

Science Board Review of the National Antimicrobial Resistance Monitoring System June 2017

The National Antimicrobial Resistance Monitoring System (NARMS) was instituted in 1996 and reviewed initially in 2007. Since then, many changes have occurred that might have impact on the future course of the NARMS program. Certainly, the heightened visibility of antimicrobial resistance (AMR) as a global health challenge, publication of the US National Strategy to Combat Antibiotic-Resistant Bacteria (CARB), and the evolution of laboratory technologies are all substantive developments that have bearing on this program. On behalf of the FDA's Science Board, a committee, consisting of Drs. Michael Apley, Lonnie King, Barbara Kowalcyk, Lee Riley, Tom Shryock and Lisa Nolan, and assisted by Emily Crarey, was charged by Dr. Patrick McDermott (Food and Drug Administration (FDA)) to review the current NARMS program. Specifically, we were asked to answer the following three questions.

1: NARMS is focused on specific commodities and sampling intervals. Could changes to sampling strategies improve our understanding of resistance dynamics within a One Health paradigm?

2: FDA publishes annual antimicrobial sales and resistance data. Are our analysis and presentation of these data adequate? What is the best way to report relationships between antimicrobial sales data and antimicrobial resistance in our national surveillance?

3: NARMS Now does whole genome sequencing (WGS) as a routine part of surveillance. What is the best way to report whole genome sequence data and trends in the resistome?

The NARMS Review Committee (NRC) appreciates and compliments the work of the multi-agency NARMS Team for its substantial efforts and progress over the last 20 years to better understand and reduce AMR. The NRC was further impressed with the significant progress that NARMS has made since its last review a decade ago. The NRC is especially complimentary of NARMS as an early adopter of cross-agency collaboration and its multidisciplinary approach to AMR surveillance and further acknowledges the importance of NARMS' One Health platform which is a model for other agencies and organizations to emulate. Notably, the NARMS team contributed to the drafting and publication of the World Health Organization Advisory Group on Integrated Surveillance of Antimicrobial Resistance.¹ The document is intended for countries in the early stages of designing an integrated surveillance system.

¹ Integrated surveillance of antimicrobial resistance: guidance from a WHO Advisory Group. http://apps.who.int/iris/bitstream/10665/91778/1/9789241506311_eng.pdf?ua=1 Accessed 6/5/2017.

Because of the past successes of NARMS and the positive working relationship it has built across the federal agencies including the FDA, The Centers for Disease Control (CDC) and United States Department of Agriculture (USDA), the NRC believes that NARMS has a unique opportunity to offer even more at a critical time in the long-standing challenge of AMR. AMR has continued to become an even greater health problem and even more costly since the initiation of NARMS almost 20 years ago. At the same time, a new commitment and momentum have recently emerged to address the difficult and vexing challenge of AMR. There are numerous new activities at the public, private and even global levels and we now have new technological advances in genomics, data analytics and bioinformatics and new data sources that have laid the groundwork to add new partnerships and collaboration. Indeed, NARMS may be reaching a point where it can improve both incrementally and transformatively.

Thus, in the following pages we offer our review, recommendations for improvement and suggestions for strategic direction, based on admiration for what the program has already accomplished and aspiration for what it can yet accomplish.

Question 1: NARMS is focused on specific commodities and sampling intervals. Could changes to sampling strategies improve our understanding of resistance dynamics within a One Health paradigm?

In considering changes to the NARMS sampling strategies to further improve our understanding of resistance dynamics within a One Health paradigm, it is important to first clarify the objectives of such a system. Originally, NARMS was established in 1996 to:²

- Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals;
- Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria;
- Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance; and
- Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals.

