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Review Article

National Antimicrobial Resistance Monitoring System: Two Decades of Advancing Public Health Through Integrated Surveillance of Antimicrobial Resistance

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Abstract

Drug-resistant bacterial infections pose a serious and growing public health threat globally. In this review, we describe the role of the National Antimicrobial Resistance Monitoring System (NARMS) in providing data that help address the resistance problem and show how such a program can have broad positive impacts on public health. NARMS was formed two decades ago to help assess the consequences to human health arising from the use of antimicrobial drugs in food animal production in the United States. A collaboration among the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration, the United States Department of Agriculture, and state and local health departments, NARMS uses an integrated ''One Health'' approach to monitor antimicrobial resistance in enteric bacteria from humans, retail meat, and food animals. NARMS has adapted to changing needs and threats by expanding surveillance catchment areas, examining new isolate sources, adding bacteria, adjusting sampling schemes, and modifying antimicrobial agents tested. NARMS data are not only essential for ensuring that antimicrobial drugs approved for food animals are used in ways that are safe for human health but they also help address broader food safety priorities. NARMS surveillance, applied research studies, and outbreak isolate testing provide data on the emergence of drug-resistant enteric bacteria; genetic mechanisms underlying resistance; movement of bacterial populations among humans, food, and food animals; and sources and outcomes of resistant and susceptible infections. These data can be used to guide and evaluate the impact of science-based policies, regulatory actions, antimicrobial stewardship initiatives, and other public health efforts aimed at preserving drug effectiveness, improving patient outcomes, and preventing infections. Many improvements have been made to NARMS over time and the program will continue to adapt to address emerging resistance threats, changes in clinical diagnostic practices, and new technologies, such as whole genome sequencing.

Keywords: antimicrobial resistance, public health, surveillance, foodborne disease, NARMS, One Health

Introduction

Drug-resistant bacterial infections pose a serious and growing public health threat globally. In the United States, they are estimated to cause more than 2 million illnesses and 23,000 deaths each year. The Centers for Disease Control and Prevention (CDC) estimates that more than 400,000 of these illnesses are caused by drug-resistant nontyphoidal *Salmonella* and *Campylobacter*, zoonotic enteric pathogens that are transmitted commonly through food (CDC, 2013).

Antimicrobial use is the single most important factor driving increases in antimicrobial resistance (CDC, 2013). Vital to the health of humans and animals, antimicrobial drugs are used for treatment and sometimes prophylaxis of

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bacterial infections. In agricultural settings, they are used to prevent, control, and treat infections, as well as to enhance growth and feed efficiency in herds and flocks of animals raised for food (Gilbert *et al.*, 2007). Antimicrobial use selects for drug-resistant bacteria, which can spread among and between humans and animals and disseminate through contaminated food, water, and environments (Marshall and Levy, 2011; Finley *et al.*, 2013). Monitoring antimicrobial resistance is critical for identifying emerging resistance and for developing and assessing the effectiveness of mitigation strategies (WHO, 2012, 2013; CDC, 2013).

The National Antimicrobial Resistance Monitoring System (NARMS) monitors antimicrobial resistance in bacteria transmitted commonly through food in the United States. In this review, we describe the role of NARMS in providing data that help address the resistance problem and show how such a program can have broad positive impacts on public health that extend beyond resistance surveillance and research.

NARMS Is Designed for Public Health

NARMS was established in 1996 after an expert panel convened by the U.S. Food and Drug Administration (FDA) in 1994 recommended establishing a national surveillance system to monitor resistance among selected enteric bacteria of animals that can cause disease in humans (FDA, 1994a, 1994b, 2000). NARMS is a collaborative effort of three federal agencies, CDC, FDA, and the United States Department of Agriculture (USDA), as well as state and local health departments in all 50 states. It is designed to help assess the consequences to human health arising from the use of antimicrobial drugs in food animal production with a view toward mitigation. Table 1 summarizes core NARMS activities along with key contributions and impacts of the program.

The main goals of NARMS are to:

(1) Monitor trends in antimicrobial resistance among enteric bacteria from humans, retail meats, and animals;
(2) Disseminate timely information on antimicrobial resistance in pathogenic and commensal organisms to stakeholders in the United States and abroad to promote interventions that reduce resistance among foodborne bacteria;
(3) Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance; and
(4) Provide data that assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals (FDA, 2012a).

NARMS advances food safety and public health in various ways. NARMS provides data on the emergence of drug-resistant enteric bacteria; movement of bacterial populations among humans, food animals, and other sources; genetic mechanisms underlying resistance; and risk factors for and outcomes of resistant infections. These data are essential for ensuring that antimicrobial drugs approved for food animals are used in ways that are safe for human health and for implementing and evaluating the impact of interventions designed to limit the spread of resistance. They also guide antimicrobial stewardship efforts aimed at preserving drug effectiveness and improving patient outcomes and they inform estimates of the burden of illness which may be used for allocating resources.

Although NARMS is focused on resistance, data from the program also help address broader food safety priorities. NARMS provides data on the prevalence of pathogens in food categories under surveillance, types of strains predominant in different foods, and shifts in serotypes among *Salmonella* isolates from food and animals over time. NARMS *Salmonella* isolates from food and animals are subtyped using pulsed-field gel electrophoresis (PFGE). To assist with outbreak investigations, PFGE patterns of those isolates are uploaded to PulseNet, the molecular subtyping network for foodborne disease surveillance. NARMS also has a network of experts and a sampling and testing program that can serve as a platform for targeted studies to characterize emerging microbial hazards in food and food animals.

