II. NARMS 2011 Executive Report Summary

This section summarizes the major findings of the National Antimicrobial Resistance Monitoring System (NARMS) for bacteria collected from humans, retail meats and food animals in calendar year 2011. NARMS testing dates back to 1996 and generates a large, complex set of data each year. FDA, CDC, USDA and others inside and outside government make use of these data to assess risks associated with foodborne microbial hazards, particularly those carrying antibiotic resistance. To highlight the most important findings, we have summarized results from the testing of *Salmonella*, *Campylobacter*, and generic *E. coli* in this report.

This summary focuses on resistance to drugs that are considered clinically important to human medicine as well as multidrug resistance patterns (described as resistance to three or more antibiotic classes) and specific co-resistant phenotypes that have been linked to severe illness in humans. Because some serotypes of *Salmonella* are more commonly found in specific animal hosts and because resistance patterns are often associated with particular serotypes, the distribution of both selected serotypes and selected resistance patterns in human, retail meat, and food animal isolates are also provided to give important information on the epidemiology of antibiotic resistance. For more details on the monitoring results and other information related to the program, refer to other sections of this report and individual agency NARMS 2011 reports for human, retail meat, and food animal isolates.

A. Important Observations

Non-Typhoidal *Salmonella*

Why It Matters

- Non-typhoidal *Salmonella* (i.e., serotypes other than Typhi, Paratyphi A, Paratyphi B, and Paratyphi C) usually causes diarrhea, fever, and abdominal cramps. Some infections spread to the blood and can be life-threatening.
- According to the CDC, non-typhoidal *Salmonella* causes approximately 1.2 million illnesses, 23,000 hospitalizations, and 450 deaths each year in the United States. Direct medical costs are estimated to be $365 million annually (CDC, 2013).
- Physicians rely on antibiotics such as ceftriaxone and ciprofloxacin for treating patients with severe *Salmonella* infections.
- Non-typhoidal *Salmonella* can sometimes be resistant to important antibiotics such as:
    - ceftriaxone
    - quinolones (ciprofloxacin and nalidixic acid)
    - multiple classes of drugs
- CDC estimates that drug-resistant non-typhoidal *Salmonella* causes 100,000 infections and 40 deaths per year (CDC, 2013).

Important Resistance Trends in 2011

- No resistance was detected in 85% of non-typhoidal *Salmonella* isolates from humans.
- Ciprofloxacin and nalidixic acid resistance remained less than 3% from all sources.
- Multi-drug resistance (MDR) among human, slaughtered chicken and slaughtered swine *Salmonella* isolates was the lowest since testing began.
- MDR in *Salmonella* isolates from retail poultry meats generally increased, with slight fluctuations.
- MDR in serotype I 4,[5],12:i:- isolates from humans continued to increase; a similar trend was observed among isolates from chickens at slaughter.

Campylobacter

Why It Matters

- CDC estimates that *Campylobacter* causes 1.3 million infections, 13,000 hospitalizations, and 120 deaths each year in the United States (CDC, 2013).
- *Campylobacter* usually causes diarrhea (often bloody), fever, and abdominal cramps, and sometimes causes serious complications.
- Physicians rely on drugs like ciprofloxacin and azithromycin for treating patients with severe disease.
- *Campylobacter* can sometimes be resistant to important antibiotics such as:
    - ciprofloxacin
    - erythromycin
- CDC estimates that drug-resistant *Campylobacter* causes 310,000 infections and 28 deaths per year (CDC, 2013).

Important Resistance Trends in 2011

- Erythromycin resistance in *C. coli* isolates from human, retail chicken and slaughtered chicken are near the lowest levels seen in several years.
- Erythromycin and gentamicin resistance in *C. jejuni* isolates from humans and chicken sources has remained less than 4% since NARMS testing began.
- 55% of *C. jejuni* and 64% of *C. coli* isolated from human clinical samples were resistant to at least one antibiotic.
- Gentamicin resistance in *C. coli* from isolates from retail chicken meat and chickens at slaughter has continued to increase since 2007.
- 2005 was the last year that fluoroquinolone drug use was permitted in poultry. Since then, there has been some increase in ciprofloxacin (a type of fluoroquinolone) resistance in human isolates of *Campylobacter*, more for *C. coli* than for *C. jejuni*. The picture is mixed for chicken sources, but there has been no definite overall decrease in resistance in isolates from chicken sources.

