COMBATING ANTIBIOTIC RESISTANCE

A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock

Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis ***2017***

The Expert Commission convened at the George Washington University Milken Institute School of Public Health (GWSPH) on November 13, 2016. The Commission's efforts have been supported by staff at the Antibiotic Resistance Action Center at GWSPH and the Natural Resources Defense Council.

Suggested citation:
Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. *COMBATING ANTIBIOTIC RESISTANCE A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017*. Washington, D.C.

A Report by the Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis

The Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis is comprised of the following members:

Lance B. Price, PhD (Co-chair), Director, Antibiotic Resistance Action Center, Milken Institute School of Public Health, the George Washington University

Jason Newland, MD, MEd (Co-chair), Director of Antimicrobial Stewardship, St. Louis Children's Hospital, Associate Professor of Pediatrics, Washington University in St. Louis

Aparna Bole, MD, FAAP, Medical Director, Community Integration UH Rainbow Babies & Children's Hospital

Valeria Bortolaia, DVM, PhD, Senior Researcher, Research Group for Genomic Epidemiology Technical University of Denmark

Jesper Larsen, DVM, PhD, Researcher, Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Denmark

Guy H. Loneragan, BVSc, PhD, Professor, Food Safety and Public Health, Texas Tech University

Steven Roach, MA, Food Safety Program Director, Food Animal Concerns Trust

Tara C. Smith, PhD, Associate Professor in Epidemiology, College of Public Health, Kent State University

Anthony D. So, MD, MPA, Professor of the Practice, Director, IDEA (Innovation + Design Enabling Access) Initiative and Strategic Policy Program, ReAct–Action on Antibiotic Resistance, Department of International Health, Johns Hopkins Bloomberg School of Public Health

Linda Tollefson, DVM, MPH, Rear Admiral, U.S. Public Health Service (Ret)

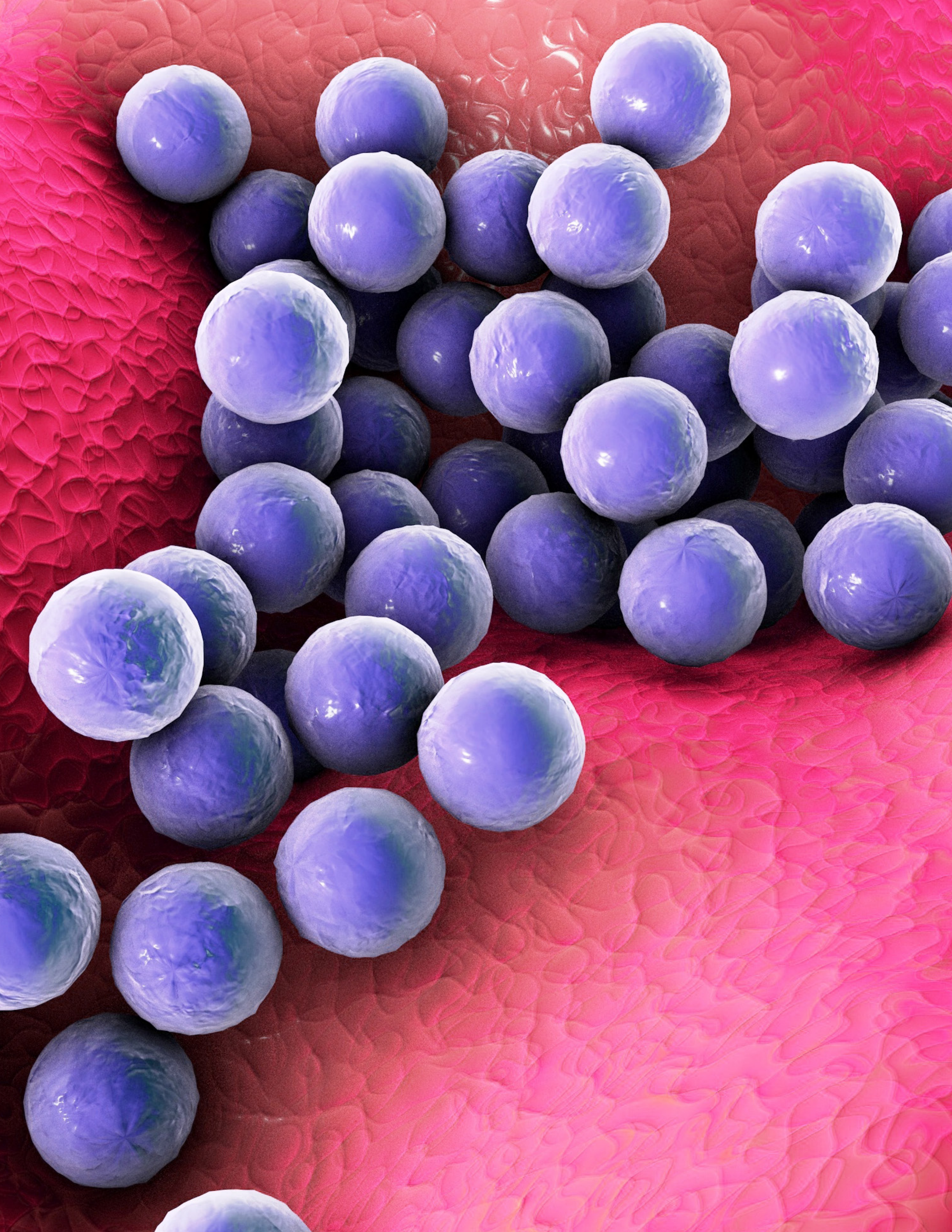
Jaap Wagenaar, DVM, PhD, Professor Clinical Infectiology, Faculty of Veterinary Medicine, Utrecht University, the Netherlands and Wageningen Bioveterinary Research, Lelystad, the Netherlands

Theoklis Zaoutis, MD, MSCE, Professor of Pediatrics and Epidemiology, Perelman School of Medicine, University of Pennsylvania; Chief, Division of Infectious Diseases, Children's Hospital of Philadelphia

Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock

Table of Contents

Throughout this document, we use "antibiotics" as opposed to "antimicrobials." The former term is commonly used, including by the Centers for Disease Control and Prevention[1], to refer to antimicrobial agents used to treat bacterial infections in both people and animals.



Executive Summary

Antibiotic resistance – as governments,[2] leading medical[3] and public health organizations around the world now agree[4,5] – is one of the most serious public health crises today.