Monitoring Resistance Using an Integrated "One Health" Approach

One Health approach

The One Health concept is based on the recognition that the health of people, animals, and the environment are interconnected and that a collaborative approach is needed to ensure optimal health for each (Lammie and Hughes, 2016). Because antimicrobial resistance is a complex and multifaceted problem that affects humans, animals, and the environment, detecting and controlling it requires a holistic and integrated ''One Health'' approach (White House, 2014a, 2015; WHO/FAO/OIE, 2015; Lammie and Hughes, 2016). Consistent with this approach, the World Health Organization (WHO) recommends integrated surveillance of resistance in foodborne bacteria, which is described 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'' (WHO, 2013). The NARMS program uses such an approach to surveillance, advancing both food safety and animal health by serving as an important tool in the decision-making process for antimicrobial drug approval and use in food animals.

NARMS surveillance

NARMS surveillance focuses on two major zoonotic bacterial causes of foodborne illness in the United States, nontyphoidal *Salmonella* and *Campylobacter*. Food animal and retail meat surveillance also include *Enterococcus* and *Escherichia coli*, common intestinal bacteria that can serve as reservoirs of resistance genes and indicators of selection pressures in Gram-positive and Gram-negative bacteria, respectively (WHO, 2013). In addition, CDC uses the NARMS human surveillance platform for monitoring resistance in *E. coli* O157, *Vibrio*, and the nonzoonotic enteric pathogens, *Shigella* and typhoidal *Salmonella*. Long-standing collaborations among epidemiologists, microbiologists, and others from public health and agriculture agencies have been essential for the program's effectiveness.

The main components of NARMS surveillance are summarized in this section and in Table 2. NARMS has adapted to changing needs and threats by expanding the catchment areas for surveillance, examining new isolate sources, adding bacteria under surveillance, adjusting sampling schemes, and modifying antimicrobial agents tested over the years. More detailed descriptions of NARMS sampling and testing

Table 1. Major Activities, Contributions, and Impact of the National Antimicrobial Resistance Monitoring System

NARMS activities	*Contributions of NARMS program and scientists*	*Examples of impact*
Surveillance of resistance	• Collects and cultures retail meat and animal samples • Performs antimicrobial susceptibility testing for isolates from humans, retail meats, and food animals • Detects emerging resistance threats and monitors resistance trends • Provides data for policy and regulatory actions, risk assessments, burden of illness estimates, and research	• Detected emerging resistance in *Campylobacter* (fluoroquinolones), nontyphoidal *Salmonella* (cephalosporins), and *Shigella* (azithromycin) • Provided data for a quantitative risk assessment on the human health impact of resistant *Campylobacter* in chicken • Provided data to estimate the number of resistant *Salmonella* and *Campylobacter* infections in humans • Provided data to support withdrawing approvals for fluoroquinolone drugs for poultry and prohibiting certain extralabel uses of cephalosporins in food animals
Outbreak isolate testing and investigation	• Conducts and rapidly reports results of antimicrobial susceptibility testing of outbreak isolates • Provides consultations on antimicrobial susceptibility profiles associated with different sources to aid outbreak investigations • Uploads PFGE patterns to PulseNet for most NARMS *Salmonella* isolates from retail meats and food animals • Shares retail meat package information with outbreak investigators	• Enables public health agencies to prioritize investigation of outbreaks caused by drug-resistant pathogens • Helped identify ground turkey and chicken as vehicles of two multistate *Salmonella* Heidelberg outbreaks, resulting in industry changes and recall of more than 36 million pounds of product • Informs analyses that attribute resistant and susceptible infections to specific sources (foods, animals, etc.)
Epidemiologic and microbiologic research	• Identifies risk factors for and clinical impact of resistant enteric infections through collaborations with FoodNet • Helps attribute enteric infections to specific sources • Performs molecular and genetic testing to better understand mechanisms and sources of resistant enteric infections • Develops and validates methods to measure resistance and characterize enteric bacteria • Maintains a repository of resistant enteric bacteria (isolate bank) for use by government, academic, and industry researchers	• Showed quinolone resistance is associated with foreign travel (*Salmonella* Enteritidis and *Campylobacter*) and poultry consumption outside the home (*Campylobacter*) • Found resistance is associated with bloodstream infections and hospitalizations (*Salmonella*) and prolonged diarrhea (*Campylobacter*) • Developed the first standardized *in vitro* antimicrobial susceptibility testing method for *Campylobacter* • Identifies genes and mobile genetic elements responsible for resistance • Facilitates drug and diagnostic test development through maintenance of an isolate bank
Communication and outreach	• Publishes online surveillance reports, interactive graphs, and downloadable, isolate-level data • Reports results of human isolates testing to submitting health agencies • Collaborates with foreign scientists on investigations and studies • Provides consultations and trainings for international surveillance and outbreak investigation activities • Serves on international advisory groups and task forces • Shares data with standard-setting organizations to establish or revise interpretive criteria	• Provides data that inform antimicrobial stewardship efforts, clinical practice, and industry policy and practices • Consults on establishment of surveillance programs in other countries • Provided data that supported lowering CLSI fluoroquinolone breakpoints for *Salmonella* and establishing azithromycin epidemiological cutoff values for *Shigella*

CLSI, Clinical and Laboratory Standards Institute; FoodNet, Foodborne Diseases Active Surveillance Network; NARMS, National Antimicrobial Resistance Monitoring System; PFGE, pulsed-field gel electrophoresis.