Escherichia coli

Why It Matters

- Generic *Escherichia coli* is used by NARMS as an indicator organism to detect both emerging resistance patterns and specific resistance genes that could potentially be transferred to other pathogenic gram negative bacteria (e.g. *Salmonella*).

Important Resistance Trends in 2011

- Ceftriaxone resistance among *E. coli* isolates from retail chicken increased from 8% in 2002 to 13% in 2011; ground turkey isolates showed a larger increase in resistance during the same time period (from 1% to 10%). There was a similar trend in *Salmonella* isolates.
- Ceftriaxone resistance among isolates from slaughtered chicken increased from 6% in 2000 to 12% in 2010, and then dropped slightly to 9% in 2011. This was the first decline observed in the last 3 years.

B. Major Findings

Non-Typhoidal *Salmonella*

Every year, an estimated 1.2 million people get sick from non-typhoidal *Salmonella* infection in the United States. Of these, approximately 23,000 are hospitalized, and 450 die from their infections. Many of these infections are foodborne.

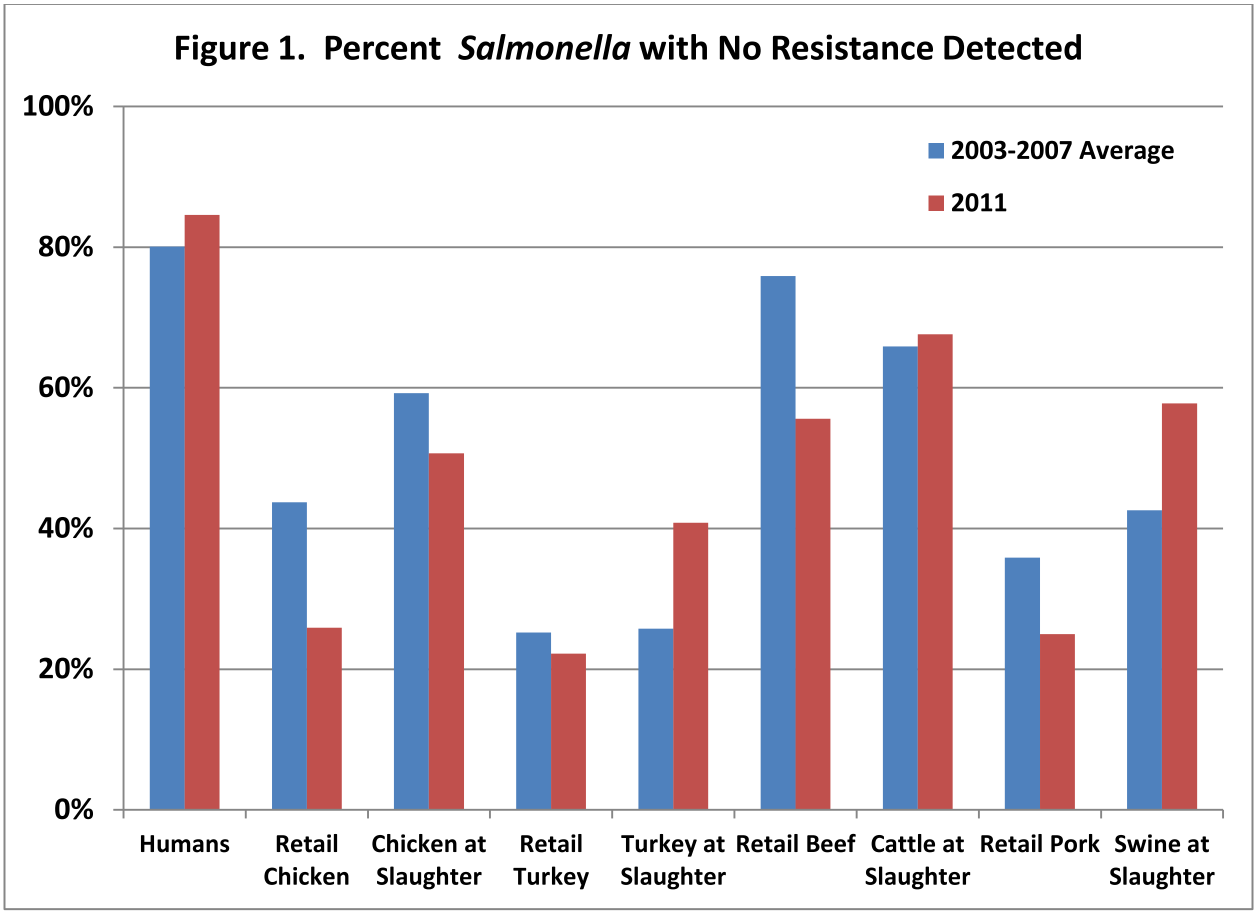
Number of Isolates Tested

A total of 3,725 non-typhoidal *Salmonella* isolates were tested, consisting of 2,344 from humans, 357 from retail meats, and 1,024 from healthy food animals at slaughter. *Salmonella* was isolated from 12% of ground turkey, 12% of retail chicken 2% of pork chops and 1% of ground beef samples.

No Resistance Detected

Figure 1 shows the proportion of *Salmonella* with no resistance to any of the agents tested in NARMS. Data from 2011 are compared with an average combined percentage from 2003-2007 to display general trends. In 2011, NARMS found that 85% of *Salmonella* isolated from humans had no resistance to any of the antibiotics tested, up from an average of 80% in previous years. Among retail poultry and poultry at slaughter, the percentage of isolates with no resistance declined in 2011, with the exception of turkeys at slaughter which increased (Figure 1.). Bovine isolates (cattle and retail beef) were more likely to have no resistance to any antibiotic tested, when compared with isolates from other food animal sources. Among retail beef, the percentage of isolates with no resistance also declined relative to the 5 year average, whereas in cattle at slaughter the percent of isolates with no resistance increased (Figure 1). Similarly the percentage of isolates with no resistance declined in retail pork and increased in swine at slaughter (Figure

1). Overall, the data present a mixed picture, with increases in resistance in some sampling frames and decreases in others.