Before the discovery of antibiotics, patients with routine bacterial infections often died. Without urgent action, that reality is likely to return as infections that are no longer treatable with today's antibiotics continue to increase. At the same time, new antibiotics are proving challenging to develop.[6] Over the last several decades, only two new classes of antibiotics have been developed and brought to market.[7,8] Additionally, doubts have been raised about whether laws recently passed by the U.S. Congress granting financial rewards to pharmaceutical companies will actually help bring antibiotics to market that are both novel and more effective than existing drugs.[9,10] Even if development work on new medicines were to begin today and eventually succeed, experience suggests that their availability for treating patients would be at least a decade away.

Antibiotic use in people and in food animal production are important drivers of antibiotic resistance.[11,12,13,14,15,16] The World Health Organization (WHO)[17], United Nations[18], European Medicines Agency[19], and the Centers for Disease Control and Prevention (CDC)[20] agree on the need to optimize use of antibiotics in both people and animals. Until we become better stewards of antibiotics, both in human medicine and in livestock production, these life-saving drugs will continue to become less effective, and the effectiveness of any antibiotics developed in the future will be at constant risk.

The 2015 U.S. National Action Plan to Combat Antibiotic-Resistant Bacteria (CARB) focuses on curbing inappropriate antibiotic use in hospitals and clinic settings and has measurable reduction goals. However, the plan to curtail antibiotic use in food animal production is narrower in scope, mainly addressing the limited phase-out of antibiotics in animal feed or water for growth promotion purposes. This is problematic given that about 70% of medically important antibiotics[21] sold in the U.S. (i.e. those identical or belonging to the same class as antibiotics used in human medicine) are sold for use in food-producing animals, not people.[22] Furthermore, the U.S. ranks second globally among users of antibiotics in food animal production, accounting for roughly 13% of the world's total.[23]

The imperative of this Commission is to keep existing antibiotics working and effective for as long as possible. We came together, as antibiotic resistance experts from the fields of infectious diseases, microbiology, veterinary and human medicine, to craft this Roadmap for how U.S. policy can and should better address the contribution to antibiotic resistance from antibiotic use in food animal production. We make specific policy recommendations in three key areas: decreasing antibiotic use, monitoring antibiotic use, and surveilling antibiotic resistance.

Summary of Roadmap Recommendations*

A. Decreasing Livestock Use of Medically Important Antibiotics

1. Set targets for reducing antibiotic use.
2. Phase out routine or programed use of medically important antibiotics.
3. Reduce the need for antibiotics by adopting non-antibiotic best practices, and by innovating new technologies, to maintain animal health and prevent disease.
4. Eliminate antibiotic use where efficacy can no longer be demonstrated.
5. Prioritize the use in veterinary practice of antibiotics that the WHO does not categorize as "critically important" for human medicine, such that:
    - A. Antibiotics in the "Critically important" category are only used to treat animals sick with a specific bacterial disease. Use of the subset of critically important antibiotics the WHO refers to as "highest priority" also should require testing that confirms the bacterium involved is not susceptible to other antibiotics.
    - B. Do not approve for food and animal use any "critically important" antibiotics, such as carbapenems, that are not currently FDA-approved for this purpose;
6. Bolster veterinary oversight of antibiotic use with other safeguards.

B. Monitoring Antibiotic Use to Reduce Antibiotic Resistance

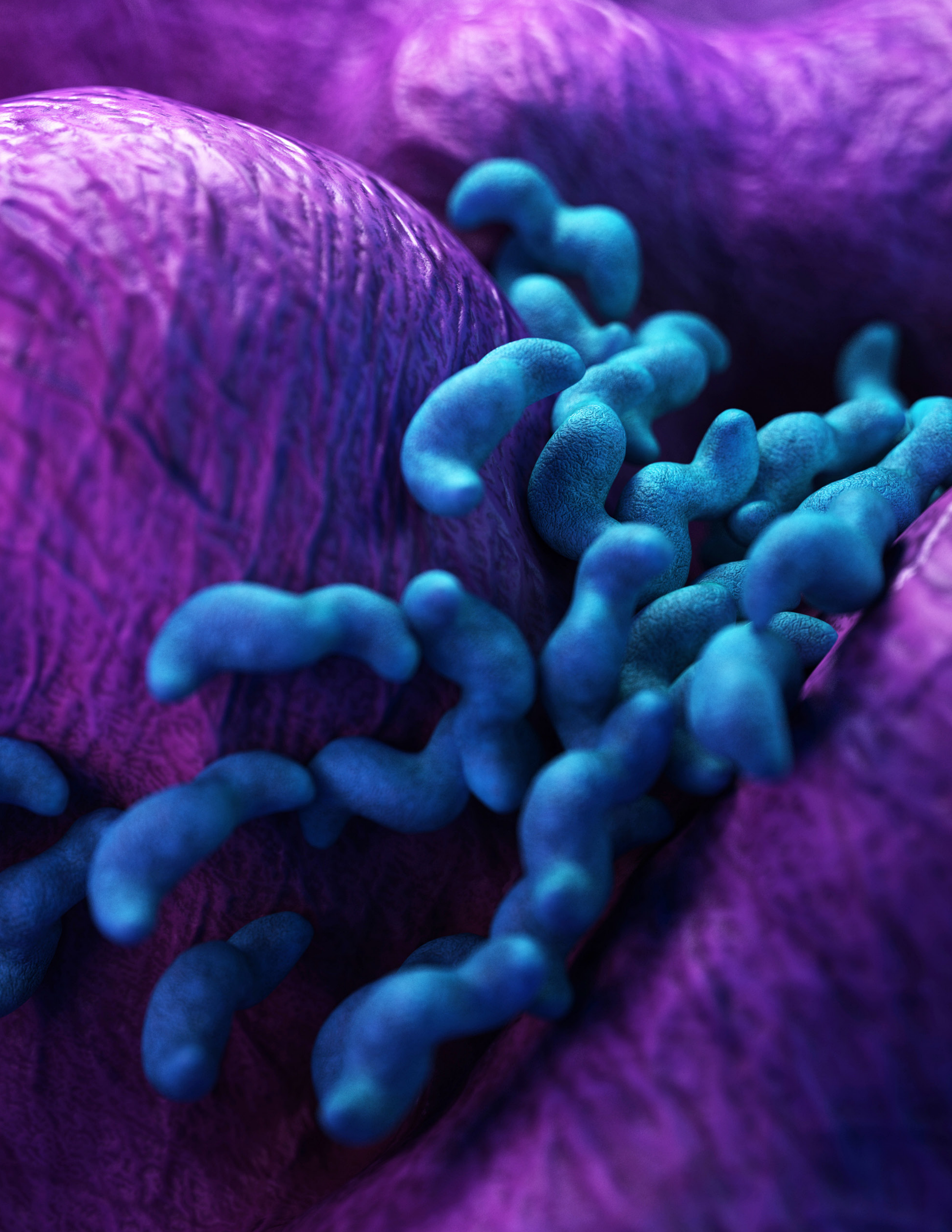
7. Develop a system for collecting detailed, comprehensive data on actual antibiotic use, and collect essential data.
8. Coordinate with and learn from the other countries in developing a comprehensive data collection system.
9. Adopt a metric for reporting data on antibiotic sales or use that better allows trends to be identified, explained and compared.

