 10 antimicrobials in the priority panel. This mixture of breakpoints and testing methods, sampling strategies, differences in serovar by country, and the incomplete nature of the isolate-level data mean that the results must be interpreted, and the country differences compared, with caution.

In 2014 in the European Union, a total of 14,412 *Salmonella* isolates from human infections were tested, constituting 16% of all confirmed human cases of illness. When examining all serovars (n = 247) and countries (n = 22) combined, the most common resistances in human *Salmonella* isolates were to tetracyclines (30.3%), sulfonamides (28.6%), and ampicillin (28.2%), followed by lower levels of resistance to trimethoprim-sulfamethoxazole (9.2%), ciprofloxacin (8.8%), chloramphenicol (6%), gentamicin (2.7%), and cefotaxime (1.1%) (26). The top three resistances mirror the order of resistance profiles in the United States (except for streptomycin, which is not reported by EFSA).

Although the United States and the European Union employ different criteria for surveillance reporting, these differences are absent or minor for most drugs. Small discrepancies are evident for extended-spectrum cephalosporins and gentamicin that have nugatory effect on reported rates of resistance. Breakpoints for ciprofloxacin have the largest affect, where application of the EUCAST criteria changes the U.S. resistance percentage in human isolate data from 0.4% to 4.3%. The EUCAST breakpoints were applied for the purposes of comparison below.

Monitoring data from food sources show some commonalities with the U.S. situation. An overall comparison between the European Union and the United States of resistance to the "older" antimicrobials of chloramphenicol, tetracycline, gentamicin, and ampicillin is shown for human isolates (Fig. 4) and broiler isolates

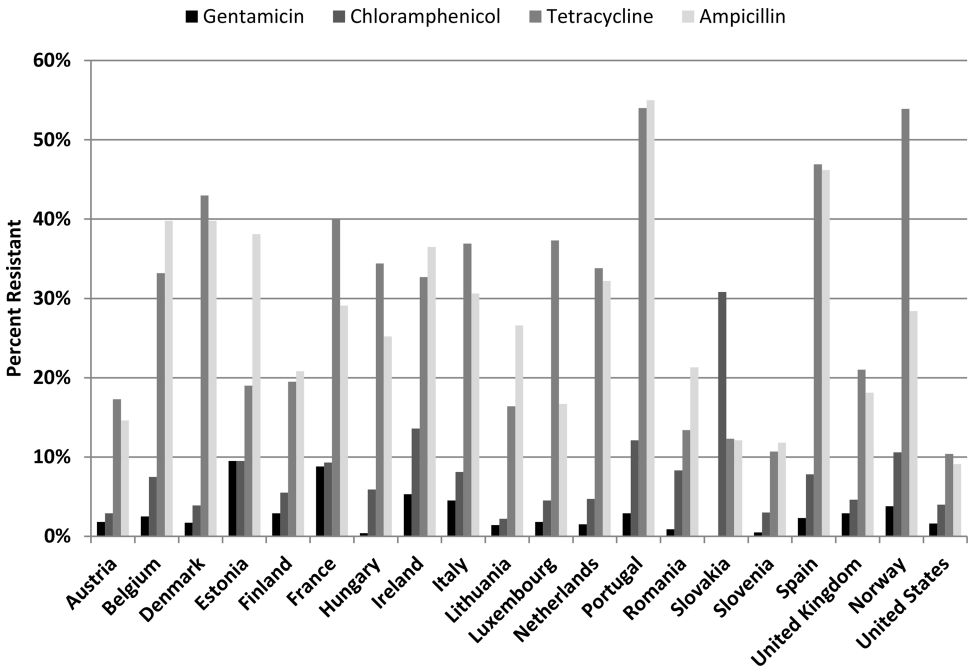


FIGURE 4 Resistance to gentamicin, chloramphenicol, tetracycline, and ampicillin in human *Salmonella* isolates from select European Union countries, Norway, and the United States. Breakpoints used for interpreting MICs were derived from the EUCAST.

(Fig. 5) of *Salmonella* spp. For human data, the U.S. surveillance data are comparable to Slovenia, which reports the lowest resistance levels for these drugs among the member states. Resistance data for broiler strains of *Salmonella* spp. show that the United States is slightly below the European Union average.

Other general features of resistance in both the European Union and the United States are evident. With some exceptions, *Salmonella* recovered from poultry meats is generally more resistant than isolates from human infections in both regions (26, 31). Among poultry isolates, resistance levels in the European Union were generally higher in turkeys than chickens. This is comparable to what was observed in the United States, where turkey isolates tended to be the most resistant, followed by those from chicken, swine, and cattle (27). One might presume that this pattern is the result of higher antimicrobial use in turkeys than in broilers, but there have been no on-farm studies that confirm a causal relationship (52). In general, fluoroquinolone resistance is higher in the European Union, and third-generation cephalosporin resistance is higher in the United States. Other resistance patterns are compared below.

Multidrug Resistance

In 2014, 10 member states tested *Salmonella* against 9 classes of antimicrobials (26). Overall, only 54.8% of human isolates were susceptible to all agents tested. MDR was high overall (26.0%) in human isolates from the European Union, with very high prevalence in some countries. Among poultry sources, MDR was low in laying hens; high in broiler meat, turkey meat, and broilers; and very high in turkeys. As with other types of resistance, MDR tends to be associated with certain serovars, generally being rare in *S.* Enteritidis. In Europe, MDR variants of *S.* Kentucky (74.6%), along with monophasic *S.* Typhimurium I 4,[5],12:i:– (69.4%) and *S.* Infantis (61.9%), are especially problematic in humans. As noted above, the United States also is witnessing a rise in MDR *S.* Typhimurium I 4,[5],12:i:–. While *S.* Kentucky rarely causes human disease in the United States, it commonly exhibits MDR.

Extended-spectrum cephalosporin-resistant *S.* Infantis (carrying the $bla_{\text{CTX-M65}}$ gene) has emerged in the United States as a public health concern. The circulating clone is similar to an Italian strain of *S.* Infantis carrying the $bla_{\text{CTX-M65}}$ gene (53). While MDR *S.* Infantis has not increased in poultry isolates collected for NARMS surveillance, EFSA reports that *S.* Infantis isolates from European Union broiler meat express very high levels of MDR (>70.0%). Isolates from Italian broilers exhibit exceptionally high levels of resistance to third-generation cephalosporins, which may be characteristic of the CTX-M clone. Particularly concerning was the detection of