Quinolones

In the United States, fluoroquinolones (like ciprofloxacin) are commonly used to treat severe *Salmonella* infections. Fluoroquinolones are also approved for the treatment and control of certain respiratory infections in swine and cattle, but these agents are not currently approved for use in poultry (Animal Drugs @ FDA). In addition, extra-label use of fluoroquinolones in food-producing animals is expressly prohibited. During its 16-year history, NARMS has found *Salmonella* resistance to ciprofloxacin to be less than 0.5% among human isolates, less than 3% among retail meat isolates and less than 1% among animals at slaughter.

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NARMS monitors *Salmonella* for resistance to nalidixic acid, as an early indicator of emerging resistance to fluoroquinolones (Crump et al., 2003). Nalidixic acid resistance among *Salmonella* from humans, chickens (retail and slaughter), cattle and swine has remained less than 3% since testing began, and nalidixic acid resistance among *Salmonella* from turkeys (retail and slaughter) has remained less than 3% since 2004. NARMS has observed a steady increase in nalidixic acid resistance among *Salmonella* serotype Enteritidis isolates from humans (from as low as 0.9% in 1996 to 7.2% in 2011), but many of these infections were likely acquired during foreign travel. No increase has been seen among the domestic retail meat or food animal isolates tested by NARMS.

Cephems

Ceftriaxone is considered a critically important drug for treating severe *Salmonella* infections (Pueges and Miller, 2010). A closely related cephalosporin antibiotic, ceftiofur, is licensed for use in food animal production (Animal Drugs@FDA). Historically, the same molecular mechanism has been responsible for resistance to both ceftriaxone and ceftiofur in NARMS isolates. Long term analysis of resistance trends revealed that overall ceftriaxone resistance has increased in *Salmonella* isolates from all sources since testing began. These and other data led to the April 2012 cephalosporin order which prohibits certain unapproved uses of cephalosporin drugs in cattle, swine, chickens and turkeys (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm285704.htm). In 2011, NARMS observed a continued rise in ceftriaxone resistance among retail ground turkey isolates (from a low of 5% in 2008 to 22% in 2011) and among certain serotypes in cattle (from a recent low of 59% in 2009 to 77% in 2011 among isolates of serotype Newport). NARMS will continue to monitor these trends over time.