C. Enhancing Surveillance and Data Integration to Inform Antibiotic Use Policy

10. Integrate available data into a single, comprehensive report.
11. Improve surveillance to detect new and emerging resistance threats.
    - A. Expand surveillance for emerging resistance using next generation sequencing technology.
    - B. Expand surveillance for important emerging pathogens,
    - C. Pilot test approaches that comprehensively detect resistance in all bacteria in a sample.
    - D. Expand surveillance at the state level.

* *Note: The numbering of the recommendations is not meant to connote any particular prioritization.*

The following report fleshes out these recommendations and the rationale for each. Many of the recommendations draw upon successful models already implemented in Denmark and the Netherlands, two European countries with robust livestock sectors, comparable in size to that found in some of the most important livestock-producing states in the U.S. Antibiotic use in food animal production in both countries has been markedly reduced, and has been generally accompanied by lowered or plateaued levels of resistant bacteria on animals and in meat, and sometimes in human populations.[24 25 26 27 28 29 30]



The Antibiotic Resistance Threat And Its Context

For a rising number of life-threatening infections, we have almost run out of safe, dependable and effective antibiotics that will treat them.[31,32] The CDC conservatively estimates that 23,000 Americans die each year of antibiotic-resistant infections.[33] Actual deaths, some experts say, may be four times higher.[34] Predictions are that the global toll from a select number of resistant infections, estimated currently at 700,000 deaths per year, will rise to 10 million annually by 2050, surpassing deaths from cancer.[35]

Many of the 2 million Americans who suffer from antibiotic-resistant infections each year have prolonged illness. Even recovered patients can be left disabled, disfigured or with permanent pain. Beyond its human costs, the antibiotic resistance epidemic poses an emerging threat to national and economic security.[36] Drug-resistant infections are estimated to cost more than $55 billion each year in extra U.S. medical costs (because of use of more expensive antibiotics, and longer and more intensive hospitalizations) and lost productivity.[37]

Doctors often recommend procedures that can be complicated by infections, including joint replacements and chemotherapy, dialysis and Cesarean delivery, confident that there will be an antibiotic available if needed. Raising poultry, pigs and cattle successfully also depends on having antibiotics that work on sick animals. But this reliance on what are now the cornerstones of modern medicine could be in jeopardy. Without stronger action today, physicians and veterinarians face a future with less effective antibiotics, where their treatment of patients and animals may need to be substantially reconsidered.

Why This Roadmap Focuses on Medically Important Antibiotic Use in Agriculture

Antibiotics are often necessary to treat sick patients and animals. But all uses of antibiotics even the most prudent can contribute to resistance. More specifically, exposing bacteria to antibiotics can spur resistance to emerge, be selected for, and then spread; that's as true for bacteria in animals as it is for bacteria in people.[38] The solution is not to avoid using antibiotics completely but rather to use them appropriately and only when necessary as the discoverer of the first antibiotic (penicillin), Sir Alexander Fleming, acknowledged more than seven decades ago.[39]

This Commission believes the antibiotic resistance crisis cannot be resolved by only addressing antibiotic use in people, given the extensive use of the drugs in food animal production. As the CDC stated unequivocally in 2013: "Scientists around the world have provided strong evidence that antibiotic use in food producing animals can harm public health...."[40] Poultry and livestock production accounts for about 70% of the medically important antibiotics (i.e. those in the same classes of antibiotics as those used in human medicine) sold in the U.S.[41] In 2015, the latest year for which data are publicly available, this translates to 21,389,200 pounds of medically important antibiotic active ingredient sold for use in food-producing animals.[42,43] These include critically important antibiotics that the WHO considers to be the highest priority for human medicine, such as macrolides, fluoroquinolones and 3rd generation cephalosporins. Compared to the rest of the developed world, as we later discuss, the U.S. is among the most intensive users of antibiotics in food animal production. Yet, as we discuss further, the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) proposes concrete and measurable goals for curbing inappropriate antibiotic use in human medicine, but fails to set equivalent, numeric goals for reducing antibiotics used in food animal production.[44]

A One Health Perspective

Experts agree that the 21st century crisis of antibiotic resistance is a "One Health" issue.[45,46] One Health is a public health concept recognizing that the health of people, animals and the environments in which they co-exist –including the bacterial ecosystem are interconnected.[47,48] Underscoring the importance of a One Health approach is the fact that scientists estimate "6 out of every 10 infectious diseases in people are spread from animals[49]", as well as a recent study suggesting that at least some outbreaks of "livestock-associated" MRSA may stem from an initial introduction of that MRSA from people onto farms.[50] The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) reiterates this approach:

"DANMAP was developed making the most of a collaborative spirit between stakeholders and with a common understanding of [antimicrobial resistance] as a serious health threat requiring a One Health approach to counter - because humans, foods and animals constitute overlapping reservoirs of antimicrobial resistance."

One Health also describes a more integrated, interdisciplinary approach to tackling infectious disease threats to global health, involving microbiologists, ecologists and epidemiologists, physicians and veterinarians. This Commission has taken a One Health approach as reflected by its make-up, as well as in its conclusions and recommendations. A One Health understanding underlies our shared sense that the antibiotic resistance crisis, whether in animal or human settings, is largely a "numbers game" the higher the use, the more resistance can emerge and spread – which Box A explains in greater detail.

A half century of science, and hundreds of individual studies and reviews, support the idea that antibiotic resistance is a numbers game; in short, the risk for emergence and enrichment of antibiotic-resistant bacteria goes up with each person or animal that is treated or exposed to those drugs.[51,52,53,54,55,56] Many scientific reviews, by renowned experts, have concluded that the existing body of evidence justifies stronger action to reduce antibiotic use in both human and animal settings.[57,58,59,60,61,62] Our goal was not to duplicate these reviews, but instead to generate consensus recommendations, based upon the existing body of science, for policies and practices that will help curtail the unnecessary use of antibiotics in food animal production.