Currently, NARMS collects food borne bacterial isolates from humans, retail meats and cecal samples from food animals for antimicrobial susceptibility testing against 15 antimicrobial agents in *Salmonella* spp. and *Escherichia coli*, 9 in *Campylobacter* spp., and 16 in *Enterococcus* spp.). Human isolates are obtained by CDC through the Foodborne Diseases Active Surveillance Network (FoodNet). Retail meat isolates are obtained by FDA.³ Retail meat isolates are

² <https://www.cdc.gov/narms/index.html>. Accessed 6/5/2017

³ <https://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM529808.pdf>

obtained by sampling retail stores in the FoodNet catchment area. Cecal samples are collected by USDA-FSIS through PR/HACCP programs from (chickens, turkey, cattle) and NARMS sampling (chickens, turkey, beef, dairy and swine) programs. Pilot studies also are used to address gaps in the current monitoring system.

Prior reviews of the NARMS sampling strategies have noted that the limited sample sizes and lack of a national sampling strategy have introduced biases that limit the interpretability and generalizability of the results. The NARMS 2012-2016 Strategic Plan sought to address these issues by improving the geographic representativeness of the samples, increasing the number of samples collected and improving the isolation methods. In 2015, CARB further recommended strengthening national One Health surveillance efforts to combat resistance and specifically recommended enhancing NARMS and expanding surveillance efforts. The NRC encourages NARMS to continue to their own analysis of their sampling strategies for potential biases that may complicate interpretation of NARMS data as well as emerging trends that could impact the overall utility and connectivity of NARMS, such as increasing use of culture-independent diagnostic tests (CIDTs), as noted below.

The NRC has chosen to answer question 1 with recommendations as to sampling methodology, utility, commodities to be sampled, and connectivity.

Recommendations:

1-1) Sampling Size / Frequency / Methodologies. The NRC recommends that NARMS conduct a thorough review of their sampling strategies to identify potential biases and areas for improvement as well as emerging trends that could impact the overall utility and connectivity of NARMS; such a review is beyond the resources of the NRC. For example, the existing sampling strategies for retail meat, animal and human isolates each have biases that NARMS should seek to minimize as the system evolves. At a minimum, such sampling biases should be well documented to ensure that NARMS data are used appropriately. For example, the NRC would like to note the potential impact of an important emerging trend among clinical laboratories on NARMS surveillance efforts. Recently, several culture independent diagnostic tests (CIDTs) have been developed to allow physicians to quickly diagnose patients with foodborne disease. While CIDTs present great opportunities – they are faster and cheaper than traditional means and can test for multiple pathogens at one time – there is a cost to their adoption. Human foodborne disease surveillance systems in the US are built on isolates obtained from cultures initially recovered from patients by clinical laboratories and forwarded to public health laboratories. As clinical laboratories adopt CIDTs, the number of isolates submitted to the surveillance system declines and, thus, the ability to detect outbreaks, monitor disease trends, track antimicrobial resistance and collect isolates for research purposes are compromised. Clinical laboratories are quickly adopting the use of CIDTs, and the CDC has flagged this as an area of concern. In fact, the CDC did not issue its annual “foodborne illness report card” in 2016 because of the impact of CIDT use on its surveillance system. The CDC has identified several short and long term strategies for ensuring that foodborne disease

surveillance systems can continue to achieve its goals under this new paradigm.⁴ It is important for NARMS, which also relies on isolates obtained through our human foodborne disease surveillance system, to consider this newly emerging practice and its potential impact on the development/modification of its sampling strategies.

NARMS also should consider how to improve the collection of epidemiologic information associated with the samples collected. Though the NRC recognizes that research is typically outside the purview of NARMS, such an approach could enable comparative studies that would enhance the utility of NARMS data as well as connectivity of the data collected. For example, there are now two processing plant testing approaches, one used for NARMS in collection of cecal isolate data and another used by FSIS to collect PR/HACCP isolate data. Currently, these may not necessarily occur in the same plant at the same time or on the same group of animals. This lack of coordination may present a missed opportunity for comparison of the two approaches. The NRC, therefore, suggests consideration of a cooperative approach between FSIS and NARMS that allows sampling to be complementary to allow adequate data comparison.