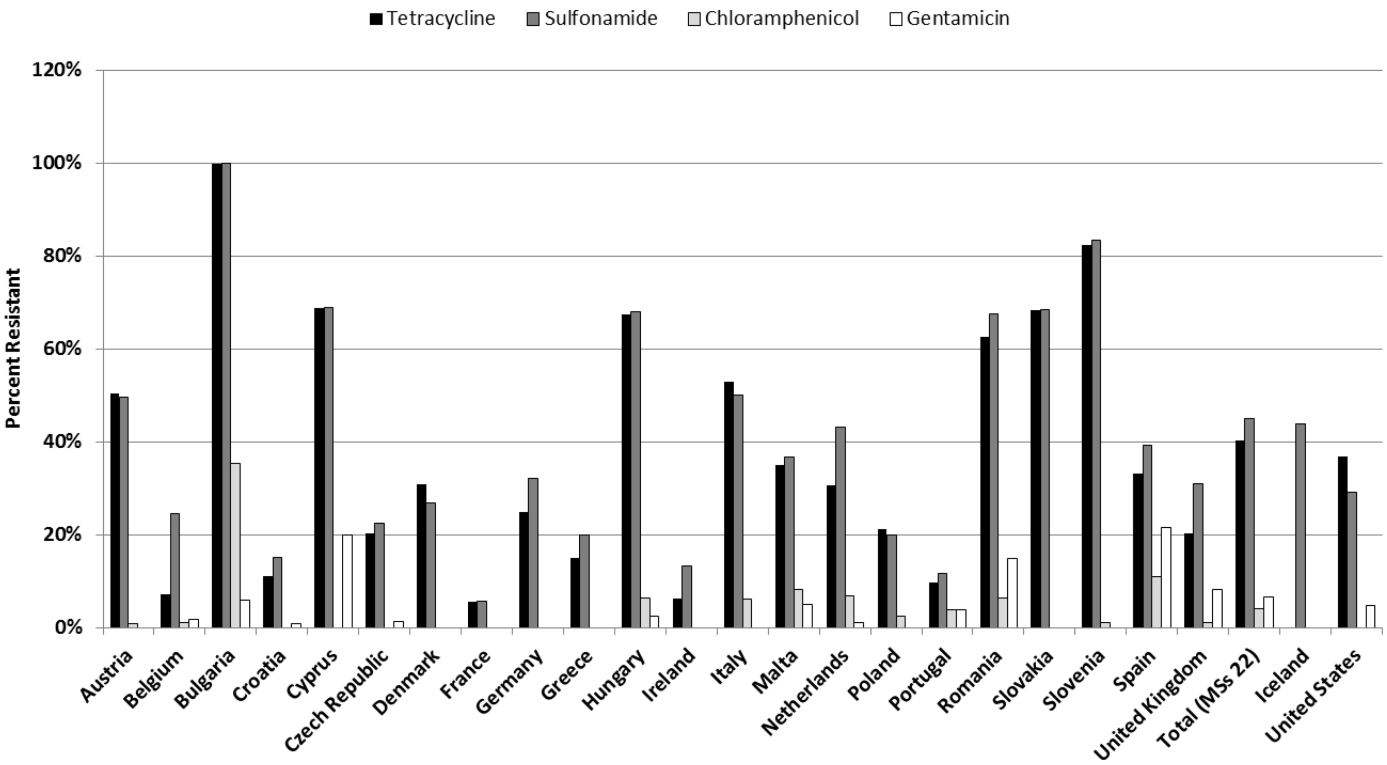


FIGURE 5 Resistance to gentamicin, chloramphenicol, tetracycline, and ampicillin in broiler *Salmonella* isolates from select European Union countries, Iceland, and the United States. Breakpoints used for interpreting MICs were derived from the EUCAST.

high-level resistance to ciprofloxacin in these isolates. The clone may be limited to chickens, because no resistance to third-generation cephalosporin was detected in fattening turkeys (26).

Much of the difference in resistance among poultry isolates from the United States and the European Union is likely due to the variation in serovar profiles of poultry isolates between the two regions. *S.* Infantis and *S.* Enteritidis are among the top three serovars in chickens and chicken meats in the European Union, but in the United States, serovar Kentucky predominates. Likewise, in European Union fattening turkeys, serovars Derby, Kentucky, and Newport account for 30% of *Salmonella* isolates, but in the United States, serovars Hadar and Reading round out the top two in turkeys and turkey meats (31).

Quinolone Resistance

A comparison of human isolates from European countries that reported data for both fluoroquinolones and extended-spectrum cephalosporins is shown alongside the U.S. data in Fig. 6. The average resistance to extended-spectrum cephalosporins is low (1.1%) in the European Union data, while ciprofloxacin resistance was found in 8.8% of all human isolates, ranging from 0% to 19% among reporting countries compared with 4.3% in the United States. The European Union resistance to ciprofloxacin is driven in part by a high prevalence of ciprofloxacin resistance in serovar Kentucky, where 84% were resistant to ciprofloxacin. This aligns with previous findings on the establishment of ST198 *S.* Kentucky in humans and poultry flocks throughout Europe and other areas (23). While this strain has been found in the United States, it has predominated in travelers and imported foods (54).

Differences between Europe and the United States for critically important resistances are evident in isolates from poultry and poultry meat (Fig. 7). In the European Union, a very high proportion of *Salmonella* from broilers (average = 53.5%; n = 23 countries) was resistant to ciprofloxacin, ranging from 0% (Denmark and Ireland) to over 80% (Bulgaria, Hungary, and Slovenia). Similarly, ciprofloxacin resistance in broiler meats (average = 42.6%; n = 11 countries) ranged from 0% (Ireland) to 97.9% (Hungary). In meat from fattening turkeys, for which only three European Union countries reported, ciprofloxacin resistance rates varied from 6.9% in France to 74.2% in Germany and 91% in Hungary. Some of the ciprofloxacin-resistant isolates were not resistant to nalidixic acid, which is common for plasmid-mediated

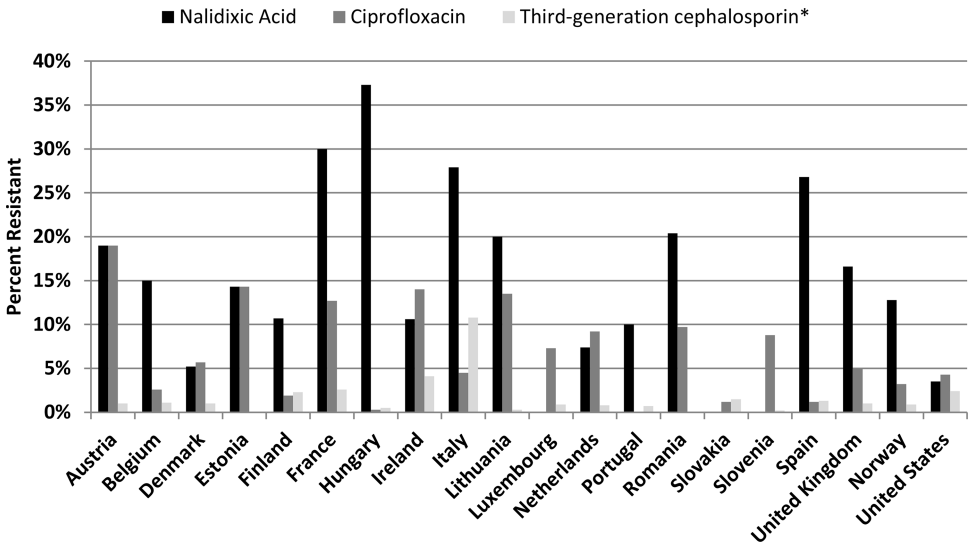


FIGURE 6 Resistance to quinolones and extended-spectrum cephalosporins in human isolates of *Salmonella* from select European Union countries, Norway, and the United States. Breakpoints used for interpreting MICs were derived from the EUCAST. Among critically important drugs (defined here as macrolides, fluoroquinolones, extended-spectrum cephalosporins, and carbapenems), azithromycin, meropenem, and colistin resistances were very rare and not reported in most countries. *Percentage based on reporting of either cefotaxime or ceftazidime resistance from the European Union or ceftriaxone from the United States.

quinolone-resistance (PMQR) mechanisms (55). In contrast, the U.S. data show that 1/143 retail chicken meat isolates in 2014 was nonsusceptible to ciprofloxacin (MIC = 0.125 μg/ml), and no other ciprofloxacin resistance was detected from any poultry sources.

Cephalosporin Resistance

Resistance to third-generation cephalosporins ranged from 0% to 10.8% in the European Union (26) and was present in 2.4% of U.S. human clinical isolates (31). Among broiler isolates, the European Union averaged 2.3% resistance to third-generation cephalosporin (cefotaxime), with resistance entirely absent from 14 of the 23 reporting countries. Resistance was higher in the United States, where ceftriaxone resistance was detected in 8.7% of broiler isolates collected at slaughter. Only Italy (27.3%) and Cyprus (8.9%) were higher. Among the 11 member states that monitor meat derived from broilers, rare resistance was reported from Belgium (3.7%) and Spain (0.8%), compared with NARMS data which showed 17.5% resistance in 2014 isolates, down from a peak of 37.9% in 2009 (Fig. 7).

CTX-M is just one of several ESBL enzymes that can confer resistance to extended-spectrum cephalosporins and most other beta-lactam antimicrobials. In 2014, EFSA reported that serovar Infantis comprised the highest proportion of broiler isolates exhibiting an ESBL phenotype (18/30, 60%), followed by serovar Paratyphi B L(+) tartrate positive (6/30, 20%). Member states did not report molecular characterization of isolates, so the determination of ESBL positivity is presumptive; however, other studies do show that CTX-M is the most prevalent ESBL in Europe (56), dominating over the TEM and SHV enzyme families. Though they predominate in the United States, AmpC enzymes, which confer resistance to most beta-lactams and beta-lactamase inhibitors, are less frequently encountered in Europe. Genes encoding AmpC enzymes are typically carried on large plasmids that harbor other antimicrobial resistance genes but can also be chromosomally located (57). Of the 18 broiler isolates with an AmpC phenotype, 9 (50%) were serovar Heidelberg. Eleven of the eighteen isolates were from the Netherlands.