Continued rise in ceftriaxone resistance led to the April 2012 cephalosporin order of prohibition which prohibits certain unapproved uses of cephalosporin drugs in cattle, swine, chickens and turkeys.

Beginning in 2011, all *Salmonella* isolates that were resistant to ceftriaxone and/or ceftiofur were screened for resistance genes and tested for susceptibility to other related drugs including imipenem (a carbapenem) and cefepime (a cephem). In 2011, one human isolate was resistant to both imipenem and cefepime; molecular characterization of this isolate revealed the presence of a gene encoding a New Delhi metallo-β-lactamase (NDM) carbapenemase. The NDM carbapenemase gene induces resistance to carbapenems, which have become antibiotics of last resort for treating human infections caused by gram-negative bacteria. Carbapenems are not approved for use in food animal production (AnimalDrugs@FDA). None of the *Salmonella* isolates from any animal source that underwent this extra testing showed imipenem resistance or carbapenemase production.

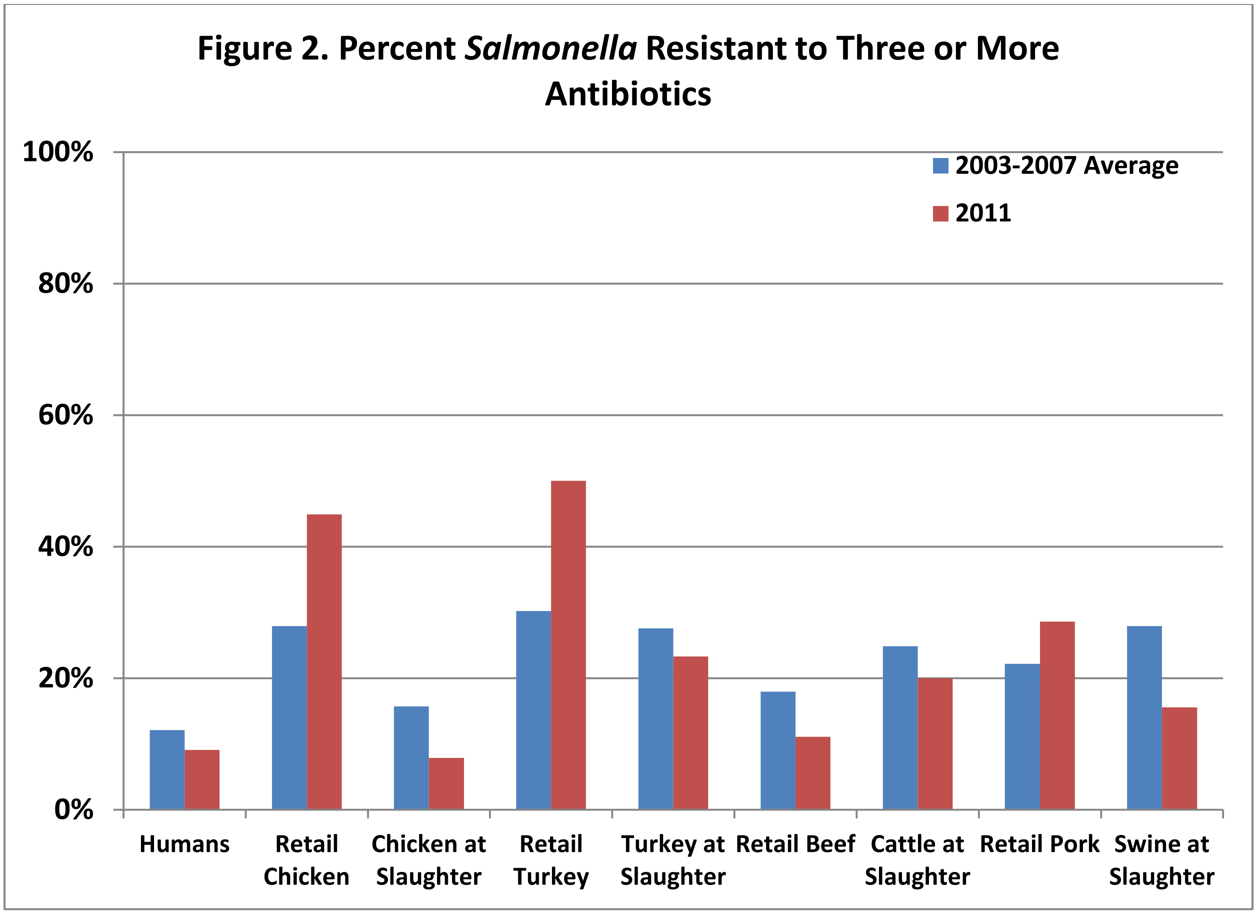
In 2011, one human-source *Salmonella* isolate was resistant to both imipenem and cefepime and found to have a carbapenemase gene. None of the *Salmonella* isolates tested for imipenem resistance from any domestic animal source showed resistance or carbapenemase production.