1-2) Utility. Similarly, the NRC finds that current NARMS sampling might be better exploited to enhance our understanding of food safety and the dynamics of antimicrobial resistance (AMR) in the food chain. As mentioned above, collection of epidemiologic data associated with the samples collected could improve the utility of NARMS data as well as the connectivity of the data. Incorporating epidemiologic data on the samples collected (e.g. methods of production, antibiotic use, health outcomes, etc.) could be incorporated into risk assessments, appropriately target risk management interventions and improve our understanding of resistance dynamics via the food chain. For example, since many producers of retail chicken feature labels stating “organic”, “raised without antibiotics” or other such similar descriptions, inclusion of such products within the ongoing sampling strategy enables a comparison with “conventionally” produced products (i.e., those not labeled as above). Further extension of this approach to the PR/HACCP or cecal sampling stage might provide substantial and meaningful insight into this market segment. NARMS isolates also could be used to detect emergence of AMR genes or unique bacterial strains. For example, NARMS rapidly examined US isolates for the presence of the colistin resistance gene, *mcr-1*, as a prelude to intervention. A similar approach might be considered with an evolving type of *Salmonella* Enteritidis in Africa that may pose a threat to the US⁵.

1-3) Commodities. In addition to the desire to improve sampling for the establishment of connectivity, there is interest in expanding monitoring to fish and other seafood, such as tilapia, salmon and shrimp, and additional products such as lamb or veal. A prerequisite for expansion

⁴ Centers for Disease Control and Prevention. 2000. Surveillance for foodborne-disease outbreaks—United States, 1993-1997.

⁵ Feasey et al. Distinct *Salmonella* Enteritidis lineages associated with enterocolitis in high-income settings and invasive disease in low-income settings. Nat Genet. 2016, 48:1211-7. doi: 10.1038/ng.3644.

of testing to other commodities would be to provide justification (ideally structured as a Hazard Characterization or Risk Profile) that describes the potential microbial hazard(s) of concern and an assessment of their potential risk to human health and food safety. Reports such as that of the United Kingdom Food Safety Agency (e.g., Risk Assessment on Methicillin-Resistant *Staphylococcus aureus* (MRSA), with a focus on Livestock-associated MRSA in the UK Food Chain, could serve as an example⁶.

1-4) Connectivity. To date, establishment of causation or lack thereof (i.e., connectivity) between antimicrobial usage in one population or market sector to the development of antimicrobial resistance among the microbes of another group or sector is problematic, as certain ‘missing links’ exist in current sampling strategies. While the NRC recognizes that the issue of connectivity is something all public health organizations have struggled with for many years, it is the desirable outcome of surveillance from a One Health standpoint, and the means of achieving it should be considered. Currently, the NARMS program is structured such that each category of isolates originating from animals (cecal or Pathogen Reduction (PR)/Hazard Analysis Critical Control Point (HACCP)), retail meat and human patients are sampled independently of one another. Thus, connectivity cannot be established among these different categories because of disjunction in space and time of collection and analysis. On-farm and environmental surveillance efforts offer the potential of strengthening the connectivity between the farm and animal/ PR/HACCP. Ultimately, generation of data sufficient to conduct a risk assessment would be desirable.

On-farm studies and environmental studies can use a One Health approach. The prior Collaboration in Animal Health and Food Safety Epidemiology approach mentioned in the 2007 Science Board Recommendations and the present USDA on-farm studies have demonstrated the feasibility and value of this type of testing. We suggest that a One Health approach to sampling would include:

- Monitoring of pre-treatment animal pathogen isolates from ill animals and those from treatment failures to understand animal health treatment approaches and outcomes;
- Environmental sampling of the production facility, waste stream and related sites;
- Recovery of food safety pathogens from feces of on-farm food animals, later at the abattoir as cecal contents, and possibly from retail products for tracking studies, with comparisons made from isolates from animals that were treated with antimicrobial agents or not; and
- Enhancing the trace-backs from human foodborne disease outbreaks to the putative source and type of contaminated food product by collection of additional “context” information about the exposure and circumstances.