Box A: One Health: Factors That Can Contribute to the Spread of Antibiotic Resistance

- The greater the quantity of antibiotics used, the more resistance will emerge and spread.[63,64,65]
- The greater the number of individuals (human or animal) that are given antibiotics, the more bacteria are exposed, and the greater the likelihood resistance will emerge and spread.[66,67]
- The longer the duration of antibiotic use, the longer the period of time over which resistance can emerge and spread.[68,69,70,71]

Editorial Note from the Commission: While exceptions may exist, these observations around antibiotic use and its impact on resistance hold true more often than not.


Z00624

Roadmap Recommendations for U.S. Policy on Use of Medically Important Antibiotics in Food Production

In March 2015, the Obama Administration released the National Action Plan to Combat Antibiotic-Resistant Bacteria (CARB).[72] It was presented as a guiding document to coordinate and map federal efforts to address antibiotic resistance, and ultimately preserve the future efficacy of antibiotics.

CARB establishes five national goals to better understand, track and reduce antibiotic use, each of them accompanied by milestones and outcomes to be achieved by 2020. However, comprehensive goals and milestones to better track, understand and reduce antibiotic use in human settings are not mirrored by similarly comprehensive goals around antibiotic use in the production of livestock and poultry. Regarding antibiotic use in food animal settings, CARB largely defers to the FDA, the federal agency responsible for regulating these uses. As laid out in the following sections, however, there are serious shortcomings to the FDA's approach. We strongly question whether current FDA efforts will lead to significant reductions in antibiotic use in food producing animals, and consequently succeed at reducing the spread of antibiotic resistance.

To address these shortcomings, the Roadmap makes policy recommendations in three key areas: decreasing antibiotic use, monitoring antibiotic use, and surveilling antibiotic resistance. These recommendations are largely aimed at both federal and state policymakers, but also go beyond government policy. For example, Appendix A offers tools that medical professionals can use to help address livestock overuse of antibiotics and Appendix C includes recommendations for universities, hospitals, and other buyers of meat and poultry to use in procuring products.

A. Decreasing Livestock Use of Medically Important Antibiotics

It is the Commission's shared sense that the statements in Box A (page 7) capture important connections between antibiotic use and antibiotic resistance. They lead in turn to the following general priorities for policy action, which are applicable not only to the U.S. but also worldwide.

Priority #1: Ensure antibiotics are used only when necessary and effective, and when non-antibiotic alternatives are unavailable, so as to reduce overall exposure of bacteria to antibiotics (see Box B), and therefore the emergence and spread of resistance.

- **A)** When directed by a veterinarian, antibiotics should be used to treat sick food-producing animals or those that have been exposed to an animal with diagnosed disease.

- **B)** Antibiotics should not substitute for good animal management practices.

Priority #2: Reduce the sale and use of medically important antibiotics, putting the highest priority on those deemed of greatest importance to human medicine.

Priority #3: Administer antibiotics for the shortest time period (duration) necessary.

While equally relevant in human medicine, these priorities are framed in terms of food animal production because that is the focus of this report. These general priorities guide our later recommendations for urgently needed changes to U.S. policy and practice.

Box B: Exposing Bacteria to Antibiotics Raises Risk for Resistance

Bacteria can become resistant simply by errors being made as their DNA is copied, something that occurs each time bacteria reproduce. They also can become resistant by picking up resistance genes from other bacteria. Using an antibiotic allows resistant bacteria that can withstand the antibiotic to survive and multiply. Other bacteria then can acquire resistance genes from these already-resistant bacteria. Because the gut harbors billions of bacteria – in food-producing animals, as well as in people – it can be a hot spot for exchange of resistance genes, including those acquired through the food supply.[73,74,75,76]

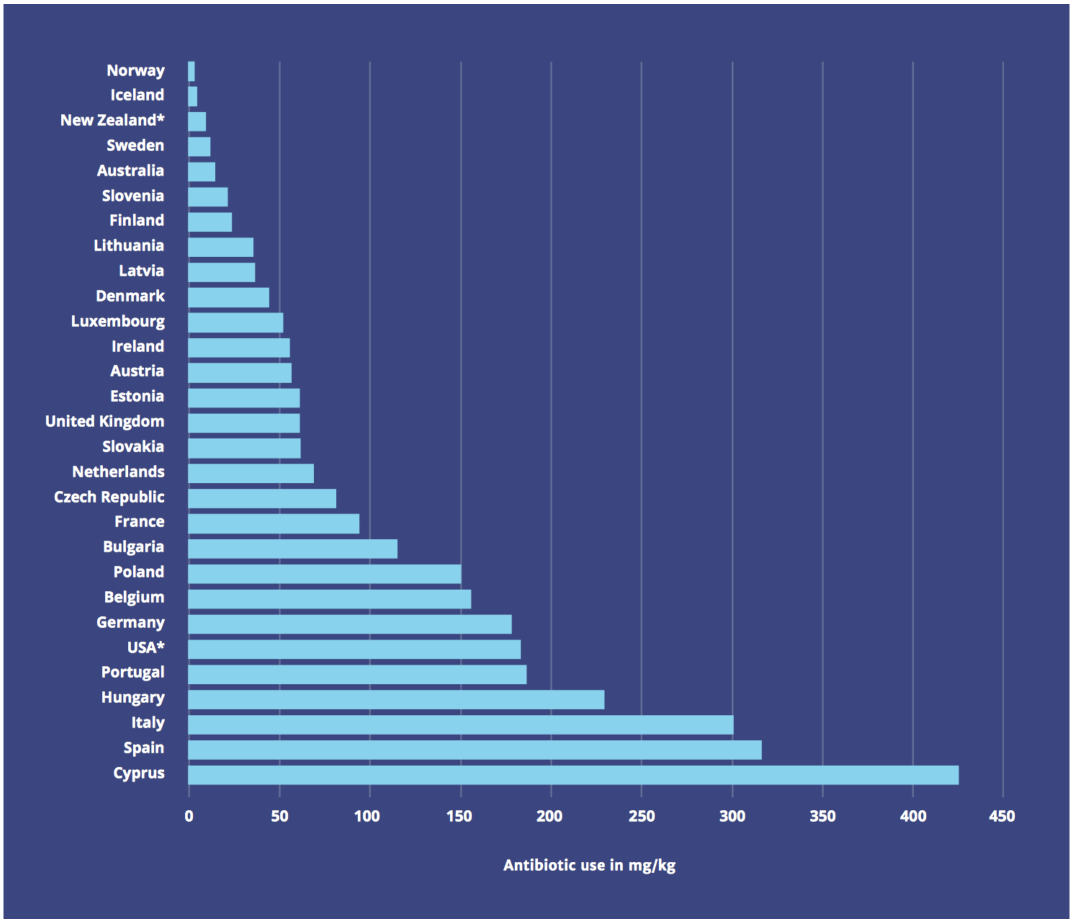
A plasmid is a small unit of DNA that can carry multiple resistance genes. Plasmids also are easily shared among bacteria in human and animal guts. Non-resistant bacteria that are easily treatable with antibiotics can become resistant to many antibiotics in an instant by picking up one of these plasmids.[77] Plasmids often carry genes that code simultaneously for resistance to both older and newer antibiotics, so that even when people or animals are exposed to or treated with older or less important antibiotics, it still can fuel growth of bacteria that are resistant to newer (often, more medically important) antibiotics. This underscores the need to thoughtfully use all antibiotics – new or old, and human or not.