Multidrug Resistance

MDR *Salmonella* among human (9%), slaughtered chicken (8%) and slaughtered swine (16%) isolates in 2011 were the lowest since testing began.

NARMS defines multi-drug resistance (MDR) as resistance to 3 or more classes of antibiotics. Some studies have shown that some patients with MDR *Salmonella* infections tend to have more severe clinical disease (Krueger, et al. 2014; Varma et al., 2005a; Varma et al, 2005b). It is important to note that some of the drugs included in the MDR resistance patterns are not used to treat *Salmonella* infections.

As described above for Figure 1, general trends in MDR were compared using a 5-year average (2003-2007) as a baseline. The prevalence of MDR in *Salmonella* isolated from humans declined from 12.1% in 2003-2007 to 9.1% in 2011. MDR increased among ground turkey isolates from a baseline of 30% to 50% in 2011. In retail chicken isolates, MDR increased from a baseline of 28% to 45% in 2011, after peaking at 49% in 2009. When the 2011 resistance levels from retail turkey and retail chicken are compared to the 5 year baseline, this increase appears to be the largest among the 9 sources tested in NARMS (Figure 2). MDR *Salmonella* among human (9% in 2011), slaughtered chicken (8%), and slaughtered swine (16%) isolates have declined in 2011 to the lowest levels since testing began. MDR resistance among retail beef and slaughtered turkeys also has declined when compared with the 5 year average (Figure 2). Overall, the data present a mixed picture, with more decreases than increases in MDR among the nine sources, but the magnitude of the increases being larger than the magnitude of the decreases.



Generally, some *Salmonella* serotypes (e.g. Typhimurium) are more likely to display MDR than others (e.g. Enteritidis) (Medalla, et al., 2013). However, increasing or decreasing trends in resistance are worth noting. MDR increased from 6% in 2007 to 27% in 2011 among serotype I 4,[5],12:i:- isolates from humans; a similar trend was observed among isolates from chickens at slaughter; from 7% in 2008 to 33% in 2011. Among serotype Heidelberg isolates from humans, MDR increased from 13% in 2006 to 34% in 2010, declining slightly to 30% in 2011. This increase was also observed among isolates from ground turkey and turkeys at slaughter; from 40% and 44% in 2006 to 93% and 60% in 2011, respectively.

MDR increased from 6% in 2007 to 27% in 2011 among serotype I 4,[5],12:i:- isolates from humans, and among serotype Heidelberg isolates, MDR increased from 13% in 2006 to 34% in 2010, declining slightly to 30% in 2011.

An important MDR pattern in *Salmonella* is the combined resistance to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline (ACSSuT). This pattern, often indicative of a specific *Salmonella* Typhimurium designated DT104, has been tracked in NARMS for many years. NARMS observed a decline in ACSSuT resistance among human, swine, and cattle isolates and continued resistance levels of less than 5% among isolates from retail poultry and poultry at slaughter. Specifically:

- the percentage of human isolates resistant to at least ACSSuT declined for the fourth year in a row to 4%, the lowest since testing began in 1996.
- 4% of isolates from swine at slaughter were resistant, a continued decline from the peak resistance of 13% in 2009.
- resistance in isolates from cattle was 13%, a slight decline from 2010 (19%).

NARMS observed a decline in ACSSuT resistance, among *Salmonella* isolates from humans, swine, and cattle and continued resistance levels of less than 5% among isolates from retail poultry and poultry at slaughter.