Table 2. Summary of Surveillance Conducted by the National Antimicrobial Resistance Monitoring System, 2016

	Humans	*Retail meats*	*Food animals*
Federal agency leading surveillance	CDC	FDA	USDA
Geographic coverage	Nationwide[a]	14 States[b]	Nationwide
Sample source(s)	Ill humans	Chicken parts, ground turkey, ground beef, and pork chops from grocery stores	Chickens, turkeys, and cattle (carcass, ground, cecal) and swine (carcass, cecal) from slaughter plants[c]
Year testing began	1996	2002	1997[c]
Bacteria tested (year testing began)	Non-Typhi *Salmonella* (1996) *Campylobacter* (1997) *Escherichia coli* O157 (1996) *Salmonella* Typhi (1999) *Shigella* (1999) *Vibrio* (2009)	Nontyphoidal *Salmonella* (2002) *Campylobacter* (2002)[d] *E. coli* (2002)[f] *Enterococcus* (2002)[f]	Nontyphoidal *Salmonella* (1997)[c] *Campylobacter* (1998)[c,e] *E. coli* (2000)[c] *Enterococcus* (2003)[c]

[a]NARMS human surveillance has been nationwide since 2003 except for *Campylobacter*, which is limited to selected laboratories in the 10 sites (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and selected counties in California, Colorado, and New York) participating in FoodNet.

[b]The 14 states participating in NARMS retail meat surveillance since 2013 are the 10 FoodNet sites (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and selected counties in California, Colorado, and New York) and Louisiana, Missouri, Pennsylvania, and Washington.

[c]Carcass (chickens, turkeys, cattle, swine) and ground product (chicken, turkey, beef) sampling began in 1997 for nontyphoidal *Salmonella*. Testing of animal samples for *Campylobacter*, *E. coli*, and *Enterococcus* was limited to chicken carcasses until cecal sampling was added in 2013.

[d]Due to low isolation of *Campylobacter* from retail ground beef and pork chops, testing of retail meats for *Campylobacter* has been limited to chicken parts and ground turkey since 2008.

[e]Isolation of *Campylobacter* from chickens at slaughter began in 1998, but nalidixic acid susceptibility and cephalothin resistance were used by USDA as identification criteria for *Campylobacter jejuni/coli* until mid-2001, which likely resulted in underreporting of quinolone-resistant *Campylobacter* during this time.

[f]Testing of retail meats for *E. coli* and *Enterococcus* is conducted at selected sites (Georgia, Oregon, Maryland, and Tennessee).

CDC, Centers for Disease Control and Prevention; FDA, U.S. Food and Drug Administration; FoodNet, Foodborne Diseases Active Surveillance Network; NARMS, National Antimicrobial Resistance Monitoring System; USDA, United States Department of Agriculture.

methods are available in NARMS surveillance reports (CDC, 2016; FDA, 2016a).

NARMS human surveillance began at CDC in 1996 with 14 public health departments and was nationwide by 2003. NARMS now tests a nationwide sample of clinical isolates of *Salmonella*, *E. coli* O157, *Shigella*, and *Vibrio*, as well as a sample of *Campylobacter* isolates from states participating in Foodborne Diseases Active Surveillance Network (FoodNet). (FoodNet is a collaborative program among CDC, 10 state health departments, USDA's Food Safety and Inspection Service [FSIS], and FDA that conducts active, population-based surveillance for laboratory-confirmed infections transmitted commonly through food) (Henao, 2015).

NARMS food animal surveillance began at USDA in 1997 with testing of carcass and ground product samples collected for regulatory purposes at slaughter and processing plants. Because shifts in FSIS priorities and industry performance often result in sampling changes, and samples are affected by interventions in the plants, trend analyses and interspecies comparisons are challenging. To overcome these limitations, sampling of cecal contents from slaughtered chickens, turkeys, cattle (dairy and beef), and swine (market hogs and sows) was added to NARMS in 2013. Cecal samples, which more directly reflect the intestinal microflora of animals just before processing, are cultured for *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococcus*.

NARMS retail meat surveillance began at FDA in 2002. Since 2013, all 10 FoodNet sites and 4 other state public health departments have participated. Retail chicken parts, ground turkey, ground beef, and pork chops are cultured for *Salmonella*, *E. coli* (selected sites), and *Enterococcus* (selected sites); chicken parts and ground turkey are also cultured for *Campylobacter*. During 2015 and 2016, sites doubled the number of samples collected each month. Five new sites will begin retail meat testing in 2017.

Detecting emerging resistance and assessing trends

Using an integrated surveillance approach, NARMS has been able to detect emerging resistance threats and assess trends in resistance in the food chain. For example, NARMS found increasing resistance to ceftriaxone, a cephalosporin used to treat invasive salmonellosis, among nontyphoidal *Salmonella* from humans, food animals at slaughter, and retail meats, with resistance varying by serotype and source (FDA, 2012b, 2013a, 2015a; Medalla *et al.*, 2013; CDC, 2016). A NARMS analysis found that ceftriaxone resistance among *Salmonella* serotypes Newport, Typhimurium, and Heidelberg isolates from humans strongly correlates with ceftriaxone resistance in isolates from ground beef, cattle, and poultry (chickens and turkeys), respectively, findings that support other evidence that specific food animals are

important reservoirs of ceftriaxone-resistant *Salmonella* (Iwamoto *et al.*, 2017).

Other types of emerging resistance detected by NARMS and linked to food animal sources include ciprofloxacin and gentamicin resistance in *Campylobacter* (Gupta *et al.*, 2004; Kassenborg *et al.*, 2004; Zhao *et al.*, 2015a) and specific multidrug resistance phenotypes in *Salmonella* serotypes Dublin, Newport, and I 4,[5],12:i:- (Gupta *et al.*, 2003; Varma *et al.*, 2006; FDA, 2013a, 2015a, 2016a; CDC, 2015a).