Use of Medically Important Antibiotics in Livestock

It is estimated that the U.S. is the second highest user of antibiotics in food animal production, with 13% of the global total, behind China at 23%.[78] The U.S. is one of the largest producers and exporters of meat and poultry, globally, but also stands out compared to many other major livestock-producing countries in terms of its consumption of antibiotics per unit of meat produced (See Figure 1). As incomes rise in many developing countries, along with their demand for animal-based proteins, and more antibiotic-intensive methods for raising food-producing animals are adopted by them, it's projected that their share of global antibiotics consumption also will rise.[79]

The Review on Antimicrobial Resistance, commissioned by the UK Prime Minister in 2014, compared agricultural antibiotic use in European Union nations with use in other developed countries, such as Australia, New Zealand and the U.S. Antibiotic use figures do not include ionophores or oligosaccharides. At about 180 mg/kg, the estimated intensity of antibiotic use in the U.S. (measured as milligrams of antibiotic active ingredient per kilogram of meat produced) is multiple times higher than countries such as Australia, Denmark, and the Netherlands, while roughly commensurate with others, such as Germany and Portugal.[80]

Figure 1: Agricultural antimicrobial use (in mg/kg of animal body weight) in 25 EU/EEA countries, Australia, New Zealand and the U.S.[81]



Work to dramatically reduce use of antibiotics in food-producing animals in the Netherlands serves as a good case study for the U.S. As recently as 2008, the Netherlands used antibiotics about as intensively as the U.S. does now. However, between 2009 and 2016, the use of antibiotics in Dutch livestock was reduced by more than 64%, after adoption of the policies and approaches described in Appendix E.[82] Despite these changes, farmers maintained or increased their profits and levels of production, while the number of resistant bacteria in livestock were reduced significantly.[83,84] These comparisons strongly suggest similar reductions also could be achieved in the U.S., if equivalent leadership were exerted, and policy changes were adopted.

Antibiotics routinely administered *en masse* – even when under veterinary supervision – raise additional concerns. Approximately 95% of the medically important antibiotics approved for use in U.S. food-producing animals by volume are sold as additives to animal feed or water, to be administered to groups rather than to individual animals.[85,86] Mass administration to flocks or herds was the typical route of delivery for medically important antibiotics given for growth promotion (now illegal in the U.S.), but it continues to be the primary way antibiotics are administered for routine disease prevention purposes. When more animals, and therefore more bacteria, are exposed to antibiotics it elevates the risk that resistance will develop and spread.

Feed or water-administered antibiotics are often labeled to allow for use over a prolonged period of time. About one-third of the medically important antibiotics still allowed for use in feed have no limits on the duration of use.[87] Even for those antibiotics for which there are specified durations, it would be within a veterinarian's prerogative to authorize several back-to-back, short duration uses for disease prevention, even in the absence of a particular disease diagnosis. This kind of usage, in terms of selection for the emergence and spread of resistance, would not appear to be much different than continuous in-feed use of low-dose antibiotics for growth promotion.

The Current U.S. Approach

The U.S. is among the 193 U.N. member states that declared in September 2016 their commitment to work together to address the root causes of the resistance crisis across human health, animal health and agriculture settings.[88] Members re-committed to preparing national action plans modeled after the WHO Global Action Plan on Antimicrobial Resistance.

CARB, completed in March 2015, sets specific, numeric goals for reducing inappropriate antibiotic use in hospitals and outpatient settings by 20% and 50%, respectively (see Table 1). Examples of inappropriate antibiotic use include antibiotics that are wrongly prescribed for viral infections, such as colds; antibiotics incorrectly given for an infection for which they lack antibacterial activity; and antibiotics prescribed for a longer period of time than is necessary. CARB also sets specific goals for better surveillance and monitoring of antibiotic resistance linked to drug use in human medicine.

Table 1. Comparing CARB's Approach: Reducing Antibiotic Use in People vs. Food-Producing Animals

Antibiotics in Human Medicine	Antibiotics in Food Animal Production
Starting point:	**Starting point:**
Accounts for 30% of all medically important antibiotics sold Preventive antibiotic normally not used in the general population Preventive use in limited circumstances, for example in patients with pre-existing conditions: Patients before surgery can get antibiotics to prevent surgical site infections Dental patients with abnormal heart valves get antibiotics prior to dental procedures	Accounts for 70% of all medically important antibiotics sold Medically important antibiotics routinely fed to flocks or herds for disease prevention, absent a diagnosis of disease Until recently, antibiotics were allowed to be used to speed up animal growth, i.e. "growth promotion"
CARB Includes:	**CARB Includes:**
Firm numerical targets for reduction of inappropriate use in different settings: 20% in inpatient settings 50% in outpatient settings	No targets for reduction Relies on FDA's elimination of growth promotion uses, estimated at 10-15% of use (at most): Concern: While growth promotion use has been eliminated, similar or identical use can continue to "prevent" diseases in animals that are not sick, as a substitute for improved management practices

CARB does not set meaningful goals related to antibiotics used in food animal production. First, it sets no numeric goals for reducing antibiotic use overall, which is worrisome given the high volume of use in the livestock sector. Second, current national efforts to monitor antibiotic use on farms are mostly non-existent and the integration of antibiotic use data with surveillance of the spread of antibiotic resistance is inadequate. Under CARB, goals for addressing these shortcomings are sparse and vague.