In some isolates, the ACSSuT pattern is linked with resistance to additional beta-lactam drugs, including ceftiofur, ceftriaxone, amoxicillin-clavulanic acid, and cefoxitin. Over the years, NARMS has detected this phenotype (abbreviated as MDR-AmpC or ACSSuTAuCx) among *Salmonella* from all types of sources tested. This highly resistant pattern typically indicates the presence of a particularly large multidrug resistance plasmid (Zhao et al., 2009, Sjölund-Karlsson et al.,2010, Glenn et al., 2013). ACSSuTAuCx resistance has remained below 5% among isolates from humans, retail poultry, poultry at slaughter, and swine since testing began. ACSSuTAuCx resistance is generally higher among cattle isolates at slaughter.

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Campylobacter

CDC estimates that *Campylobacter* causes over 1.3 million illnesses and 120 deaths in the United States each year. Most people who become ill from *Campylobacter* get diarrhea, abdominal pain and fever. *Campylobacter jejuni* (or *C. jejuni*) and *Campylobacter coli* (*C. coli*) cause most campylobacteriosis. Many of these infections are foodborne, and poultry is a major source of human *C. jejuni* infections.

Number of Isolates Tested

A total of 2,634 *C. jejuni* and *C. coli* isolates were tested, including 1,423 from humans, 634 from retail poultry (603 from retail chicken and 31 from ground turkey), and 577 from chickens at slaughter. All sources except retail ground turkey yielded higher proportion of *C. jejuni* than *C. coli*.

No Resistance Detected

In 2011, 45% of *C. jejuni* and 36% of *C. coli* isolated from humans had no resistance to any of the antibiotic tested in NARMS. In retail and slaughtered chicken isolates, approximately 42-48% of *C. jejuni* and *C. coli* isolates had no resistance to any of the antibiotics tested. There are no clear upward or downward trends observed among the human and poultry isolates.

In 2011, 45% of *C. jejuni* and 36% of *C. coli* from human isolates had no resistance to any of the antibiotics tested in NARMS. There are no clear upward or downward trends observed among the human and poultry isolates.

Macrolides

The macrolide erythromycin is considered a drug of choice for the treatment of severe campylobacteriosis in humans (Allos and Blaser, 2010). Macrolides are also authorized for use in food-producing animals (Animal Drugs @ FDA). In 2011, NARMS observed a drop in erythromycin resistance among *C. coli* from human, retail chicken and slaughtered chicken to the lowest levels seen in several years (4%, 5%, and 3 %, respectively). Like other global surveillance programs, NARMS finds that *C. coli* isolates from human and chicken sources are more likely to be resistant to erythromycin than *C. jejuni*, which causes most campylobacteriosis. In the United States, *C. jejuni* from human and chicken sources has exhibited erythromycin resistance rates of less than 4% since NARMS testing began.

In 2011, erythromycin resistance in *C. Coli* from human, retail chicken and slaughtered chicken was at the lowest levels in several years (3%, 5%, and 3%, respectively). *C. jejuni* from humans and chicken sources has exhibited erythromycin resistance rate of less than 4% since NARMS testing began.

Quinolones

The fluoroquinolone ciprofloxacin is an alternative therapy for treating campylobacteriosis in humans (Allos and Blaser, 2010). FDA approvals of two veterinary fluoroquinolones, sarafloxacin and enrofloxacin, were withdrawn in April 2001 and September 2005, respectively, due to resistance concerns. See
http://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm
Since 2005, NARMS has observed no consistent decreases in ciprofloxacin resistance among *C. jejuni* and *C. coli* isolates from humans or chicken sources. Many human cases of fluoroquinolone-resistant campylobacteriosis are linked to foreign travel (Kassenberg et al, 2004).

Since 2005, NARMS has observed no consistent decreases in ciprofloxacin resistance among *C. jejuni* and *C. coli* isolates from humans or chicken sources.