Outbreak Isolate Testing and Investigation

NARMS provides data that aid the investigation of outbreaks. PFGE patterns for *Salmonella* isolates from NARMS retail meat and animal testing are uploaded to PulseNet; when one of these patterns matches that of an outbreak strain, the meat product or meat derived from that food animal class can be investigated as a possible source of the outbreak.

CDC NARMS began antimicrobial susceptibility testing of human clinical isolates from enteric disease outbreaks in the early 2000s and has expanded this testing over the past 5 years. CDC prioritizes testing of outbreak isolates, reports results to investigators immediately, and includes test results in outbreak summaries posted online. This testing allows CDC and health departments to prioritize investigation of outbreaks involving resistant pathogens. Moreover, because resistance profiles vary by source, they can provide important clues about the source of ongoing outbreaks. CDC also links NARMS outbreak isolate results with data in the National Outbreak Reporting System (NORS) to glean information about food and animal sources of resistant and susceptible human infections.

The value of NARMS in outbreak investigation was highlighted during two multistate *Salmonella* Heidelberg outbreaks. In 2011, PFGE patterns of multidrug-resistant *Salmonella* Heidelberg from human cases matched those from two ground turkey samples purchased as part of routine NARMS surveillance during the time of the outbreak. These matches led public health officials to target ground turkey as a possible source. In this outbreak, a total of 136 illnesses were reported from 34 states and the outbreak resulted in a recall of over 36 million pounds of ground turkey products, one of the largest FSIS Class I recalls in history (CDC, 2011; Routh *et al.*, 2015). Because NARMS retail meat sites collect information from retail meat packages, NARMS data have also been used to link outbreak strains with the particular brands(s) involved. In 2012, when another multistate outbreak of *Salmonella* Heidelberg infections was investigated, NARMS retail chicken surveillance isolates matched the outbreak strain isolated from humans and were found to be significantly associated with a single poultry producer (Grinnell *et al.*, 2013).

NARMS Research—Characterizing Resistant Infections and Bacteria

NARMS epidemiologists and microbiologists conduct research to characterize resistant infections and bacteria and better understand the spread of resistance. NARMS laboratories and databases house specimens and data for more than 200,000 bacterial strains from humans, food animals, and retail meats, making the program a natural platform for applied research.

Epidemiologic research

Epidemiologic studies using NARMS data have advanced our understanding of resistance trends, risk factors for acquiring resistant enteric infections, and clinical outcomes of resistant infections. Many studies have linked data from NARMS with data from FoodNet or other surveillance systems, enhancing the value of each system. The studies have informed policy changes, regulatory actions, and recommendations aimed at reducing resistant infections.

Collaborations among scientists from NARMS and other public health surveillance systems have helped to identify risk factors for human infections with antimicrobial-resistant pathogens. A FoodNet-NARMS case–control study identified international travel and eating poultry at a commercial establishment as risk factors for acquiring fluoroquinolone-resistant *Campylobacter* infections (Kassenborg *et al.*, 2004). Another case–control study and a field investigation found that consuming uncooked ground beef, consuming runny scrambled eggs or omelets prepared in the home, taking an antimicrobial agent to which the strain is resistant, and exposure to a dairy farm were risk factors for infection with multidrug-resistant *Salmonella* Newport, which emerged and became widely disseminated in humans and cattle in the United States in the late 1990s and early 2000s (Gupta *et al.*, 2003; FDA, 2006; Varma *et al.*, 2006). Antimicrobial use in humans was found to be a risk factor for infection with multidrug-resistant *Salmonella* Typhimurium in another study (Glynn *et al.*, 2004).

Greene *et al.* (2008) found no significant differences in region of residence or age distribution when patients with multidrug-resistant and pansusceptible Typhimurium infections were compared. However, the authors found that multidrug-resistant Newport infections were less commonly found in the South census region and in children <2 years of age compared with pansusceptible Newport infections. Using linked data from NARMS and FoodNet, O'Donnell *et al.* (2014) found that the majority of patients with nalidixic acid–resistant *Salmonella* Enteritidis infections had recently travelled to another country, critical information for evaluating the consequences of domestic quinolone use and for identifying possible sources of domestically acquired quinolone-resistant infections, such as imported seafood and spices (Bae *et al.*, 2016). Phenotypic susceptibility data from NARMS and PFGE data from PulseNet and NARMS have been used in microbial subtyping models for *Salmonella* Hadar to attribute most human infections to turkey (Vieira *et al.*, 2016).

Studies linking NARMS data with FoodNet and outbreak data suggest that resistant infections have worse clinical outcomes than susceptible ones. Antimicrobial-resistant *Salmonella* infections were found to be associated with more bloodstream infections, hospitalizations, and hospitalizations that were longer than 3 d compared with pansusceptible infections (Varma *et al.*, 2005a, 2005b; Krueger *et al.*, 2014). Nelson *et al.* (2004) found that ciprofloxacin-resistant *Campylobacter* infections result in a longer duration of diarrhea than ciprofloxacin-susceptible infections.

Microbiologic research

NARMS has played a central role in developing and expanding methods to measure and understand the context of antimicrobial resistance. NARMS contributions to phenotypic susceptibility testing methods include development of

the first standardized *in vitro* antimicrobial susceptibility testing methods for *Campylobacter* (McDermott *et al.*, 2004, 2005), publication of a pefloxacin disk diffusion method for *Salmonella* fluoroquinolone resistance screening (Skov *et al.*, 2015), and definition of the susceptible azithromycin minimum inhibitory concentration (MIC) range for *Shigella* (Howie *et al.*, 2010). NARMS microbiologists have also developed polymerase chain reaction- and microarray-based methods for molecular detection of resistance (Gay *et al.*, 2006; Jackson *et al.*, 2007; Frye *et al.*, 2010) and demonstrated that whole genome sequencing (WGS) can predict antimicrobial resistance with a high degree of accuracy in nontyphoidal *Salmonella* (McDermott *et al.*, 2016), *Campylobacter* (Zhao *et al.*, 2015b), and *E. coli* (Tyson *et al.*, 2015).