⁶ (https://www.food.gov.uk/sites/default/files/mrsa_risk_assessment_feb17.pdf) or The Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance CAC/GL 77- 2011 (www.fao.org/input/download/standards/11776/CXG_077e.pdf) offer formal guidelines to begin the evaluation

Question 2: FDA publishes annual antimicrobial sales and resistance data. Are our analysis and presentation of these data adequate? What is the best way to report relationships between antimicrobial sales data and antimicrobial resistance in our national surveillance?

2-1) Adequacy of the Data. The Animal Drug User Fee Act (ADUFA) antibiotic sales reporting data are collected with considerations to business confidentiality and primary sales of product as key contextual information. As such, this reporting is outside the scope of the NARMS program and the NRC's review. However, the NRC has concerns about the accuracy of the increased reporting granularity in antimicrobial sales reporting based on species estimates. The limitations of these data are expressed by the FDA. For example, in a recent Q&A document provided from the FDA/CVM, "the animal data represent a summary of the volume of product sold or distributed (through various outlets) by the manufacturer and not the volume of product purchased by the end user for administration to animals."⁷ Thus, there is a concern on the part of the NRC that the attempt to expand granularity of the ADUFA antimicrobial sales data may result in inappropriate use of the data regardless of the caveats expressed by the Agency.

During discussion and consideration of the food animal sales data, the question arose as to why human prescribing and sales data are not reported so that these data can be evaluated in the same manner as the food animal sales data. The NRC could not uncover an explanation for this reporting difference.

Antimicrobial susceptibility data from the different branches of NARMS are easily accessed online. More problematic is the determination of when significant trends in Minimal Inhibitory Concentration (MIC) distributions are occurring. A transparent discussion easily interpreted by the lay public would be a valuable addition. The points covered could include:

- The effect of isolate source on interpretation;
- Classifying a shift in the reported resistance percentages as significant or, conversely, classifying resistance profiles as stable or declining; and
- The challenges of comparing disparate datasets.

2-2) Best Reporting Scheme. The fundamental question that reporting of these data seeks to answer is "does the use of antibiotic X in food animals relate to antibiotic X resistance seen in food for human consumption, human microflora or human foodborne illness? This cannot be answered from combinations of ADUFA antimicrobial sales data and NARMS data due to the disparity of the datasets and the lack of granularity. The method of collection does not allow removal of or compensation for population or temporal sampling biases. Comparing trends in antimicrobial sales for animal use with the change of resistance prevalence in human foodborne bacteria without also considering human sales data is likely to be misleading.

⁷ Food and Drug Administration Center for veterinary Medicine – Questions and Answers: Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals – Accessed 5-25-2017 at <https://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm236149.htm>

Therefore, additional NARMS resources should be invested in investigating potential associations in actual use (not sales data) and resistance trends at the user level (e.g., on-farm studies as suggested above), rather than to modify the extent or methods of evaluation for the existing systems. The current systems may be informative (accurately or inaccurately) to policy creation (accurately or inaccurately depending on use), but much more detailed data are necessary to drive the progression of antibiotic stewardship. The recent paper by Grohn *et al.*, 2017⁸ highlights the challenges and limitations of connecting national sales data of antimicrobial agents and AMR monitoring data.

Question 3: NARMS Now does whole genome sequencing (WGS) as a routine part of surveillance. What is the best way to report WGS data and trends in the resistome?

The NRC divided Question 3 into two parts: 1) What is the best way to report WGS data? and 2) What is the best way to represent trends in antimicrobial resistance prevalence of foodborne pathogens? Both questions pertain to modifying a laboratory-based surveillance system for foodborne bacterial pathogens using new technology and how this surveillance system may be most effectively used to address relevant public health concerns. Importantly, such a surveillance system needs to be able to provide information that cannot be generated by existing surveillance systems. It will need to be usable to facilitate direct public health interventions as well as to raise new research questions that have not been previously considered.