Aminoglycosides

Gentamicin is categorized as a highly important antibiotic for human medical therapy according to criteria outlined in FDA's guidance on evaluating the safety of new animal drugs (FDA, 2003). It is used in humans for the treatment of severe infections, including some *Campylobacter* infections (Allos and Blaser, 2010). Gentamicin is also used in food animals, including poultry, where it is approved for injection in day-old chicks and 1- to 3-day old turkey poults for the prevention of early mortality associated with bacterial infections (Animal Drugs @ FDA). Gentamicin is also approved as a dip for turkey eggs. Gentamicin resistance among *C. jejuni* isolates from humans, retail chicken meat and chickens at slaughter was less than 2% between 2007 and 2011. However, during that same period, gentamicin resistance among *C. coli* increased from 0% to 12% among isolates from humans, 1% to 18% among isolates from retail chicken meat, and 1% to 6% among isolates form chickens at slaughter. The cause of this surge in resistance is unknown.

Gentamicin resistance among *C. jejuni* isolates from humans, retail chicken meat and chickens at slaughter was less than 1% in 2011. However, between 2007 and 2011, gentamicin resistance among *C. coli* increased from 0% to 12% among isolates from humans, 1% to 18% among isolates from retail chicken meat and 1% to 6% among isolates from chickens at slaughter

Escherichia coli

In NARMS, generic *E. coli* are used as indicator organisms to detect both emerging resistance patterns and specific resistance genes that could potentially be transferred to other pathogenic gram negative bacteria (e.g. *Salmonella*). NARMS tests *E. coli* isolates for resistance to the same critically important antibiotics that are used in *Salmonella* testing. The NARMS Executive Report includes data on generic *E. coli* isolated from retail meat and slaughtered chickens only. NARMS does not conduct ongoing surveillance of resistance among generic *E. coli* isolated from healthy humans.

Number of Isolates Tested

In 2011, a total 1,684 *E. coli* were tested, consisting of 341 from retail chickens, 368 from ground turkey, 215 from ground beef, 146 from pork chops, and 614 from slaughtered chickens.

No Resistance Detected

Among isolates from retail meat and chickens at slaughter, ground beef and pork chops were more likely to have no resistance to any of the antibiotics tested (80% and 52%, respectively).

Poultry isolates were less likely to have no resistance (25% of isolates from retail chicken, 13% from ground turkey, and 21% from slaughtered chickens).

Quinolones

As with *Salmonella*, *E. coli* isolates from retail meat and slaughtered chickens have shown little resistance to ciprofloxacin (less than 1%). Additionally, nalidixic acid resistance has remained low; resistance among isolates from all animal sources was less than 3% in 2011.

Cephems

Ceftriaxone resistance among *E. coli* isolates from retail chicken increased from 8% in 2002 to 13% in 2011; ground turkey isolates showed a larger increase during the same time period (from 1% to 10%). This trend was similar in *Salmonella*. Resistance among isolates from slaughtered chicken also increased from 6% in 2000 to 12% in 2010 but dropped slightly to 9% in 2011. This was the first decline seen in the last 3 years. In 2011, ceftriaxone resistance among *E. coli* isolated from ground beef and pork chops was low (0.5% and 0%, respectively). Resistance from these sources has remained less than 7% since testing began.

Ceftriaxone resistance among *E. coli* isolates from retail chicken increased from 8% in 2002 to 13% in 2011; ground turkey isolates showed a larger increase during the same time period (from 1% to 10%). This trend was similar in *Salmonella*. Resistance among isolates from slaughtered chicken also increased from 6% in 2000 to 12% in 2010, but dropped slightly to 9% in 2011. This was the first decline seen in the last 3 years.

Resistance to Other beta-lactams

E. coli isolates were also screened for resistance to other drugs, including carbapenems. None of the *E. coli* isolates from retail meat or slaughtered chickens displayed phenotypes indicative of carbapenemase production.

Multidrug Resistance

Among *E. coli* isolates from retail poultry, NARMS observed a general increase in MDR among retail chicken (35% in 2002 to 38% in 2011) and ground turkey (53% to 64% during the same period), with some fluctuations. As with the *Salmonella* data, MDR among retail cattle (6%) and swine (9%) were at the lowest levels since testing began.

Summary

The NARMS program captures a wide spectrum of resistance findings. For some important drug/ organism/ source combinations, declining or low (or no) resistance was observed in 2011. For other combinations NARMS observed increases in resistance. All of these data are carefully considered when evaluating and monitoring the safety of antibiotics used in the food-producing animals.

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