Colistin Resistance

Following the discovery of transmissible colistin resistance mediated by the *mcr-1* gene in *E. coli* in China, (58) colistin-resistant *Salmonella* isolates were found in several countries (59). Colistin resistance was reported in The Netherlands (21.5%) and Denmark (5.9%) in 2014 (26). Overall, EFSA reports colistin resistance in *Salmonella* recovered from broilers (8.3%), laying hens (13.5%), and turkeys (1.8%) (Fig. 7). Most of these (72% of broilers and 80% of laying hens) were sero-

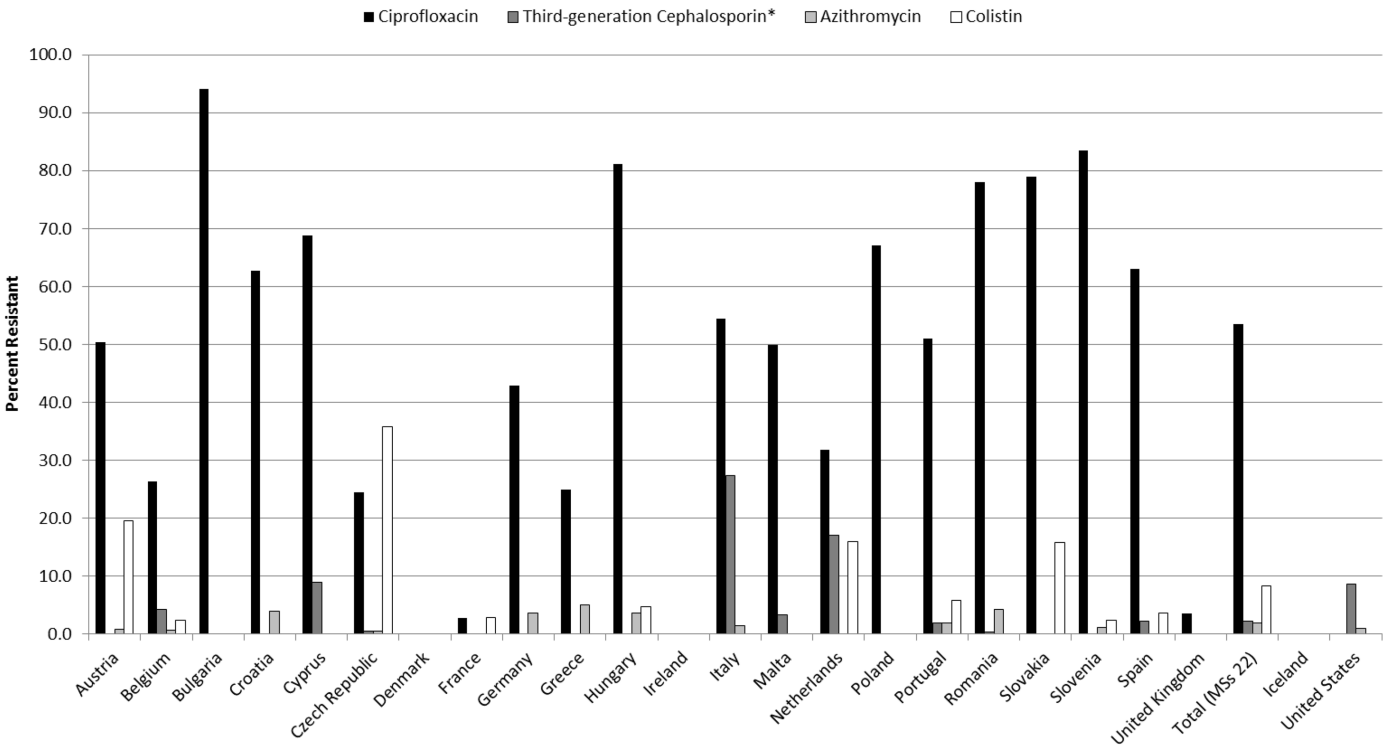


FIGURE 7 Resistance to quinolones, extended-spectrum cephalosporins, macrolides, and colistin in broiler strains of *Salmonella* from select European Union countries, Iceland, and the United States. Breakpoints used for interpreting MICs were derived from the EUCAST. Among critically important drugs (defined here as macrolides, fluoroquinolones, extended-spectrum cephalosporins, and carbapenems), azithromycin, meropenem, and colistin resistances were very rare and not reported in most countries. *Percentage based on reporting of either cefotaxime or ceftazidime resistance from the European Union or ceftriaxone from United States.

var Enteritidis, which may reflect a level of intrinsic resistance. Numerous separate studies have detected the *mcr-1* gene in food animal and human *Salmonella* strains from several European countries (60–62) and from human strains in the United States (63). Additionally, *mcr-1* has been found in multidrug-resistant isolates, raising the possibility of coselection (64). While colistin has been used routinely in livestock in several countries, it is not marketed or available for use in food animals in the United States. Therefore, NARMS does not test for phenotypic colistin resistance in routine surveillance. In addition, the *mcr-1* gene was not found in whole-genome sequence data on over 6,500 U.S. *Salmonella* genomes, mostly from retail meats (65).

Other Resistances

In regard to other critically important antibiotics, azithromycin resistance remains rare in *Salmonella* from both continents, ranging in detection from <0.1% of U.S. isolates to 1.7% of strains from Denmark. Similarly, azithromycin resistance in *Salmonella* from chickens and turkeys was identified but was not frequent (Fig. 7).

Very few cases of carbapenem-resistant *Salmonella* infections have been reported in humans in the European Union and the United States (66–69), and resistance has only occasionally been found in *Salmonella* and other Gram-negative bacteria from food animals (70, 71). The impact of these sporadic findings on public health is of paramount concern. While currently, this impact appears to be small, there is speculation that carbapenemase genes can transfer between humans, animals, and the environment and that the use of third-generation cephalosporins may maintain bacterial populations that express these genes (70). Regardless, as of the writing of this article, carbapenem resistance had not been reported in any retail meat or food isolates of *Salmonella*.

Tigecycline also is not licensed for veterinary use, is not targeted in NARMS, and is an optional drug for susceptibility testing in the European Union. The 2014

EFSA data show microbiological resistance to tigecycline in 9.3% of all *Salmonella* spp. from broilers and 8% from turkeys. Most tigecycline resistance was associated with serovar Infantis in poultry, and most resistant strains had MICs just above the ECOFF breakpoint at 2 or 4 μg/ml. Resistance to tigecycline in *Salmonella* is thought to be mediated by regulatory gene mutations leading to increased efflux.

RESISTANCE IN OTHER REGIONS

Few countries have ongoing surveillance of antimicrobial susceptibility in *Salmonella* from food-producing or companion animals. Most data on antimicrobial resistance in *Salmonella* is derived from cases of human clinical illness. Sustained integrated surveillance of the food chain exists to different degrees outside the European Union and North America. In South America, for example, the Colombian Integrated Program for Antimicrobial Resistance Surveillance (COIPARS) monitors *Salmonella* from poultry farms, slaughterhouses, and retail poultry for resistance (72). In Southeast Asia, some *Salmonella* resistance data are systematically collected and published in periodic summary reports. The Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) (73) began in 2000 and tracks antimicrobial resistance in food animal *Salmonella* throughout Japan.

In 2013, JVARM reported *Salmonella* resistance data collected from 2008 to 2011 on isolates from diagnostic samples from livestock and poultry infections (73). MICs were determined for a total of 688 *Salmonella* isolates: 301 from cattle, 236 from pigs, and 151 from chickens. Most were serovars Typhimurium (244 isolates, 35.5%), Choleraesuis (85 isolates, 12.4%), and Infantis (48 isolates, 7%).

JVARM reports that resistance rates against most antimicrobials studied were largely unchanged during the 2008 to 2011 sampling interval, with some slight declines (73). For compounds tested in both 2008 and 2011, resistances were as follows: tetracycline, 61% and 46%; ampicillin, 37% and 24%; kanamycin, 19% and 13%; chloramphenicol, 19% and 11%; nalidixic acid, 11% and 9%; gentamicin, 6% and 3%; cefazolin, 1.8% and 3.6%. Among critically important antimicrobial agents, resistance to cefotaxime was found in 1.7% of pig strains and 3% of chicken strains in 2010. In 2011, cefotaxime resistance was present in 10% of cattle isolates. Resistance to nalidixic acid was most common in pig isolates (16% to 21%). No resistance to colistin or ciprofloxacin was detected (73).