Brief History of FDA Efforts

More than four decades ago, the FDA made a scientific finding that certain antibiotics given to food-producing animals at "sub-therapeutic" levels (e.g. for growth promotion, feed efficiency, and disease prevention) posed a threat to human health because of antibiotic resistance concerns.[89] FDA subsequently proposed in 1977 to withdraw approvals for such uses of penicillins and tetracyclines, but it did not follow through.[90] While CARB largely defers to FDA to address antibiotic use in food animal production, FDA's efforts to date have targeted only a small portion of total antibiotic use. As described below, the agency has set no targets for reduction of use, and has included few safeguards to monitor and adjust for changes in usage levels. Moreover, a recent assessment by the independent Government Accountability Office (GAO), published in March 2017, concludes that without clearer objectives, still-inadequate data collection and no metrics in place for measuring effectiveness, the agency cannot know whether the steps it has taken have improved the management of antibiotics used in food animal production.[91]

Phase-out of growth promotion claims, but approval for disease prevention use continues

In its 2013 Guidance for Industry #213[92], the FDA urged drug makers to voluntarily remove growth promotion language or "claims" from their medically important antibiotic products sold for use in animal feed or drinking water. Companies removed those claims and FDA subsequently codified the changes in January 2017. However, the elimination of antibiotics for growth promotion alone is not likely to significantly reduce antibiotic use in food animal production; both the animal pharmaceutical industry and the FDA estimate that growth promotion use accounts for no more than 10% to 15% of all antibiotic sold for use in animals.[93] Furthermore, many of the same antibiotics sold for use as growth promoters are also FDA-approved and labeled for the purpose of disease prevention, including at dosage levels and durations that are similar to or the same as those previously approved for growth promotion.[94,95] This means that mass administration of medically important antibiotics for long periods of time may continue.

Veterinary oversight without other safeguards

Under Guidance #213, the sale of medically important antibiotics for use in feed or drinking water for disease prevention, control or treatment can continue, but the FDA recently put such uses under the oversight of a veterinarian. Purchasing the antibiotics requires a feed directive (called a VFD) or a veterinary prescription.

However, there are no policies or tools in place to monitor and track how well veterinarians oversee or prescribe the use of these antibiotics in livestock production. For instance, there are no systems to compare antibiotic prescription patterns among veterinarians, or even to identify high prescribers as the first step in helping them modify their use of antibiotics. In addition, there are no systems or means for discouraging farms from shopping around for a veterinarian who might be more willing than his or her peers to prescribe antibiotics. In these two respects, the U.S. suffers by comparison to

Denmark and the Netherlands, where such systems are in place (described on page X). Finally, U.S. veterinarians are frequently employed by and write prescriptions on behalf of large meat production companies. A 2011 GAO report supports the concern that conflicts of interest could interfere with the determination of whether antibiotics for these food-producing animals are in fact necessary.[96]

Recommendations to Decrease Livestock Use of Medically Important Antibiotics

To successfully combat the crisis of antibiotic resistance, the U.S. must meaningfully reduce use of antibiotics in food animal production, as well as in human medicine. The recommendations below draw on science and successful efforts to reduce antibiotic use in human medicine in the U.S. and in livestock production in Europe.

We acknowledge there may be significant cultural differences between the U.S. and countries such as Denmark and the Netherlands that may affect how some of our recommendations would be implemented. However, many of these recommendations already are being implemented in the U.S. within human medicine (See Table 1), by some U.S. food producers, and by some individual states. Our broad recommendations also can be adapted to different sectors and institutions (e.g. hospital food service, restaurants, etc.) in ways that the appendices to this report explain further.

Recommendation No. 1: Set targets for reducing antibiotic use

Antibiotic use reduction targets are a well-established policy tool for achieving change. For example, the Dutch livestock sector and government were able to reduce sales and use of antibiotics in food animal production by more than 60% in part by setting reduction targets. (See Appendix E.) Analyses of their efforts have pointed to target-setting as a key component of success in both Denmark and the Netherlands.[97]

CARB also found value in setting reduction targets in both inpatient and outpatient settings. We recommend that similar reduction targets be established in food animal production. Target setting should be accompanied by strong data collection programs and benchmarking to ensure that reductions are achieved and high users are identified for improvements.

While reduction targets ideally would be set at the federal level, state governments and even private actors can make significant contributions by setting their own targets.

Recommendation No. 2: Phase out routine or programmed antibiotic use

We recommend a policy to phase out the routine or programmed administration of medically important antibiotics over long periods of time to flocks or herds of animals. ('Programmed' use of antibiotics refers to when animal management protocols or guidelines have been written so that antibiotics are regularly administered at a particular phase of production, irrespective of any particular disease diagnosis.) This can be combined with target setting, as in the Netherlands, or pursued independently as in Denmark. Both countries have phased out antibiotic growth promoters and other uses of antibiotics in the absence of disease, and have achieved reductions of 45% to 60%. The American Academy of Pediatrics[98] and the European Medicines Agency/European Food Safety Authority[99] also recommend only using antibiotics to control or treat disease. The U.S. should follow this lead.

Absent federal action, states also can take steps to phase out routine or programmed antibiotic use in food-producing animals within their borders. California has already done so by banning the use of antibiotics for disease prevention "in a regular pattern of use," starting in 2018.[100]

The private and public sectors also can take action. Major food companies that have instituted policies to phase out the routine use of antibiotics for all or some of the meat they source include Chipotle, Chick-fil-A, Panera, Subway, KFC and McDonalds. Public schools and hospitals also are increasingly purchasing meat and poultry where antibiotics are either disallowed or allowed only for treating or controlling disease, but not allowed for routine use for disease prevention. Even individuals and families can set goals for themselves by purchasing meat that reflects responsible antibiotic use practices.

Both private and public sector actors should also take action to support antibiotic stewardship programs that emphasize better management practices to prevent disease and reduce or avoid the need for antibiotics in the first place.

Recommendation No. 3: Reduce the need for antibiotics by adopting non-antibiotic best practices, and by innovating new technologies, to maintain animal health and prevent disease.

Even where antibiotics are being used to treat disease, there often are opportunities to reduce or avoid that use altogether by changing animal management practices or investing in new technologies, such as vaccines, to keep animals from getting sick in the first place. Non-antibiotic disease prevention is confirmed in both science and practice. For example, in February 2017, the European Medicines Agency along with the European Food Safety Authority, published an extensive scientific opinion detailing evidence-based management practices in food animal production that reduce or avoid the need for antibiotics.[101] Additionally, Kansas State University[102], the American College of Veterinary Internal Medicine[103], and the National Pork Board[104] also emphasize that responsible antibiotic use involves reducing the need for antibiotics, such as non-antibiotic measures to improve animal health and prevent disease.