NARMS scientists and collaborators have used NARMS isolates for bacterial genetic studies that have improved our understanding of the nature, behavior, and sources of antimicrobial resistance and the genes, mobile DNA elements, and mutations responsible for resistance. These studies have helped to characterize emerging cephalosporin, aminoglycoside, and quinolone resistance genes in *Salmonella* (Zhao *et al.*, 2001; Folster *et al.*, 2009; Sjölund-Karlsson *et al.*, 2009), aminoglycoside resistance genes in *Campylobacter* (Zhao *et al.*, 2015a), and macrolide resistance genes in *Shigella* (Howie *et al.*, 2010). Early studies identified the genes responsible for high-level gentamicin and streptogramin resistance in *Enterococcus* (Jackson *et al.*, 2005, 2007, 2008). NARMS scientists have also identified the contribution of efflux pumps and mutations in topoisomerase and 23s ribosomal RNA (rRNA) genes to resistance or decreased susceptibility to fluoroquinolones and macrolides (Ge *et al.*, 2005; Whichard *et al.*, 2007; Ladely *et al.*, 2009).

Comparing strains of enteric bacteria from the different sampling sources is a key component of NARMS integrated surveillance. NARMS studies have shown that certain bacterial subtypes, antimicrobial resistance, and mobile elements (e.g., plasmids and integrons) tend to come from particular food animal sources, some of which are also associated with human disease. For example, NARMS researchers found that the increase in cephalosporin resistance in *Salmonella* Heidelberg in 2009 was due to the dissemination of plasmid-encoded bla_{CMY} genes, and the identification of identical sequence types for IncI1 plasmids in strains from humans, chicken carcasses, and retail chicken breasts supported other evidence that chicken products are an important source of human infection (Folster *et al.*, 2012). A study of cephalosporin-resistant *Salmonella* Typhimurium found that while most isolates had plasmid-encoded bla_{CMY} genes, nearly all isolates from chicken sources had IncI1-bla_{CMY} plasmids, while those from cattle had IncA/C-bla_{CMY} plasmids (Folster *et al.*, 2014), information that can help identify sources of human Typhimurium infections and refine targeted interventions aimed at limiting resistance at its source.

Molecular studies of NARMS isolates from different sources can also provide information about how resistance spreads. For example, when NARMS detected emerging multidrug resistance in *Salmonella* Albert isolates from humans, retail ground turkey, and turkeys at slaughter, molecular characterization of isolates and their plasmids suggested that resistance was the result of horizontal gene transfer rather than clonal expansion (Folster *et al.*, 2015).

On-farm pilot studies

In 2011, USDA's Agricultural Research Service developed pilot studies (e.g., Schmidt *et al.*, 2015; Webb *et al.*, 2016) with federal, academic, and industry scientists to explore the prospects for a preharvest surveillance component in NARMS. The studies determined the logistical and technical challenges associated with gathering data and isolates from major food animal species and production types. The studies investigated the prevalence of resistance in select dairy cattle, beef cattle, swine, broiler, and turkey farms, providing data on the relationship between on-farm and slaughter plant resistance profiles. They also explored the feasibility of obtaining species-specific antimicrobial use data on farms, data that are urgently needed to understand the drivers of resistance in agricultural settings and assess the impact of antimicrobial stewardship initiatives and other interventions (CDC, 2013; WHO, 2013, 2014; White House, 2015). Knowledge gained and lessons learned from these pilot studies are assisting in the development of new food animal surveillance programs focused on the collection of data on antimicrobial use and resistance in animal agriculture.

Data for Regulatory Actions and Policy

Data from NARMS are used for regulatory and policy decision-making related to antimicrobial drug approvals, as well as the implementation and assessment of public health interventions. Figure 1 shows a timeline with selected NARMS activities and related policy and regulatory actions.

NARMS data are used in preapproval risk assessments for food animal antimicrobial drugs, where human food safety implications must be considered (Gilbert *et al.*, 2007). FDA recommends a qualitative risk assessment approach outlined in FDA guidance No. 152 (FDA, 2003). In this type of safety review, resistance trends and types, along with information on genetic mechanisms of resistance and pathogen prevalence, are evaluated taking into consideration the importance of the antimicrobial class for use in human medicine; the process for ranking antimicrobial classes is described in Appendix A of the guidance (FDA, 2003). NARMS data are also used to devise risk management strategies that limit resistance associated with the use of FDA-approved antimicrobial products in food animals (FDA, 2003).

Antimicrobial resistance data are also vital to FDA's postapproval safety monitoring efforts and policies. For example, NARMS data informed FDA policy on the use, in food animals, of fluoroquinolones and cephalosporins, two critically important antimicrobial classes for human health (FDA, 2003; Collignon *et al.*, 2016). Data from NARMS and other sources showed a rise in fluoroquinolone resistance among *Campylobacter* from humans following the approvals of sarafloxacin (1995) and enrofloxacin (1996) in poultry, that poultry was a source of human infection, and that fluoroquinolone-resistant *Campylobacter* infections in humans were a health hazard (Smith *et al.*, 1999; FDA, 2000, 2005a; Gupta *et al.*, 2004; Kassenborg *et al.*, 2004; Nelson *et al.*, 2004). FDA used these data to conduct a quantitative risk assessment (FDA, 2001a) and to support the withdrawal of the poultry approvals for sarafloxacin in 2001 and, after a lengthy hearing, enrofloxacin in 2005 (FDA, 2001b, 2005a, 2005b; Nelson *et al.*, 2007). Withdrawal of the poultry fluoroquinolone approvals marked the first time animal drugs