In 2012, JVARM added sampling of bacteria from animals at slaughter (12). The top serovars again were Typhimurium (37.5%), Choleraesuis (12.6%), and Infantis (6%). Between 2012 and 2013, a total of 365 *Salmonella* isolates (140 from cattle, 143 from pigs, and 82 from chickens) were subjected to antimicrobial susceptibility testing (12). Resistance was most frequent in *Salmonella* from cattle and swine for streptomycin (67.9% and 70.0% respectively), tetracycline (34.5% to 66.1% and 53.0% to 66.7%, respectively), and ampicillin (34.5% to 60.7% and 25.3% to 45.0%, respectively). Resistance to cefazolin and cefotaxime was rare in *Salmonella* isolates from cattle and chickens (0% to 8.9%). Resistance to colistin was found in a few isolates from pigs and chickens (0% to 8.9%). When comparing resistance between 2008 and 2009 with data from 2012 to 2013, overall resistance to most antimicrobials was stable in Japan except for nalidixic acid, which increased significantly (0.6% to 5.0%) in *Salmonella* from cattle, and kanamycin, tetracycline, and chloramphenicol resistance, which decreased significantly in isolates from pigs. Among the 212 *Salmonella* isolates tested between 2012 and 2013 from broilers at slaughter, resistance was common for streptomycin (77.7% to 84.7%), tetracycline (74.5% to 82.2%), ampicillin (22.9% to 31.9%), kanamycin (31.9% to 42.4%), and trimethoprim-sulfamethoxazole (31.9% to 48.3%). Resistance to nalidixic acid was high (29.8% to 19.5%), but resistance was infrequent for cefazolin (5.9% to 7.4%), cefotaxime (5.1% to 7.4%), and chloramphenicol (0% to 0.8%) (12). The JVARM program is planning to add retail meat testing in the near future.

China has one of the largest food animal production economies of any country. It is estimated that there are about 30 million annual cases of salmonellosis in China (74). One study estimated that between 1994 and 2005, about 22% of foodborne diseases in China were caused by *Salmonella* (75). While China works to implement an integrated national antimicrobial resistance monitoring system suited to its annual production volume, the status of resistance in *Salmonella* can be assessed only from a limited number of targeted studies, most of which target retail meats or human cases of salmonellosis or focus on specific resistance traits.

A 2005 survey by Yan et al. (76) examined raw retail samples of pork ($n = 45$), chicken ($n = 120$), beef ($n = 45$), mutton ($n = 45$), seafood ($n = 96$), and milk powder ($n = 36$) in nine cities in Hebei province in northern China. The most common serovars were Agona (13.6%), Senftenberg (9.9%), Meleagridis (8.6%), and Derby (8.6%). MDR was most common in serovars Derby,

Indiana, and Saintpaul. Among critical antimicrobial agents, nalidixic acid resistance was found in 31% of isolates, most commonly in isolates recovered from chicken (14/16, 74%). Ceftriaxone resistance was found in two (2.5%) isolates, and ciprofloxacin resistance was detected in eight (9.9%) isolates. Two years later, a study by Yang et al. (77) examined retail meats consisting of 515 chicken, 91 pork, 78 beef, and 80 lamb samples from nearby Shanxi Province in 2007 to 2008. The most common serovars were Enteritidis (31.5%), Typhimurium (13.4%), Shubra (10.0%), Indiana (9.7%), and Derby (9.5%). In addition to the common resistance to sulfamethoxazole (67%), trimethoprim/sulfamethoxazole (58%), and tetracycline (56%), a very high proportion of isolates were resistant to nalidixic acid (35%), ciprofloxacin (21%), and ceftriaxone (16%). Of particular interest, nearly all isolates of serovars Shubra (89%) and Indiana (88%) were resistant to more than antimicrobials, much higher than in other serovars (77).

A 2011 study by Bai et al. (78) examined resistance in *Salmonella* from large-scale chicken and swine abattoirs in Henan, China, where 128/283 (45.2%) chicken samples and 70/240 (29.2%) pig samples yielded *Salmonella* isolates for antimicrobial susceptibility. The most common resistance was to nalidixic acid (91%), followed by ampicillin (66%) and tetracycline (47%). Ciprofloxacin resistance was detected in 11 (8.6%) poultry strains, all of which were serovar Indiana and 6 of which also carried an ESBL. In the pig strains, the most common resistance was to tetracycline (67%), followed by nalidixic acid (64%) and chloramphenicol (60%). Ciprofloxacin resistance was found in 10% (7/70) of the isolates, 5 of which also carried an ESBL. This study shed light on the nature of MDR in serovar Indiana in China, where 11 of 198 isolates were coresistant to ciprofloxacin and cefotaxime and harbored $bla_{\text{CTX-M-65}}$ and *aac(6')-Ib-cr* genes, typically carried by plasmids and conferring resistance to the front-line drugs for salmonellosis. Another important study, by Lai et al., examined resistance in *Salmonella* in the Shandong province of China from 2009 to 2012. This survey showed a general rise in resistance during the sampling interval, with ciprofloxacin resistance appearing in 42% of salmonellae in 2012 (79).

Various later reports described the MDR traits found in serovar Indiana in China (77, 80, 81). In a study of ESBL-producing *Salmonella* from production environments in China, Zhang et al. (82) explored the genetic constituents of resistance in CTX-M-producing *Salmonella* isolates from chickens and pig facilities. They found that serovars Typhimurium and Indiana most commonly carried various transmissible CTX-M alleles, which in some cases was coupled to PMQR along with other resistance determinants. Serovar Indiana showed higher resistance levels than serovar Typhimurium. This combination of ESBL and PMQR in *Salmonella* has been noted in other studies from China (83, 84).

Despite that fact that *Salmonella* serovars and resistance can display distinct geographic characteristics, *Salmonella* clones have shown a remarkable ability to spread worldwide. This presents a perpetual public health issue concerning the international spread of new resistant clones as has been seen in the past. The striking example of global dissemination illustrated by MDR DT104 is a case in point. This strain spread to almost all countries and became a major driver of resistance reported in many regions (85–87). However, there has been a decrease in reported MDR DT104 in the past 10 years (41). Recent phylogenetic analysis indicates that the strain may have initially emerged in Europe in the early 1970s, followed by multiple transmission events between countries and hosts (88), likely related to the trade in breeding animals, human travel, and international sales of food products. The case of DT104 exemplifies the need to consider salmonellosis in the context of a global One Health paradigm, where resistance gaining ascendancy in animals can gain a foothold and spread around the world to become a major cause of resistant human infections.

ANTIMICROBIAL-RESISTANT *SALMONELLA* FROM COMPANION ANIMALS

Companion animals pose a public health risk for human salmonellosis in many countries (2, 89, 90). Although the prevalence of *Salmonella* in companion animals, especially in dogs and cats, varies greatly (ranging from 0% and 70% [2, 91, 92]), a number of serovars important to human health have been found in pet animals. Hoelzer (2) reported that among the top 20 most common human *Salmonella* serovars, 15 have been isolated from domestic dogs and cats, including Typhimurium, Enteritidis, Newport, Heidelberg, Montevideo, Muenchen, Oranienburg, Braederup, Agona, Infantis, Thompson, Paratpyhi B, Stanley, Tennessee, and Hadar. According to a 2006 annual report of the National Veterinary Services Laboratories of the U.S. Department of Agriculture (USDA), serovars Newport, Typhimurium, Montevideo, and Enteritidis were the most common serovars isolated from sick dogs and cats in the United States (93).

Because companion animals, especially dogs and cats, are considered family members, many antimicrobials that are important to human health have been used in veterinary practice to treat infections of dogs and cats, including category I antimicrobial agents, such as third/fourth-generation cephalosporins, fluoroquinolones, nitroimidazoles, penicillin beta-lactam inhibitors; category II agents, such as first/second-generation cephalosporins, penicillin, lincosamides, macrolides, and trimethoprim-sulfonamides; and category III agents, such as chloramphenicol, sulfonamides, and tetracycline (94–97). There is an increased concern about the rapid emergence and spread of MDR bacteria from pets to humans due to the extensive use of antimicrobial agents in these animals and their close contact with humans (98). Various MDR bacteria such as *E. coli*, *Salmonella*, *Staphylococcus*, *Pseudomonas*, *Streptococcus*, *Klebsiella*, *Proteus*, and *Enterococcus* have been isolated from diseased dogs and cats (95–100).