In the private sector, McDonald's has incorporated this principle into its 2015 Vision for Antimicrobial Stewardship for Food Animals which articulates four goals for its global meat supply chains, including: "Utilize animal production practices that reduce, and where possible eliminate, the need for antimicrobial therapies and adopt existing best practices and/or new practices that would result in subsequent reductions of antimicrobial use."[105]

Recommendation No. 4: Eliminate antibiotic use where efficacy can no longer be demonstrated.

Antibiotic products that are FDA-approved for use in livestock or poultry production must have been shown to be efficacious at the time of approval. Those approvals, however, may have occurred decades ago and may no longer be accurate. Newer data may be available showing reduced efficacy as a result of significant changes in animal agriculture since the drugs were first approved. Some drugs were first approved over 50 years ago and have never been re-evaluated by the FDA.

Recommendation No. 5: Prioritize the use of antibiotics in veterinary practice that the WHO does not categorize as "critically important" for human medicine.

Among all antibiotics considered medically important by the World Health Organization (WHO)[106] are some categorized as "critically important" for human medicine. On this list are several classes of antibiotics that are FDA-approved for use in food-producing animals in the U.S., including 3rd-generation cephalosporins, fluoroquinolones, macrolides, aminoglycosides, penicillins and polymyxins.[107,108] With respect to use of these critically important antibiotics, we recommend policies ensuring that in veterinary practice:

A. Antibiotics in the "critically important" category are used only to treat animals sick with a specific bacterial disease. Use of the subset of 'highest priority' critically important antibiotics (also defined by the WHO)[109] should require testing that confirms the bacterium involved is not susceptible to other antibiotics.

B. Critically important antibiotics that are not currently FDA-approved for food animal use in the U.S., such as carbapenems, should never be approved;

The Netherlands, as described in a recent European Commission audit, provides one example of a policy framework that prioritizes the use in animals of antibiotics considered to be of lower importance for human medicine.[110] All antibiotics used in farming there are available only under a veterinarian's prescription. Since 2012, a work group of the Royal Netherlands Veterinary Association (KNMvD) has had a system for classifying these antibiotics and how they are to be used in order to reduce the selection for antibiotic resistance. First-tier or first choice antibiotics can be given empirically under an existing farm treatment plan and protocol, after a problem has been diagnosed. Second-choice antibiotics are only used after a veterinarian's clinical exam and testing has substantiated the need for them. Third-choice antibiotics are the most restricted, because they are considered the highest priority for human medicine, such as fluoroquinolones and 3rd generation cephalosporins; they are to be used in individual animals only after veterinary testing substantiates that there are no first- or second-tier alternatives.

Similar policies in the U.S. to prioritize the use in animals of non-critically important drugs would be meaningful, but only if combined with the phase-out of medically important antibiotics used routinely in the absence of a disease diagnosis (such as for disease prevention), per Recommendation No. 2.

In addition to or absent U.S. federal action, state and local governments could incorporate these restrictions on the use of critically important antibiotics in food-producing animals in legislation or purchasing criteria. Private purchasers of meat and/or poultry products likewise could build this recommendation into their supply chain standards or policies.

Recommendation No. 6: Bolster veterinary oversight of antibiotic use with other safeguards.

In Denmark and the Netherlands, stricter veterinary oversight was instituted and combined with other safeguards to counter the likely increase in prescription use of antibiotics following restrictions placed on growth promotion and disease prevention uses. Those safeguards include: restrictions placed on certain kinds of uses, restrictions on veterinarian profits from the sales of antibiotics, and new accountability measures such as benchmarks for antibiotic use by farms and veterinarians (e.g. "Yellow card" or comparable programs to identify high users of antibiotics and help them to improve their performance). (See Appendix E).

Some safeguards along these lines are already in place in U.S. human medicine. The American Medical Association, for example, cautions U.S. physicians that profiting from the sale of health-related products, including antibiotics, from their own offices creates a financial conflict of interest, is unethical and therefore not allowed.[111] Also, under the Physician Payments Sunshine Act of the

Affordable Care Act, manufacturers of pharmaceuticals as well as medical devices must divulge financial payments to physicians and hospitals, and these become a matter of public record.[112]

The U.S. government can and should play a key role to ensure stronger veterinary oversight of antibiotic use in food animal production. State governments also can implement strong data and benchmarking policies regarding antibiotic use in food-producing animals within their borders. Similarly, major purchasers of meat and poultry can track the use of medically important antibiotics in their supply chains and benchmark performance to drive reductions.

Table 2. Comparing U.S. Veterinary Oversight Provisions to Denmark and the Netherlands

	United States	Denmark (DK) and the Netherlands (NL)
Restrictions	Growth promotion uses ended; Routine disease prevention allowed	Both DK and NL have banned growth promotion and disease prevention uses
Veterinarian oversight, accountability	Vet oversight mostly required, except for select over-the-counter injectable antibiotics No limits on profiting from sales No tracking of how much individual vets prescribe antibiotics No farm registration of vets required	Vet oversight of antibiotics required in DK, NL DK - Farms required to have a contracted veterinarian at all times NL - Requires farms to have a one-to-one relationship with a veterinarian. DK -Vet profiting from direct sales capped at 10% (profits hit 30% before cap)

B. Monitoring Antibiotic Use to Reduce Antibiotic Resistance

The collection of antibiotic use data is critical for managing and minimizing antibiotic resistance, as recognized by the GAO[113], the World Organization for Animal Health (OIE)[114] and the WHO.[115]

Better data are essential to fully understand how and why antibiotics are used in food animal production and how that use varies by species, region and over time. Understanding patterns of use and trends in antibiotic resistance can help policymakers direct resources so it has the greatest possible impact. It also will allow for the success (or failure) of specific interventions to be better monitored so that adjustments can be made. Similarly, food animal producers need better data to develop improved antibiotic use strategies, including setting targets for and tracking progress toward reducing unnecessary use.

The usefulness of antibiotic use data is influenced by the choice of metric in reporting that data. The choice of a particular metric can, in turn, reflect the setting in which antibiotic use occurs as well as the robustness of the underlying data. Also guiding the choice of metric is the purpose for which those data are being utilized (i.e. tracking trends in antibiotic use; comparing antibiotic use between countries or between animal species; or for determining any association between particular antibiotic uses and resistance).[116]

The Current U.S. Approach to Data Collection

Antibiotics sold for use in food animal production far outstrip those sold for use in human medicine. To successfully address the antibiotic resistance crisis, reliable data on how and why antibiotics are used in food animal production is a critical element. Without such information, national efforts to confront the crisis of antibiotic resistance are likely to fall short.