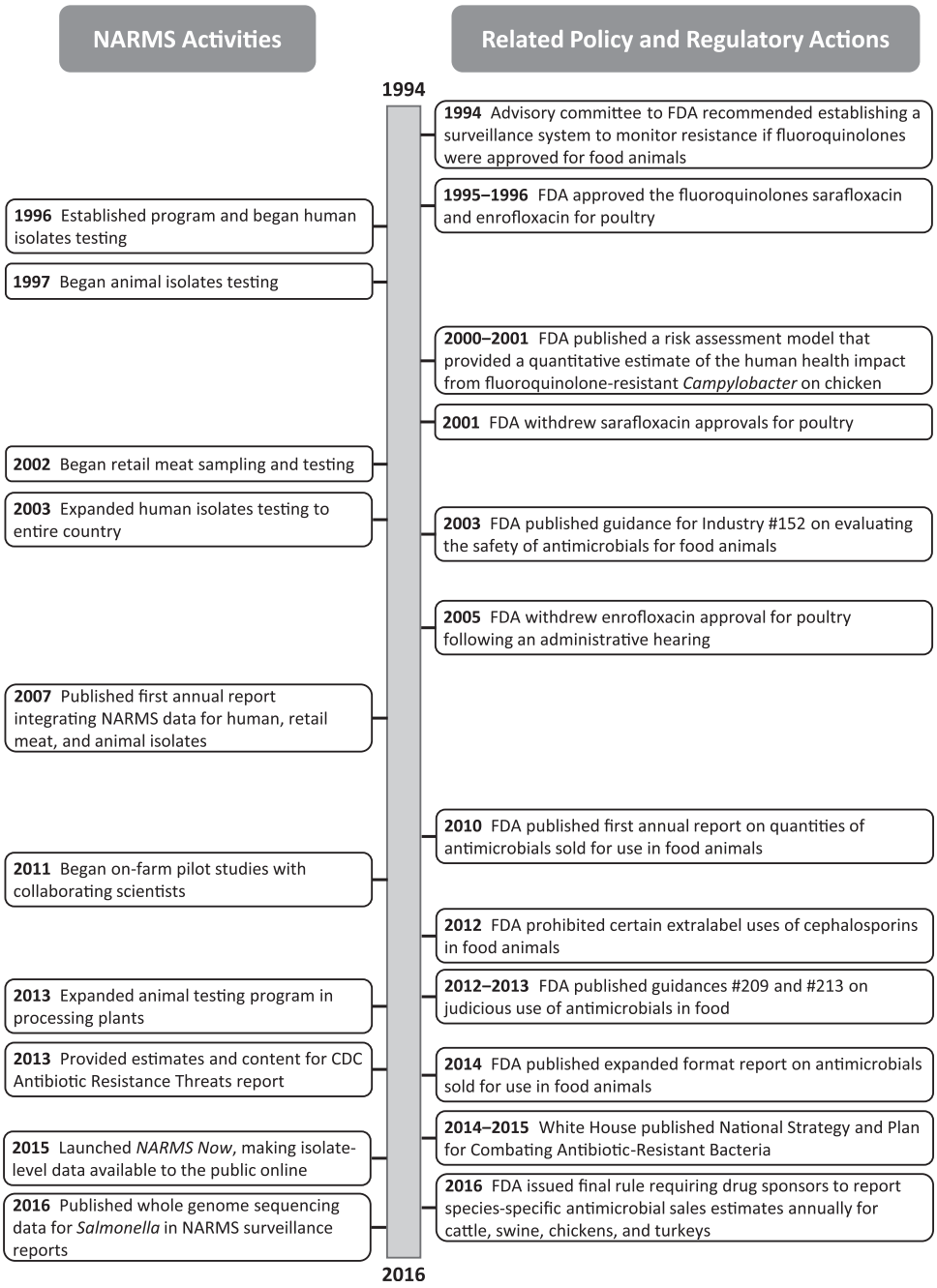

FIG 1. Selected NARMS activities and related policy and regulatory actions, 1994–2016. NARMS, National Antimicrobial Resistance Monitoring System.

were removed from the market because of the associated emergence of resistance in humans (Nelson *et al.*, 2007). Data from NARMS and other sources showed a rise in resistance to third-generation cephalosporins among *Salmonella* isolates from food animals at slaughter, retail meats, and humans, which prompted FDA to issue an order prohibiting certain extralabel uses of cephalosporins in cattle, swine, chickens, and turkeys in 2012 (FDA, 2012b).

Data from NARMS and other sources will be used to help assess the impact of FDA guidance No. 213 (FDA, 2013b). This guidance, which took effect on January 1, 2017, will result in the phasing out of the use of medically important antimicrobial drugs in feed or water for animal production (e.g., growth promotion) purposes and phasing in veterinary oversight for therapeutic uses of these drugs in food animals; veterinary feed directives and prescriptions will be required to administer medically important antimicrobial drugs in feed and water, respectively (FDA, 2013c, 2014).

CDC has also used NARMS data for policy-related activities. The U.S. Department of Health and Human Service's Healthy People initiative provides science-based 10-year national objectives for improving the health of Americans. NARMS data are used for assessing progress on several food safety objectives in Healthy People 2020 related to antimicrobial resistance in *Salmonella* and *Campylobacter* isolates from humans (DHHS, 2016).