Currently, there is no surveillance program in the United States for antimicrobial resistance in bacteria from companion animals, and antimicrobial use in these animals is not routinely monitored. Therefore, no reliable data are available to assess the trend of antimicrobial resistance in bacteria isolated from companion animals. Several reports have shown that the increased use of antimicrobials to treat diseased dogs and cats is associated with the emergence of antimicrobial resistance in *Salmonella*. Among these reports are early U.S. NARMS Animal Arm reports (1997 to 2004), which feature data on antimicrobial resistance in *Salmonella* isolated from sick dogs and cats. The *Salmonella* isolates were submitted to the USDA National Veterinary Services Laboratory in Ames, IA, and tested for susceptibilities to 16 antimicrobials. *Salmonella* isolated from diseased dogs and cats had varied rates of resistance to different antimicrobials: ampicillin (24.6% to 58.8%), streptomycin (23.7% to 58.8%), tetracycline (22.7% to 53.8%), sulfamethoxazole (6.3% to 58.8%), and chloramphenicol (9.4% to 43.8%) (101). When surveillance first began in 1997, *Salmonella* isolates from sick dogs (n = 38) were susceptible to amoxicillin/clavulanic acid, ceftiofur, ceftriaxone, cephalothin, gentamicin, nalidixic acid, and trimethoprim/sulfamethoxazole, but 1 year later, isolates appeared resistant to all of these drugs except nalidixic acid. By 2002, resistance to amoxicillin/clavulanic reached 30.3%, ceftiofur 29.5%, ceftriaxone 29.5%, cephalothin 31.2%, and trimethoprim/sulfamethoxazole 12.3%. While dog isolates from 1997 were susceptible to most drugs tested, cat isolates (n = 28) from that same year were resistant to amoxicillin/clavulanic acid (10.7%) and ceftiofur, ceftriaxone, and cephalothin (10.7%) but were susceptible to gentamicin, nalidixic acid, and trimethoprim/sulfamethoxazole. All *Salmonella* isolates from sick dogs and cats from 1997 to 2004 were susceptible to amikacin and ciprofloxacin (Table 2). Overall, these NARMS data show that *Salmonella* isolates from sick dogs and cats have increased in their resistance to amoxicillin/clavulanic acid, ceftiofur, gentamicin, and nalidixic acid over the years, with nalidixic acid resistance first appearing in dog isolates in 2000 and in cat isolates in 2004. Analysis of all 5,709 *Salmonella* isolates from domestic food and companion animals collected for NARMS in 1997 and 1998 showed that extended-spectrum cephalosporin-resistance levels differed significantly among host animal species, with higher resistances found in isolates from turkeys, horses, cats, and dogs. All *Salmonella* isolates resistant to extended-spectrum cephalosporins carried the bla_{CMY} gene (102).

Other countries have also reported antimicrobial resistance in *Salmonella* from companion animals. A 2005 to 2006 Canadian survey of pet dog feces showed that 23.2% of the dogs carried *Salmonella*, and 20% of the *Salmonella* isolates were resistant to at least one antimicrobial, while 14% were resistant to multiple antimicrobials. The most common pattern, found in 13.3% of isolates, was resistance to amoxicillin/clavulanic acid, ampicillin, cefoxitin, ceftiofur, and ceftriaxone (103). Among the resistant *Salmonella* isolates, 79.2% were *S*. Heidelberg, 12.5% were *S*. Kentucky, and 8.3% were *S*. Indiana (103). A Belgian study by Van Immerseel et al. (104) showed that the prevalence of *Salmonella* in different cat groups (healthy house cats, group-housed cats, and sick cats) ranged from 0.36% to 51.4%. In this study, *S*. Typhimurium, *S*. Enteritidis, *S*. Bovismorbificans, and *S*. 4:i:– were identified. Most *S*. Typhimurium isolates from group-housed cats were resistant to ampicillin, chloramphenicol, and tetracycline; *S*. 4:i:– from diseased cats was resistant to ampicillin, chloramphenicol, sulfonamides, tetracycline, and trimethoprim/sulfamethoxazole. The resistance genes bla_{TEM}, *cat*, *sul*2, *tet*(A), and *dfrA* were identified in this *S*. 4:i:– isolate. Another study in the Netherlands found that 1% of diarrheic dogs were positive for *Salmonella* and that 53% of the *Salmonella* isolates were resistant to cephalexin, 37% to tetracycline, 14% to amoxicillin/clavulanic acid, 6% to trimethoprim/sulfonamides, and 4% to enrofloxacin (98).

S. Typhimurium DT104 with the ACSSuT resistance profile was first isolated in the United Kingdom from sea gulls in the mid-1980s, but not from humans until 1989. During the past 30 years, the strain has become preva-

TABLE 2 Percentage resistance of *Salmonella* isolated from clinical companion animals[a]

	1997		1998		1999		2000		2001[c]	2002		2003		2004	
Antimicrobials[b]	Dog *n* = 38	Cat *n* = 28	Dog *n* = 57	Cat *n* = 29	Dog *n* = 57	Cat *n* = 25	Dog *n* = 44	Cat *n* = 17	Dog *n* = 64	Dog *n* = 92	Cat *n* = 19	Dog *n* = 68	Cat *n* = 32	Dog *n* = 53	Cat *n* = 22
Amoxicillin/ clavulanic acid	0	10.7	7.0	6.9	10.5	8.0	13.6	17.6	29.7	38.0	10.5	20.6	3.1	26.4	18.2
Ampicillin	31.6	53.6	24.6	48.3	26.3	40.0	34.1	58.8	35.9	43.5	26.3	29.4	25.0	30.2	31.8
Apramycin	0	3.6	1.8	0	0	4.0	4.5	0	1.6						
Cefoxitin							11.4	17.6	29.7	37.0	10.5	20.6	3.1	22.6	13.6
Ceftiofur	0	10.7	7.0	6.9	8.8	8.0	11.4	17.6	29.7	37.0	10.5	20.6	3.1	22.6	13.6
Cephalothin	0	10.7	8.8	13.8	14.0	8.0	11.4	23.5	29.7	39.1	10.5	26.5	9.4		
Chloramphenicol	13.2	28.6	21.1	20.7	17.5	36.0	25.0	35.3	29.7	43.5	18.5	26.5	9.4	28.3	22.7
Gentamicin	0	0	10.5	6.9	1.8	12.0	6.8	11.8	9.4	5.4	5.3	17.6	3.1	1.9	9.1
Kanamycin	18.4	32.2	12.3	27.6	12.3	24.0	9.1	35.3	10.9	20.7	5.3	19.1	12.5	9.4	0
Nalidixic acid	0	0	0	0	0	0	4.5	0	1.6	15.2	0	4.4	0	5.7	4.5
Streptomycin	23.7	35.7	33.3	51.7	31.6	48.0	31.8	58.8	39.1	44.6	21.1	32.4	21.9	32.1	27.3
Sulfisoxazole	31.6	50	31.6	48.3	29.8	44.0	34.1	58.8	40.6	38.0	21.1	30.9	6.3	30.2	31.8
Tetracycline	36.8	57.1	31.6	44.8	33.3	48.0	31.8	52.9	45.3	45.7	26.3	38.2	25.0	30.2	22.7
Trimethoprim/ sulfamethoxazole	0	0	5.3	3.4	10.5	4.0	2.3	11.8	1.6	16.3	5.3	7.4	3.1	0	0

[a]The data were obtained from the animal arm of NARMS report (http://www.ars.usda.gov/Main/docs.htm?docid=18034). All isolates were obtained from the National Veterinary Services Laboratories.
[b]The resistant breakpoints were adopted from early CLSI guidelines as descripted in the NARMS 1997 to 2004 reports. All isolates were susceptible to amikacin, ceftriaxone, and ciprofloxacin (resistant breakpoints of 64 ug/ml and 4 ug/ml were used for ceftriaxone and ciprofloxacin, respectively).
[c]No cat isolates were tested in 2001.

lent in humans, food animals, and companion animals in many countries (98, 105). *S.* Typhimurium DT104 in humans significantly increased in England and Wales from 1991 to 1995, from 259 in 1990 to 2,873 in 1994 and 3,837 in 1995. Most of the human *S.* Typhimurium DT104 isolates had R-type ACSSuT. Further epidemiologic studies indicated that cats played an important role in the epidemic spread of this organism through many populations (106). A similar report from Scotland during the same time period showed that *S.* Typhimurium DT104 was isolated in 1% to 2% of cat fecal samples, and the cats shed the organism for at least 7 to 14 weeks (107). MDR Typhimurium var. Copenhagen DT104 also was isolated from horses, dogs, and cats in Germany (108). The dog and cat isolates had R-type ACSSuT. Two horse isolates showed additional resistance to florfenicol, gentamicin, kanamycin, and trimethoprim. In the United States, several human outbreaks of MDR *S.* Typhimurium DT104 with R-type ACSSuT or ACKSSuT were associated with small-animal veterinary clinics and animal shelters in Idaho, Minnesota, and Washington in 1999 to 2000. During these outbreaks, cats were confirmed as a source of infections (109, 110). A number of MDR *S.* Typhimurium outbreaks associated with pet rodents were also reported in the United States from 2003 to 2004 (111). The *S.* Typhimurium isolated from patients and pet hamsters showed the same R-type ACSSuT resistance profile and an indistinguishable pulsed field gel electrophoresis profile.