3-1) What is the best way to report WGS data? In addition to the NARMS surveillance system, surveillance systems for bacterial foodborne pathogens in the United States include the CDC's Foodborne Disease Outbreak Surveillance System (FDOSS), Foodborne Disease Active Surveillance Network (FoodNet), National Case- and Laboratory-Based Surveillance for Enteric Diseases, and PulseNet. These systems report bacterial subtyping data based on species, serotypes, and in the case of PulseNet, genotypes. Genotyping tests have included, primarily, pulsed field gel electrophoresis (PFGE), but also multilocus variable numbers of tandem repeats analysis (MLVA), and multilocus sequence typing (MLST). These systems are primarily designed to 1) detect outbreaks, 2) assess temporal trends in species, serotype, and drug resistance incidence, and 3) compare geographic distributions of key foodborne bacterial pathogens and their resistance profiles. Interventions based on these databases have been mostly directed at outbreak investigations—detecting outbreaks and identifying, removing, and tracking vehicles implicated in the outbreaks. Surveillance descriptions of changing patterns of AMR have so far made limited contributions to effective interventions to reduce the prevalence of AMR in foodborne pathogens. PFGE information has been used on a subset of these outbreaks to implement interventions (e.g., product recall). Most of the time, however, serotype data are

⁸ Grohn et al (2017) A proposed analytic framework for determining the impact of an antimicrobial resistance intervention. *Anim Health Res Rev.* 2017, 16:1-25. doi: 10.1017/S1466252317000019.

sufficient to initiate such interventions. For a new surveillance system based on WGS to have advantage over existing systems, it needs to be able to provide information that could be used to do more than just controlling outbreaks, as well as to address the problem of AMR.

In the US, recognized outbreaks of foodborne illnesses comprise a small fraction (<10%) of the total number of such illnesses that occur each year.^{9, 10} Indeed, most foodborne illnesses are sporadic occurrences. Current surveillance systems are not set up to deal with human sporadic or endemic foodborne diseases. Consequently, most sporadic enteric infections are not reported because a patient may not seek medical care, a healthcare provider may not obtain a specimen for culture even if a patient seeks care, and culture results may not get reported to the local county health department even if a specimen is cultured. As such, risk factors or vehicles and sources of sporadic infections are rarely determined. If a surveillance system based on WGS database, together with context information (e.g., demographic, geographic, clinical, recent food intake history, travel, etc.) could be used to address this deficiency, it could create a new opportunity to devise more effective public health control of foodborne illnesses. The CDC's FoodNet is one sentinel surveillance system that may serve as a source of such data and enteric pathogens from sporadic infections.

WGS provides the most discriminating strain-typing information for each microbial isolate. The ease, speed, and decreasing cost of WGS have made it possible to apply WGS to epidemiologic investigations, including for disease surveillance. However, one major limitation of WGS technology is that the large and highly discriminating data it generates are not amenable to quick and simple analyses. The large WGS data must be converted into simple formats that are easily interpretable, exportable, and exchangeable within and across laboratories. Thus, a consensus protocol to report WGS data needs to be developed.

3-1.A. Develop a nomenclature system for strains characterized by WGS. WGS data currently generated by NARMS are deposited into the NCBI database as shotgun or bioprojects. While this approach and information are helpful for researchers, they do not facilitate practical use of the data for public health purposes. The practical use of WGS data for surveillance and other public health applications will require creation of a simple nomenclature system. At this time, there is no standardized protocol to assign a genotype name to a strain that has undergone WGS. This issue is currently being addressed by PulseNet at CDC that will convert their genotype surveillance system based on PFGE to WGS. If not done already, NARMS should be involved in this discussion with PulseNet to develop a nomenclature system for strains characterized by WGS.