NARMS data have also been used to estimate the number of illnesses and deaths in the United States caused by drug-resistant *Campylobacter*, nontyphoidal *Salmonella*, *Salmonella* Typhi, and *Shigella*. These estimates were published in a landmark CDC report entitled Antibiotic Resistance Threats in the United States, 2013 (CDC, 2013). Publication of the report was followed by several White House-level actions related to combating antimicrobial resistance, including release of a presidential executive order and publication of a national strategy and action plan for combating antibiotic-resistant bacteria (White House, 2014a, 2014b, 2015).

Communication and Outreach

Reporting NARMS surveillance data

Data reporting is a challenge for integrated antimicrobial resistance surveillance systems due to the quantity and complex nature of the data and the need to communicate it to a diverse range of stakeholders. NARMS scientists produce annual NARMS Integrated Reports that aggregate data on bacteria recovered from humans, retail meats, and food animals at slaughter (FDA, 2015a, 2016a). These reports summarize trends in the prevalence of resistance to antimicrobial drugs important in human and veterinary medicine and specific multidrug-resistance patterns, including those linked to severe illness in humans. An emphasis is placed on reporting resistance that is important for human health. NARMS agencies use comparable laboratory methods and meet regularly to reach consensus on data reporting. To facilitate integrated reporting, FDA maintains a database that houses NARMS data for human, retail meat, and animal isolates. CDC also produces annual NARMS reports with more detailed resistance data for zoonotic and nonzoonotic enteric bacterial pathogens isolated from humans (CDC, 2016).

NARMS data are readily available to the public online. NARMS has developed a number of tools to make surveillance findings transparent and accessible to both scientists and nonspecialists. Since 2009, the integrated report has been accompanied by online interactive graphs that allow users to visualize findings across sample sources, drugs, and years. To provide timely downloadable data in a user-friendly format, NARMS Now was launched in 2015. NARMS Now: Integrated Data has data for NARMS nontyphoidal *Salmonella* and *Campylobacter* surveillance isolates from all sources and for NARMS *Enterococcus* and *E. coli* isolates from food animals at slaughter and retail meats (FDA, 2015b). NARMS Now: Human Data has downloadable data for *Salmonella* (typhoidal and nontyphoidal), *Campylobacter*, *Shigella*, and *E. coli* O157 surveillance isolates from humans (CDC, 2015b). Both NARMS Now sites include interactive graphs, tables, maps, and downloadable data. NARMS Now will include links to the genomic sequence data submitted to the National Center for Biotechnology Information (NCBI) at the National Institutes of Health as they become available.

Working with standard-setting organizations

NARMS scientists work with consensus organizations like the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to provide data that inform antimicrobial susceptibility testing methods and development of interpretive criteria, including clinical breakpoints and epidemiological cutoff values (ECVs or ECOFFs); the latter are based on MIC distributions. Broth microdilution methods and quality control ranges for *Campylobacter* susceptibility testing established by FDA NARMS scientists were approved and published by CLSI (McDermott *et al.*, 2004, 2005; CLSI, 2006). Clinical outcomes data along with NARMS human clinical isolates data were used to revise fluoroquinolone clinical breakpoints for *Salmonella* (CLSI, 2012), and collaborative studies have resulted in updates to fluoroquinolone disk diffusion interpretive criteria for *Salmonella* (CLSI, 2015), as well as azithromycin broth microdilution and disk diffusion ECVs for *Shigella* (CLSI, 2016). Through such collaborations and data sharing, NARMS augments the scientific basis for setting interpretive criteria for susceptibility testing, serving both surveillance and clinical medicine purposes.

Participating in international activities

Antimicrobial resistance is a global problem and cited by WHO as one of the top health challenges (WHO, 2015). With extensive and expanding global trade and travel, international activities and collaborations are very important for monitoring and combating resistance. As members of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), NARMS scientists have provided advice and helped develop a document to guide countries in designing surveillance programs to monitor resistance in the food chain (WHO, 2013). The federal agencies participating in NARMS have also provided trainings on foodborne disease and antimicrobial resistance surveillance and have supported investigations and capacity-building activities in developing countries. In addition, NARMS has collaborated with well-established antimicrobial resistance monitoring programs in several countries and has ongoing collaborations with the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). NARMS scientists have served on international resistance task forces, including the *ad hoc* Codex Intergovernmental Task Force on Antimicrobial Resistance, which developed Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (Codex Alimentarius Commission, 2011), and the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), which works to enhance collaborations between the United States and the European Union.

The Future

New technologies: challenges and opportunities

New technologies, such as WGS and culture-independent diagnostic testing (CIDT), present opportunities and challenges for NARMS surveillance. WGS is poised to transform the microbiology laboratory by providing an unprecedented level of detail about bacteria and reducing a series of specialized tests to a single comprehensive analytical workflow. WGS allows rapid screening of bacteria for the genetic determinants of genus, species, serotype, subtype, pathotype, and antimicrobial resistance. This makes it possible to quickly distinguish genetic determinants of resistance, greatly enhancing our ability to compare and contrast strains of bacteria from different sources. WGS can not only assist in

tracking resistance trends and mechanisms but also help solve outbreaks, including those caused by resistant pathogens, by providing high discriminatory power (Deng *et al.*, 2016). In addition, WGS can be used retrospectively to look for newly identified resistance genes, even for resistance to drugs that are not under surveillance, all without entering the laboratory.

Implementing WGS nationwide for food safety purposes poses both technological and operational challenges that will require changes in infrastructure and expertise. Technologies are rapidly evolving and standardized methods with quality controls must be used by staff in dozens of public health laboratories trained to use newly-acquired sequencers. Data systems will need to be adapted to house, manage, and transmit the volume of data generated by WGS. Allele databases for major foodborne pathogens are still being developed and there is an urgent need for bioinformatics tools and expertise (Deng, 2016). Since WGS cannot identify novel resistance genes, phenotypic susceptibility testing of some isolates will still be necessary to detect emerging resistance, and ongoing curation of resistance gene databases will be needed to add new genes as they are found.