Multidrug-resistant *S.* Typhimurium with high-level fluoroquinolone resistance has been isolated from dogs and cats in Japan (112). These isolates had MICs of >256 μg/ml for nalidixic acid, 24 to 32 μg/ml for ciprofloxacin, and 24 to 32 μg/ml for norfloxacin. Two of the isolates had R-type ACSSuT in addition to resistance to nalidixic acid and ciprofloxacin (ACSSuTNCp). Another isolate from a dog showed additional resistance to trimethoprim/sulfamethoxazole, trimethoprim, and gentamicin (112).

Contaminated dog and cat foods are increasingly recognized as a risk factor for *Salmonella* infections in pets. Several surveys conducted in the United States and Canada showed that the prevalence of *Salmonella* in pet foods and treats ranged from 21% to 50% (2). A survey was conducted by the U.S. FDA to investigate the prevalence and antimicrobial resistance of *Salmonella* in dog treats sold in the U.S. market (113). Investigators found that 41% of animal-derived pet treats were contaminated with *Salmonella* and 26% of the isolates were resistant to tetracycline, 23% to streptomycin, 19% to sulfamethoxazole, 8% to chloramphenicol, and 8% to ampicillin. More than one third (36%) of the *Salmonella* isolates were resistant to at least one antimicrobial, and 13% of isolates displayed resistance to four or more antimicrobials. Two isolates were identified as *S.* Typhimurium DT104, with the characteristic R-type ACSSuT. One *S.* Typhimurium isolate was resistant to kanamycin in addition to the above five antimicrobials. One *S.* Brandenburg isolate was resistant to eight antimicrobials, including ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, gentamicin, apramycin, and cephalothin. Pet foods are also a risk factor for human infections. A multistate outbreak of tetracycline-resistant *Salmonella* serovar I 4,[5],12:i– was attributed to frozen feeder rodents. This outbreak caused over 500 clinical illnesses between 2008 and 2010 (114).

Salmonella has also been isolated from other types of pets, such as lizards, snakes, turtles, birds, and fish. Unfortunately, most reports do not contain antimicrobial resistance information for these isolates (115–117). Reptiles are considered a natural reservoir of *Salmonella* and constitute a significant source of human salmonellosis (2, 89, 90). The U.S. NARMS animal testing component reports from 1997 to 2004 feature antimicrobial susceptibility data on *Salmonella* isolated from exotic animals, including lizard, snakes, iguanas, and other reptiles and turtles. Those isolates showed low levels of resistance to most antimicrobials tested: a little over 10% resistance to ampicillin, streptomycin, sulfamethoxazole, and tetracycline but <10% resistance to amoxicillin/clavulanic acid, cefoxitin, ceftiofur, ceftriaxone, cephalothin, chloramphenicol, gentamicin, kanamycin, nalidixic acid, and trimethoprim/sulfamethoxazole. They were all susceptible to amikacin and ciprofloxacin (101).

These data indicate that companion animals are important reservoirs of *Salmonella* and that many *Salmonella* strains isolated from companion animals have developed resistance. Furthermore, some *Salmonella* isolates showed high resistance to medically important antimicrobials. To protect public health, there is a need to establish an antimicrobial resistance surveillance program for companion animals. There are ongoing discussions on how existing U.S. surveillance programs can fill this void.

ANTIMICROBIAL RESISTANCE GENES

To fully interpret the antimicrobial resistance data, it is important to characterize the underlying genetic mechanisms in bacteria from humans, animals, and food (16). Acquired resistance in *Salmonella* results from muta-

tions in chromosomal genes (both structural and regulatory sequences) and by acquisition of preformed, exogenous genes transmitted on mobile elements such as plasmids, integrons, and transposons. While both mech anisms can lead to rapid changes in bacterial populations, horizontal gene transfer is more consequential in the evolution of resistance in *Salmonella*, where a single plasmid conjugation event can confer resistance to seven or more agents (118). Following conjugative transfer, mobile DNA elements can be maintained as extrachromosomal plasmids or be incorporated wholly or partially into the chromosome as genomic islands. Detailed information on the genes and their context provides insights into the evolution of resistance and its sources.

THE IMPACT OF ROUTINE WHOLE-GENOME SEQUENCING

The DNA sequence information on the number and types of different resistance genes in *Salmonella* is growing at a very rapid rate, perhaps faster than for any other pathogen at this time. This is due to a push in the public health arena for early adoption of whole-genome sequencing (WGS) as a tool for food safety monitoring and outbreak investigations. Specialists in food safety have spearheaded initiatives to set data quality standards, provide proficiency testing, explore analytical approaches, and foster data sharing arrangements to deploy WGS globally to combat infectious diseases (119). As of this writing, the National Center for Biotechnology Information (NCBI) pathogen detection web portal (https://www.ncbi.nlm.nih.gov/pathogens/) lists *Salmonella* first among genera with completed genomic sequence (>100,000 genomes), followed by *E. coli/Shigella* (>37,000), *Listeria* (>16,000), and *Campylobacter* (>14,000), with the majority of each belonging to environmental (including food) isolates and with several hundred new genomes being uploaded weekly. Currently, most of the *Salmonella* genomes are generated by the U.S. FDA's GenomeTrakr program, which submitted an average of 2,400 *Salmonella* genomic sequences per month in 2015 (120). The unprecedented stream of WGS data on current strains of *Salmonella* will soon expand greatly when the CDC PulseNet program and other food safety monitoring systems worldwide shift away from pulsed field gel electrophoresis to WGS for routine surveillance and outbreak investigations. Based on past PusleNet testing volumes in the United States alone, this will add approximately 45,000 more *Salmonella* genomic sequences annually to public databases.

Beginning in test year 2014, the U.S. NARMS program began including WGS analysis of *Salmonella* in annual reports and uploading the raw WGS data to the NCBI. In addition, the WGS has been determined for all the historical *Salmonella* (currently over 6,500 isolates) recovered from retail meat sources since testing began in 2002. These genomes also are available in the public domain at NCBI and have accompanying susceptibility phenotypes (Bioproject number PRJNA290865). As WGS data accumulate in NARMS and other surveillance programs, methods for analyzing and reporting changes in the resistome will augment traditional susceptibility information (see Chapter 28). Studies show a very high correlation between the presence of known resistance genes and clinical resistance in *Salmonella* (121, 122) and other foodborne bacteria (123, 124). Thus, it is a simple process to predict resistance in *Salmonella* with a high degree of accuracy for most major drug classes based on WGS data alone. The NARMS web page (35) provides simple and powerful tools to explore the *Salmonella* resistome in U.S. national surveillance. Resistome Tracker (125) is one publicly available tool that provides visually informative displays of antibiotic resistance genes in *Salmonella*. Similar tools to quickly identify the resistance (and other) genes in sequence reads have been incorporated into automated analytical processes at NCBI (https://www.ncbi.nlm.nih.gov/pathogens/) or can be applied locally using software applications and resistance gene databases freely available on the web (e.g., ResFinder, CARD). The development of simple bioinformatics tools will enable a comprehensive, near-real-time monitoring of the resistome in *Salmonella* from foods, the environment, animals, and human infections that will be accessible by all interested parties.

After many years of surveillance and research, and especially with the large amounts of WGS data now being generated through surveillance programs, much is known about the specific alleles underlying resistance in different *Salmonella* serovars. Michael and Schwarz (126–128) have published three comprehensive reviews on this topic since 2006. Table 3 shows the WGS-based resistome of the U.S. *Salmonella* isolates that are deposited at NCBI. While the canon of resistance genes is changing very rapidly, the current status in *Salmonella* is summarized below.