The nomenclature system for WGS data should be comprised of names of 1) species, 2) serotype, and 3) genotype of each strain tested. Since bacterial speciation is based on 16S ribosomal DNA sequences, species data can be readily obtained from the WGS data. Serotype

⁹ Centers for Disease Control and Prevention. 2000. Surveillance for foodborne-disease outbreaks—United States, 1993-1997

¹⁰ Mead et al. 1999. Food-related illness and death in the United States. *Emerg Infect Dis* 5:607-625.

data may also be obtained from WGS for some of the enteric bacterial species by *in silico* serotyping, using algorithms such as the SerotypeFinder (<https://cge.cbs.dtu.dk/services/SerotypeFinder/>) developed for *E. coli*, hosted by the Center for Genomic Epidemiology in Europe. NARMS could be involved in developing a similar *in silico* serotyping database for all of the foodborne enteric bacterial species that are currently included in its surveillance system. NARMS should continue to perform serologic tests on the isolates subjected to WGS until *in silico* serotyping consistently and reliably matches with the serologic test results.

There are many possible ways to assign a genotype name to a strain subjected to WGS. One way is to use the schema already adopted for MLST. WGS data can be analyzed *in silico* to create a database of MLST (wgMLST). Phylogenetic classification of species such as *E. coli* by MLST based on 7 housekeeping gene sequence analysis closely overlaps with *E. coli* WGS phylogenomic classification. The wgMLST database for enteric pathogens is currently hosted by Warwick Medical School in United Kingdom under the name EnteroBase (<http://enterobase.warwick.ac.uk/>), which assigns a genotype name (e.g., ST69, ST131, ST131 complex, etc.) for each strain based on nucleotide sequence differences in the 7 genes. The schema used at the EnteroBase database could be modified to compare more than 7 genes (or other genes, such as recognized virulence genes). Eurosurveillance recently produced a report (Vol. 22, June 8, 2017) entitled: "PulseNet International: Vision for the implementation of whole genome sequencing (WGS) for global food-borne disease surveillance" <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22807>, which recommends using wgMLST for the purpose of surveillance and nomenclature. It is recommended that NARMS consider adoption of this system of nomenclature to allow international comparison of genotypes.

3-1.B. Reporting WGS data. Once the nomenclature system for WGS data is developed, the genotype names can be used in NARMS surveillance reports, just as they are currently done with names of species and serotypes. NARMS has established a publicly accessible and interactive reporting display system (NARMS Now) that allows users to obtain foodborne bacterial pathogen data by species, serotype, drug-resistance frequency, temporal trend, and geographic distribution. However, it does not currently include genotype data. Once the nomenclature system for WGS-based strain types is established, strain genotype names could be incorporated into this interactive reporting system. A new type of visual that could be included in this reporting system is a phylogenomic depiction of the genotypes, such as that constructed by the eBURST algorithm (<http://eburst.mlst.net/>), which could show genotype cluster distributions within a serotype.

3.2. What is the best way to report trends in AMR of foodborne pathogens? To the NRC, resistomes represent the totality of all drug-resistance genes in a microbial niche. Such data cannot be subjected to trend analysis. Metagenomics data obtained from culture-independent analyses of clinical samples would not be amenable to any meaningful interpretations in a surveillance system. These new applications of genome sequencing technology may be useful for research purposes and investigation of disease transmission under special circumstances, but they cannot be effectively used to conduct surveillance. What is important is how to use

the WGS data of individual bacterial isolates to report drug resistance prevalence trends and distribution.