CIDT, which is increasingly being adopted by clinical laboratories, presents challenges to surveillance systems based on traditional microbiology. While CIDT offers many benefits, such as rapid turnaround time, it reduces the number of isolates available for antimicrobial susceptibility testing. Until methods are developed that identify pathogens and their properties directly from specimens, ''reflex culturing'' (culturing a sample with a positive CIDT) is needed (Henao *et al.*, 2015; Iwamoto *et al.*, 2015; Huang *et al.*, 2016). New strategies, for example, metagenomics, single cell sequencing, or targeting specific amplicons, could make it possible to catalog the ''resistome'' in a biological sample, identifying all resistance genes present regardless of the bacterial source.

NARMS as a platform for addressing emerging issues

NARMS' infrastructure and partnerships provide it with the flexibility needed to answer important public health questions about emerging resistance and pathogens. NARMS can use existing sample sources for *ad hoc* studies, such as those that assessed the prevalence of methicillin-resistant *Staphylococcus aureus* (Ge *et al.*, 2017), vancomycin-resistant enterococci, and *Clostridium difficile* in retail meats. When the colistin resistance gene *mcr-1* was discovered on a transferable plasmid in *E. coli* isolates from animals and raw meat and *E. coli* and *Klebsiella pneumoniae* isolates from humans in China in 2015 (Liu *et al.*, 2016), NARMS scientists used WGS data to confirm that this mechanism was not present in over 55,000 enteric bacteria (*Salmonella*, *E. coli*, *Shigella*) that had been sequenced, including over 5000 *Salmonella* from NARMS. Furthermore, USDA scientists incubated 2000 NARMS cecal content samples in culture medium enriched with colistin and found that the gene *mcr-1* was present in two *E. coli* strains isolated from swine (Meinersmann *et al.*, 2016a, 2016b, 2017).

Sampling can also be expanded within NARMS to food animals or retail food products not currently tested, such as seafood, which is largely imported from countries with extensive antimicrobial use in aquaculture (Sapkota *et al.*, 2008; NMFS, 2015; FDA, 2016b). NARMS has also begun to explore using imported food testing data from FDA's Office of Regulatory Affairs to identify possible food vehicles for resistant infections that have not been linked to domestic food sources or international travel.

Long-standing partnerships with other surveillance programs, such as FoodNet, can continue to facilitate epidemiologic investigations of emerging resistance. Partnerships between NARMS and Vet-LIRN, the Veterinary Laboratory Investigation and Response Network (FDA, 2016d), will continue to expand and can help address the potential role of companion animals in the ecology of resistance, while broadening interdisciplinary collaborations could help provide a better understanding of the role of environmental pathways (e.g., water, soil, wastes, wildlife) in the dissemination of resistant organisms, both of which are underexplored areas in the One Health model (Lloyd, 2007; Finley *et al.*, 2013). Other programs conduct surveillance for animal pathogens, including those that are zoonotic, and there may be opportunities for NARMS to collaborate on specific projects, especially as the use of WGS expands.

Through the Antibiotic Resistance Solutions Initiative (CDC, 2017), CDC is supporting state and local health departments to expand WGS capacity to include screening all *Salmonella* and many more *Campylobacter* and *Shigella* isolates from humans for resistance genes and to collect more epidemiologic data from patients with resistant infections. These activities should enhance detection of emerging resistance and assessment of resistance trends, aid identification of sources and outcomes of resistant infections, and help prioritize investigation of resistant outbreaks. FDA's planned expansion of retail meat surveillance to more sites will increase the geographic representativeness of sampling and the sample size, providing more information about emerging resistance in food animal sources.

Antimicrobial sales and use data

A long-standing gap in NARMS has been the lack of detailed antimicrobial use data in food-producing animals in the United States. Currently, only a limited amount of data is available on the quantities of antimicrobial drugs sold and distributed for use in food animals in the United States. Without knowing how a specific antimicrobial drug is used in each type of food animal, it is difficult to fully evaluate the drivers of resistance or to assess the impact of interventions (WHO, 2013; FAO, 2016). Therefore, FDA has recently expanded antimicrobial sales data reporting requirements for drug sponsors to include species-specific estimates for cattle, swine, chickens, and turkeys (FDA, 2016c) and, through cooperative agreements, plans to fund projects to enhance monitoring of antimicrobial use in food animals. In addition, USDA's National Animal Health Monitoring System (NAHMS) has designed surveys for antimicrobial use data collection on farms in 2017. The data collected from these initiatives will help to guide antimicrobial stewardship efforts and support microbial food safety risk assessments.

Conclusion

NARMS is a long-standing, multiagency collaborative program that provides essential information about antimicrobial resistance in enteric bacteria and serves as an efficient and flexible platform for detecting and characterizing

emerging resistance threats in humans, food animals, and food. NARMS data have been widely used to formulate science-based policies, regulatory actions, educational efforts, and other initiatives aimed at reducing resistance and preventing human infections. Many improvements have been made to NARMS over the past two decades, and the program will continue to change as bacteria evolve and new technologies become available.

Continued use of an integrated One Health approach to surveillance and research is critical for effectively addressing the complex and multifaceted problem of antimicrobial resistance. Such an approach facilitates detection of emerging resistance threats and trends, data comparisons, and generation of hypotheses about sources of resistant and susceptible infections. Securing more detailed data about on-farm management practices, including the quantities of antimicrobials used in each food animal species, and analyzing these data in conjunction with resistance data will help us better understand resistance trends and facilitate identification and evaluation of targeted interventions designed to reduce resistance and protect public health.

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