Fluoroquinolone Resistance

Fluoroquinolone resistance has been well characterized in *Salmonella* and other bacterial pathogens. It has long been known that a combination of mutations in specific

TABLE 3 Acquired antimicrobial resistance genes in nontyphoidal *Salmonella*[a]

Antimicrobial class	Resistance genes
Rifampicin	*arr-2*, *arr-3*
Fluoroquinolone	*qnrA1*, *qnrA2*, *qnrB1*, *qnrB11*, *qnrB12*, *qnrB17*, *qnrB19*, *qnrB2*, *qnrB25*, *qnrB26*, *qnrB3*, *qnrB32*, *qnrB34*, *qnrB35*, *qnrB37*, *qnrB38*, *qnrB4*, *qnrB40*, *qnrB4*, *qnrB47*, *qnrB48*, *qnrB51*, *qnrB6*, *qnrB69*, *qnrB7*, *qnrB9*, *qnrD*, *qnrS1*, *qnrS2*, *qnrS3*, *qnrS4*, *qnrVC4*, *aac(6')Ib-cr*, *norA*, *oqxA*, *oqxB*, *qepA*
Aminoglycoside	*aac(2')-Ia*, *aac(2')-Ib*, *aac(2')-Ic*, *aac(3)-IIa*, *aac(3)-IId*, *aac(3)-IIe*, *aac(3)-IVa*, *aac(3)-Ia*, *aac(3)-Id*, *aac(3)-Ik*, *aac(3)-VIa*, *aac(6')-33*, *aac(6')-IIa*, *aac(6')-IIc*, *aac(6')-Ib*, *aac(6')-Ic*, *aac(6')-If*, *aac(6')-Ii*, *aac(6')-Im*, *aac(6')-Iz*, *aac(6')-aph(2")*, *aacA4*, *aadA1*, *aadA10*, *aadA11*, *aadA12*, *aadA13*, *aadA14*, *aadA15*, *aadA16*, *aadA17*, *aadA2*, *aadA22*, *aadA23*, *aadA24*, *aadA3*, *aadA4*, *aadA5*, *aadA6*, *aadA7*, *aadA8*, *aadA8b*, *aadB*, *aadD*, *ant(6)-Ia*, *aph(2")-Ib*, *aph(3')-III*, *aph(3')-IIa*, *aph(3')-IIb*, *aph(3')-IIc*, *aph(3')-Ia*, *aph(3')-Ic*, *aph(3')-Id*, *aph(3')-VIa*, *aph(4)-Ia*, *aph(6)-Ic*, *armA*, *rmtB*, *rmtE*, *spc*, *sph*, *strA*, *strB*
Beta-lactam (*bla* genes)	ACT-4, ACT-5, ACT-6, ACT-7, CARB-1, CARB-2, CARB-3, CARB-5, CARB-6, CEPH-A, CKO-1, CMG, CMY-15, CMY-16, CMY-17, CMY-18, CMY-2, CMY- 20, CMY-22, CMY-23, CMY-24, CMY-3, CMY-30, CMY-32, CMY-33, CMY-36, CMY-4, CMY-41, CMY-42, CMY-44, CMY-46, CMY-47, CMY-48, CMY-5, CMY-53, CMY-54, CMY-56, CMY-58, CMY-59, CMY-6, CMY-61, CMY-64, CMY-68 ,CMY-70, CMY-83, CMY-87, CMY-98, CTX-M-1, CTX-M-11, CTX-M-14, CTX-M-14b, CTX-M-15, CTX-M-2, CTX-M-24, CTX-M-27, CTX-M-3, CTX-M-5, CTX-M-55, CTX-M-65, CTX-M-8, CTX-M-9, DHA-1, DHA-2, DHA- 3, DHA-5, HERA-3, HERA-5, HERA-6, KPC-2, LEN1, LEN11, LEN9, MAL-1, MIR-3, MIR-5, MOR-1, MOR-2, NDM-1, OKP-B-12, OXA-1, OXA-10, OXA- 114, OXA-129, OXA-134, OXA-17, OXA-2, OXA-21, OXA-23, OXA-27, OXA-278, OXA-335, OXA-34, OXA-36, OXA-4, OXA-48, OXA-50, OXA-58, OXA-61, OXA-66, OXA-9, OXA-90, OXY-1-4, OXY-1-5, OXY-2, OXY-2-7, OXY-2-8, OXY-5-1, OXY-6, OXY-6-1, OXY-6-2, PAO, PER-2, SED1, SHV-1, SHV-100, SHV-105, SHV-11, SHV-12, SHV-122, SHV-129, SHV-2, SHV-25, SHV-28, SHV-39, SHV-45, SHV-99, TEM-1, TEM-10, TEM-104, TEM-105, TEM-106, TEM-116, TEM-12 ,TEM-123, TEM-124, TEM-126, TEM-127, TEM-135, TEM- 141 ,TEM-143, TEM-144, TEM-148, TEM-154, TEM-155, TEM-156, TEM-157, TEM-159, TEM-162, TEM-166, TEM-169, TEM-171, TEM-176, TEM-183, TEM-199, TEM-1A, TEM-1B, TEM-1C, TEM-1D, TEM-2 ,TEM-205, TEM-213, TEM-22, TEM-30, TEM-33, TEM-42, TEM-52, TEM-52B, TEM-57, TEM-59, TEM-63, TEM-67, TEM-7, TEM-70, TEM-76, TEM-79, TEM-90, TEM-95, VEB- 5, VIM-1, Z, ZEG-1
Beta-lactam (other)	*cepA-29*, *cfxA*, *cfxA3*, *cphA1*, *mecA*, *hugA*
Phenicol	*cat(pC221)*, *catA1*, *catA2*, *catA3*, *catB2*, *catB3*, *catB7*, *catQ*, *cml*, *cmlA1*, *fexA*, *floR*
Trimethoprim	*dfrA10*, *dfrA12*, *dfrA14*, *dfrA15*, *dfrA16*, *dfrA17*, *dfrA18*, *dfrA21*, *dfrA23*, *dfrA24*, *dfrA25*, *dfrA27*, *dfrA29*, *dfrA31*, *dfrA32*, *dfrA5*, *dfrA7*, *dfrA8*, *dfrB1*, *dfrB3*, *dfrB5*, *dfrG*
Macrolides/ lincosamides	*ere*(A), *erm*(42), *erm*(A), *erm*(B), *erm*(C), *erm*(D), *erm*(F), *erm*(G), *lnu*(A), *lnu*(C), *lnu*(F), *lsa*(A), *mef*(A), *mef*(B), *mph*(A), *mph*(B), *mph*(C), *mph*(E), *msr*(A), *msr*(C), *msr*(D), *msr*(E), *vga*(A)
Polymyxin	*mcr-1*
Sulfonamide	*sul1*, *sul2*, *sul3*
Tetracycline	*tet*(32), *tet*(38), *tet*(39), *tet*(41), *tet*(A), *tet*(B), *tet*(C), *tet*(D), *tet*(E), *tet*(G), *tet*(H), *tet*(J), *tet*(K), *tet*(L), *tet*(M), *tet*(O), *tet*(P), *tet*(Q), *tet*(W), *tet*(X)
Fosfomycin	*fosA*
Fusidic acid	*fusA*, *fusB3*

[a]NCBI last accessed 4 March 2017. Total number of genomes, N = 81,936: U.S., n = 38,725; non-U.S., n = 27,095; unknown origin, n = 16,116.

regions of the topoisomerase genes encoded by *gyrA*, *gyrB*, *parC*, and *parE* confers resistance to fluoroquinolones in *Salmonella* and other enterics. More recently, PMQR determinants have been identified including multiple alleles of *qnrA*, *qnrB*, *qnrD*, and *qnrS*, which function by protecting the topoisomerase targets from inhibition resulting in decreased fluoroquinolone susceptibility (129). A total of 32 *qnr* genes have been identified in *Salmonella* (Table 3). The *qnrB19* allele has emerged to become the predominant one in *Salmonella* in the United States, where it is present in 0.5% of resistant human strains. The quinolone efflux pump encoded by *qepA* (130, 131), a bifuntional enzyme encoded by *aac(60)-Ib-cr* (132), and the *oqxA* gene (133) are known also to affect quinolone MICs in *Salmonella* isolates. The PMQR gene, *oqxAB*, also mediates resistance to nalidixic acid and chloramphenicol, as well as olaquindox. It has been found in multiple serovars in China (134) and in *S.* Typhimurium strains in Europe (135). It appears to augment the development of fluoroquinolone resistance in *Salmonella* (136) and can be selected by florfenicol exposure (137).

Beta-lactamase Resistance

Resistance to the β-lactam class of compounds is conferred by at least 1,177 beta-lactamase genes. Michael and Schwarz report that 13 beta-lactamase families have been identified in *Salmonella*, including ACC, CMY, CTX-M, DHA, PER, PSE, SCO, SHV, and TEM, as well as 4 carbapenemases of types KPC, NDM, OXA, and VIM (126). To this list can be added FOX (in a U.S. clinical strain of serovar Newport), multiple HERA alleles

(prevalent in U.S. turkey isolates), and LAP (in a U.S. clinical strain of *S.* Saintpaul) (121), as well as HUGA and CEP (in United Kingdom clinical isolates), VEB (linked to *armA* in a U.S. clinical isolate), and ZEG (in a U.S. riverine isolate) (NCBI Bioproject number PRJNA290865). In the United States, the bla_{CMY} gene is present in most strains exhibiting resistance to extended-spectrum cephalosporins. Carbapenems are not used in U.S. agriculture, nor are they approved for food-producing animals in any country. No carbapenemases producing salmonellae have been found in NARMS testing, and two cases have been associated with travel (66, 69).