For enteric bacterial pathogens, the NRC recommends reporting AMR prevalence by species or serotypes, e.g., *Shigella sonnei*, *Salmonella Enterica* Typhimurium. However, it is increasingly recognized that the prevalence of AMR even within a species or serotype is greatly influenced by the clonal composition of the strains among the species or serotypes analyzed. All microbes are not equally susceptible to the selective pressure of AMR drugs. Food animal drug sales and use data may correlate with the proximal selection of new drug-resistant lineages, but they are less likely to affect more distal drug-resistance prevalence in a human community or populations. That is, there are many intervening factors that influence what happens to enteric bacterial pathogens from their initial selection in the food animal reservoir (proximal selection) to their ingestion by consumers in a community. These intervening factors (e.g., meat distribution system, processing, consumer behavior and other host factors) ultimately influence the relative distribution of resistant and susceptible clonal lineages of such pathogens in a community (distal drug-resistance prevalence). AMR prevalence in a community is therefore greatly affected by the number and type of dominant lineages circulating in a community. Even within a single genotype, AMR frequency can vary, just as the AMR prevalence within a species or serotype varies. Reporting of AMR trends, therefore, needs to incorporate genotype data and should be reported as frequency of resistance to a drug, temporal trend, and geographic distribution by specific genotypes.

Drug-resistance genes can be identified from WGS data by algorithms such as ResFinder. Such genes may occur on mobile elements such as plasmids or integrons, and WGS will be able to provide such information. One caveat using sequence information to correlate with clinical resistance profile of a specific bacterial strain is that the sequence information may miss high-level resistance resulting from so-called heteroresistant strains upon exposure to an antimicrobial drug. Clinical resistance can also result from factors such as loss of an outer membrane protein or porin and induction of efflux pumps, which cannot be easily predicted from WGS data. Thus, both phenotypic and genotypic (all drug-resistance genes found in WGS data) drug resistance should be reported.

In addition to reporting resistance prevalence by serotypes or species as is currently done by NARMS, resistance prevalence should be reported by specific genotypes based on a WGS genotyping nomenclature ultimately adopted. It should be reported as frequency of resistance to a drug, temporal trend, and geographic distribution by specific genotypes.

A Final Note: Considerations for Strategic Direction

The NRC felt compelled to offer some additional considerations for the NARMS Team as it begins a strategic planning process. However, the NRC is very sensitive to budgetary constraints, competing interests and capacity limitations of the NARMS' agencies. Thus, we surface the following ideas for consideration, not as mandates or recommendations, but rather, as stimulants for conversation and consideration of a broader horizon for NARMS, especially at a time when AMR continues to profoundly threaten human and animal health. The NRC believes in the work and importance of NARMS but also wants to ensure its future success and relevancy.

The NRC envisions NARMS continuing its important work in monitoring trends in resistance among key enteric bacteria, improving our understanding of the emergence, persistence and spread of resistance and ultimately, to help to improve prevention tactics and intervention strategies that reduce resistance in foodborne bacteria. However, this mission can be accelerated and much more might be accomplished if NARMS considers the following:

1. The addition of an environmental surveillance component to truly complete the One Health platform and add to our understanding of the movement of pathogens and resistant genes across the three domains of One Health.
2. Consider expanding the trend analysis to include food animal pathogens and changing resistance patterns within this domain. While NARMS Now focuses on human health outcomes, we lack critical knowledge of AMR in the billions of food animals produced each year. Improving the health, safety and productivity of these animals is also a public health strategy.
3. Better integrate across the various programs and components within the NARMS' activities. Some of the components seems quite independent and perhaps need better integration into the total NARMS program. Improved connectivity could add further value; e.g., better connecting data from slaughter and retail foods with human isolates and shifting from association to causality if possible; in addition, understanding potential AMR changes along the entire food chain over time could be informative.
4. Evaluate a possible on-farm component; this might be possible in coordination with the National Animal Health Monitoring System (NAHMS) implemented by USDA APHIS. Perhaps NARMS could begin a more in-depth study along with NAHMS – this could be done on a rotating 5-7 year plan with NAHMS as it rotates its data collection within specific commodity groups. It might be possible to consider a “sentinel farm” approach and longitudinal studies with the support of APHIS and/or strategic partnerships with universities.
5. Increase efforts to broaden collaboration with new AMR programs that have been started or expanded across government agencies and programs; e.g., FoodNet, diagnostic labs and the expanded sources created as part of CARB; there may be exceptional opportunities to use the NARMS data and approach with other programs that were not available earlier.

6. Consider a more in-depth and integrated collaboration with global organizations and other countries that have also increased their interest and commitment to AMR. With the increasing use of WGS techniques, comparisons will be easier and more meaningful.
7. Consider how data may be collected in such a way to be useful for purposes beyond the current NARMS objectives; e.g., risk assessment, attribution studies and detecting newly emerging resistant bacteria in our food supply.
8. While still likely premature, it is not too early to envision how NARMS might integrate with some microbiome studies and projects. Integration of NARMS with this rapidly expanding science could be mutually beneficial in developing better understanding of resistance genes and microbial profiles in healthy animals.
9. Facilitate the research opportunity presented by the recent approval of avilamycin for use in chickens and pigs to study the mechanisms of AMR dissemination. To date, this new antibiotic has not been used in the U.S. and has no human health analogue. Thus, its approval presents a unique opportunity to explore the development and transmission of resistance to a new drug over a period of time. Since avilamycin's spectrum of activity includes enterococci and perhaps *Campylobacter*, which are currently collected by NARMS, a retrospective evaluation comparing baseline MICs prior to introduction in the US as well as the prospective analysis following introduction of the drug is possible. Epidemiological outbreak investigation data collection improvements to supplement microbiological data on human foodborne bacterial disease outbreaks associated with food commodities could also be explored.
10. Better exploit the use of WGS surveillance data. In addition to the traditional depiction of surveillance data, a WGS surveillance database can potentially be used to stimulate new public health interventions and research not possible by a system based on species, serotypes, and PFGE. The following are some examples:
 - a. Strain clusters based on WGS genotype designations could be analyzed to identify hidden outbreaks among sporadic cases of foodborne disease before overt outbreaks are recognized. Such clusters can be used to design case-control studies to identify contaminated food vehicles or sources. Isolates obtained from sentinel surveillance systems such as the FoodNet can be used for such purposes.
 - b. Genotype information obtained from a recognized outbreak or a vehicle of an outbreak can be used as a reference to quantify the proportion of sporadic cases in a community attributable to an implicated vehicle.
 - c. The surveillance system can be used to identify clusters of AMR subclones within a genotype to facilitate case-control studies to trace their source or risk factors for infection with them or to identify newly emerging resistance traits.
11. Expand the uses of AMR phenotypic and genotypic data based on WGS surveillance data. Some examples are shown below:
 - a. The more granular strain type data provided by WGS may facilitate epidemiologic studies to identify risk factors for sporadic drug-resistant infections caused by dominant genotypes before any outbreaks become recognized.

- b. Sporadic infections in a community can be studied to determine the proportion of AMR infections attributable to a set of genotypes. Such information may also be used to determine the proportion of sporadic illnesses in a community attributable to a single product during a time period. Risk factors for infection with such genotypes can be sought and removed if found.
- c. Information on the distribution of AMR genotypes in a community can be used by clinicians to make better informed decisions on the choice of an empirical drug to treat a patient with foodborne illness who requires antimicrobial drug treatment.

Again, the NRC only wishes to share these ideas that surfaced in our conversations as a stimulus for discussion. Many more changes will certainly take place over the next decade, and we believe that the NARMS Team should not only improve “what is” but should also create “what isn’t”. NARMS has become a respected leader in AMR and must continue to add value to its mission and perhaps even consider an expansion in its mission. We also state this with an understanding of important caveats including funding issues, trade-offs in priorities and the need for greater partnerships and collaborations. These ideas are certainly beyond the three questions to which we have responded and not included as recommendations but only for strategic thinking. Finally, we include these ideas because of our confidence in the NARMS Team, their past success and desire to ensure continuous learning, improvement, future relevance and leadership of this outstanding program.