Macrolide Resistance

Among the critically important macrolide class of drugs, only azithromycin has been explored as a treatment for salmonellosis, mainly for *S.* Typhi. Resistance to azithromycin (MIC, ≥16 μg/ml) in NTS has been associated with the presence of *mphA* (121, 138) and *mphE* (unpublished data), although other macrolide resistance genes have been found in *Salmonella*, including *ere*(A), *lnu*(F), *mef*(B), and *msr*(E) (121, 126, 138). The full complement of known macrolide-lincosamide resistance genes in *Salmonella* is shown in Table 3.

Trimethoprim-Sulfonamide Resistance

Trimethoprim-sulfonamide has long been a recommended treatment for salmonellosis. At least 42 trimethoprim resistance genes have been identified in bacteria, 19 of which have been detected in *Salmonella*. These include *dfrA1*, *dfrA3*, *dfrA5*, *dfrA7*, *dfrA8*, *dfrA10*, *dfrA12*, *dfrA13*, *dfrA14*, *dfrA15*, *dfrA16*, *dfrA17*, *dfrA18*, *dfrA19*, *dfrA21*, *dfrA23*, *dfrA24*, *dfrA25*, *dfrA27*, *dfrA29*, *dfrA31*, and *dfrA32*, along with *dfrB1*, *dfrB3*, *dfrB5*, *dfrB6*, and *dfrG*. At least eight of these have been found in U.S. isolates (*dfrA1*, *dfrA5*, *dfrA7*, *dfrA8*, *dfrA12*, *dfrA14*, *dfrA15*, *dfrA17*, and *dfrA18*). Sulfonamide resistance mediated by *sul1*, *sul2*, and *sul3* are common in *Salmonella*.

Tetracycline Resistance

Among the 46 tetracycline resistance genes identified in bacteria to date (139), 20 have been reported in *Salmonella*. These include energy efflux pumps encoded by *tet*(A), *tet*(B), *tet*(C), *tet*(D), *tet*(E), *tet*(G), *tet*(H), *tet*(J), *tet*(K), and *tet*(L). The *tet*(A) and *tet*(B) genes are consistently the most common ones identified. Ribosomal protection mechanisms conferred by *tet*(M) and *tet*(O), as well as rare instances of *tet*(X), which encodes a tetracycline-degrading enzyme, have been found in U.S. isolates of *Salmonella* (121), usually along with other *tet* genes.

Aminoglycoside Resistance

Aminoglycoside resistance is coded by a wide range of alleles, which is complicated by the use of two different naming systems in the literature. More than 146 alleles have been found in bacteria. Resistance occurs by ribosomal modification, efflux, and enzymatic inactivation. Among these mechanisms, those based on enzymatic modification of the drug are most common in the clinical setting. These enzymes function through three general reactions resulting in phosphorylation, adenylation, or acelylation. The streptomycin phosphotransferases encoded by *strA* and *strB* (also designated *aph*) are the most common overall, present in about 27% of resistant U.S. strains (Table 3) (121). A total of 23 3′O-adenyltransferase (*aad*) genes have been identified in *Salmonella*, including *aadA1*, *aadA2*, *aadA3*, *aadA4*, *aadA5*, *aadA6*, *aadA7*, *aadA8*, *aadA8b*, *aadA10*, *aadA11*, *aadA12*, *aadA13*, *aadA14*, *aadA15*, *aadA16*, *aadA17*, *aadA21*, *aadA22*, *aadA23*, *aadA24*, *aadA26*, and *aadA27* (126). At least 10 of these have been found in U.S. isolates. Various forms of the *aac* gene family conferring gentamicin resistance are present in *Salmonella*. These include *aac(2′)-Ia*, *aac(2′)-Ib*, *aac(2′)-Ic*, *aac(3)-IIa*, *aac(3)-IId*, *aac(3)-IIe*, *aac(3)-Iva*, *aac(3)-Ia*, *aac(3)-Id*, *aac(3)-Ik*, *aac(3)-Via*, *aac(6′)-33*, *aac(6′)-IIa*, *aac(6′)-IIc*, *aac(6′)-Ib*, *aac(6′)-Ic*, *aac(6′)-If*, *aac(6′)-Ii*, *aac(6′)-Im*, *aac(6′)-Iz*, *aac(6′)-aph(2″)* (bifunctional enzyme conferring coresistance to low levels of fluoroquinolones), and *aacA4*.

At least six RNA methylase enzymes (ArmA, RmtA, RmtB, RmtC, RmtD, and NpmA) are known, which reside on mobile elements, often with other resistance genes, and confer very high levels of resistance to various aminoglycosides (140). Among the *Enterobacteriaceae*, ArmA is the most frequently identified, and both *armA* and *rmtC* have been found in *Salmonella* (141, 142). An interesting feature of aminoglycoside resistance revealed by WGS is the propensity for *Salmonella* to harbor numerous aminoglycoside resistance genes (and often other resistance gene classes) within a single bacterium (121). In fact, a small minority of aminoglycoside-resistant strains sequenced to date in the United States was found to carry just one resistance gene, and many carry five or more alleles. For example, one U.S. isolate of *S.* I 4,5,12:i:– has the aminoglycoside genotype *aph(3′)-Ic*, *aac(6′)-IIc*, *rmtE*, *aph(3′)-Ia*, *strA*, *strB*, *aph(3′)-Ic* along with unrelated resistance determinants coded by bla_{SHV-12}, bla_{TEM-1B}, *ere*(A), *anrB19*, *sul1*, *sul2*, *tet*(B), *tet*(A), and *tet*(M). The advantage of carrying so many resistance determinants all conferring resistance to the same drug class is not obvious but may partly reflect the fact that

aminoglycosides have been used longer than most drug classes in food animal production and that individual strains have adapted to accommodate the array of genes enriched by decades of selective pressures.

Phenicol Resistance

Chloramphenicol was the first broad-spectrum antibiotic to be used both orally and systemically, and it has been used around the world to treat *Salmonella* infections. Resistance in *Salmonella* is associated with the presence of chloramphenicol acetyltransferase genes encoded by a small number of variants of *catA* (*catA1*, *catA2*, *catA3*) and *catB* (*catB2*, *catB3*, *catB7*, *catB8*), as well as efflux by *cmlA* (*cmlA1*, *cmlA4*, *cmlA9*) and *floR*. Acetylation blocks binding of the drug to the ribosome target. The fluorine atom of florfenicol prevents acetylation, circumventing modification by the *cat* genes. Florfenicol efflux resistance also results from expression of *floR* and *fexA*.

Colistin Resistance

Colistin (polymyxin E) is now considered a reserve drug for treating MDR Gram-negative bacteria, including carbapenem-resistant strains. The first report of mobile colistin resistance gene *mcr-1* was reported in late 2015 in *E. coli* in China (58). Soon thereafter, several instances of *mcr-1* in *Salmonella* were reported (143–148). In the NCBI database, there are now at least five alleles of *mcr* designated *mcr-1* through *mcr-5*.

CONCLUDING REMARKS

The global challenge of antimicrobial resistance is being addressed on many fronts. The nature and magnitude of resistance in the agriculture/food sector is perhaps best evaluated by examining resistance in the principal foodborne bacterial pathogen *Salmonella*. The situations in North America and Europe, where surveillance data are extensive, provide a good backdrop to a global understanding of resistance in this important pathogen, including resistance data to measure the impact of drug use restrictions designed to limit resistance.

Overall, antimicrobial resistance surveillance data for *Salmonella* show common and unique features in different regions, where resistance to older drugs is generally highest and serovar differences impact overall trends. Differences in resistance by serovar often illustrate the most salient trends, as demonstrated by fluoroquinolone-resistant *S.* Kentucky in Europe or MDR *S.* Dublin in the United States.

The contribution of zoonotic infections from companion animals is not well understood or adequately addressed by surveillance programs. However, the relative ease with which the resistome of *Salmonella* can be evaluated by examination of WGS data heralds a new era in antimicrobial resistance monitoring where the resistance allele will become more prominent as the hazard under surveillance. As more is learned about the array of resistant strain types infecting humans, the range of sources causing human infections will become clearer, including the proportion of those arising from companion animals and other sources. Along with more detailed drug use information, this will lead to a better understanding of the sources and drivers of resistance and better interventions to protect public health.

ACKNOWLEDGEMENTS

We acknowledge our FDA colleagues Claudine Kabera and Chih-Hao Hsu for help with the tables and graphs, and John Graham and Adrienne Ivory for review of the manuscript.

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