In the U.S., data related to food animal production are collected along three data streams. Since 2009, drug companies have been required to supply the FDA with information on antibiotics sales for use in food-producing animals, which the agency publicly issues as an annual report. It includes information on the intended route of administration (e.g. via animal feed, drinking water or injection), and the antibiotics' dispensing status (i.e. over-the-counter, prescription, or veterinary feed directive). Starting in 2017, the FDA also will require drug companies to estimate antibiotic sales broken down by major food-producing species (cattle, swine, chickens and turkeys). The agency cautions that these estimates may be incomplete and not match actual antibiotic use at the farm level.

The U.S. Department of Agriculture (USDA) collects the only publicly available data on actual farm-level use of antibiotics. Data is collected through voluntary farm surveys on animal health and management, conducted since 1983 by the agency's National Animal Health Monitoring System (NAHMS). Information for each livestock sector is collected only once per five- to seven-years; the questions asked can vary from one survey to the next. Both factors make year-to-year comparisons basically impossible, and trends more difficult to establish, while also eroding the data's usefulness in assessing the impacts on farm practice of any specific policy changes related to antibiotic use. Finally, the surveys are voluntary, and therefore not comprehensive by definition. Voluntary surveys also may be unintentionally biased, since farms that choose to participate may not accurately reflect the industry as a whole.

In 2011, the U.S. Government Accountability Office summarized the program's shortcomings as follows:

"....NAHMS is limited by long lag times (approximately six years) between surveys of the same species, changes in methodology and survey populations between studies, reliance on voluntary participation by food animal producers, and collection of qualitative, rather than quantitative information on antibiotic use."[117]

Further illustrating the shortcomings, the chicken and turkey surveys do not ask about antibiotics use (See Table 3). Only beef, dairy and swine producers are asked about what antibiotics have been used on their farms in the last six months, the route of administration, the age of the animals (e.g. nursery or finisher pigs), and general reason for use (e.g. growth promotion, disease prevention, disease control, disease treatment). The USDA recently announced that antibiotic-specific surveys for swine farms and beef feedlots are being conducted in 2017.[118] While they may provide some additional data, these surveys will carry the same aforementioned limitations as other NAHMS surveys[119], while also combining reporting on antibiotics used for treatment, control and prevention purposes so as to make it impossible to distinguish between those uses.[120]

Table 3: Overview of major poultry, livestock studies conducted by NAHMS, 2006-2016

	Year studies were conducted, 2006 - 16	Information on antibiotic use	Information on antibiotic resistance
Chicken	2007, 2010		
Turkey	2007, 2010		
Swine	2006, 2012	✓	✓
Beef (cow-calf)	2007	✓	✓
Beef (feedlot)	2011	✓	✓
Dairy	2007, 2014	✓	✓

The USDA collects some limited, additional antibiotic use data from farms as part of annual surveys of farm finances in its Agricultural Resource Management Survey (ARMS) program, jointly conducted by the National Agricultural Statistics Service (NASS) with the Economic Research Service.[121] NASS also collects important information on the number of animals raised in the U.S. that are needed to interpret antibiotic use data. The ARMS surveys included questions about antibiotic use in swine farms in 2004, 2009, and 2015 and on broiler farms in 2006 and 2011. These surveys, however, contain much less detail on antibiotics than the aforementioned NAHMS surveys; they provide only general information on whether or not a farm used antibiotics for a specific purpose (e.g. growth promotion, disease prevention, or treatment), and provide no information on specific antibiotics used. These data also carry the additional limitations of the data collected under NAHMS as they are sporadic and voluntary.

In short, antibiotic use information available in the U.S. is simply inadequate to fully address the antibiotic resistance threat to human health. Without more detailed and comprehensive information, we cannot have an accurate picture of how antibiotics are sold, distributed, and used in food animal production. The absence of this is likely to hamper policymakers and healthcare leaders trying to tackle antibiotic resistance because changes and trends cannot be accurately tracked, and resources may not be focused where they are most needed.

Examples of Comprehensive Data Collection Systems

Successful models do exist for collecting and analyzing how and why antibiotics are used in food animal production (See Box C). In each model, the government, livestock industry and veterinarians all play important, albeit somewhat different, roles.

In Denmark, a national database called VETSTAT serves as a repository for data on drug usage at the herd level. It is collected from three sources allowed to dispense antibiotics: veterinary pharmacies, veterinarians and feed mills.[122] VETSTAT, funded by the Danish Ministry of Food, Agriculture and Fisheries, is then used as a resource to set national goals and thresholds, as well as to benchmark antibiotic use at the individual farm level. In the Netherlands, an expert panel of the independent Netherlands Veterinary Medicines Authority (known as SDa), reviews the data from 40,000 livestock farms, sets benchmarks on antibiotic use and issues an annual report on its findings. The data come from the large animal production sectors themselves, which have recently instituted centralized registration systems that monitor antibiotic use on all farms, and from FIDIN, the federation of the Dutch veterinary pharmaceutical industry, which reports on annual sales of antibiotics.

These different models for data collection Illustrate different approaches to ensuring farm anonymity. In the Netherlands, the industry associations maintain and track the data and provide anonymized information on usage to the independent SDa. In Denmark, the government can access farm-specific data more freely, but the public must make a special request to access it.

Recommendations for Improving U.S. Data Collection

The following recommendations encompass a discussion of the essential data that should be collected (See Box D), potential sources of data, as well as options for metrics that synthesize the available data and allow for comparisons of antibiotic use.

Recommendation No. 7: Develop a system for collecting detailed, comprehensive data on actual antibiotic use, and collect essential data

We call on federal agencies, working with states and producer groups, to develop a system for collecting detailed, reliable data on the use (not just sales) of antibiotics at the farm level, or at the level of the veterinarians overseeing their use.

The FDA acknowledges that gathering information on the way medically important antibiotics are used is essential to measuring whether its current strategy is working to ensure that antibiotics are used appropriately in food-producing animals. However, the agency has no system in place to collect ongoing and comprehensive use data, nor does it have any stated intention to build such a system. Each of the current separate programs collecting data pertaining to U.S. antibiotic sales or use – FDA's collection of sales data, USDA's NAHMS surveys, feed mill records and existing state databases – should be molded into a unified system modeled on the experience in Denmark and the Netherlands.

Development of unified data collection systems in Denmark and the Netherland has been critical to their success in reducing antibiotic use (over baseline levels) by 47% and 64%, respectively. To ensure success, or even to measure progress of CARB, the U.S. must also have a good data collection system. That system should be mandatory, not voluntary, and should be comprehensive enough to encompass certain essential data.

Box C: Comparing U.S. Data Collection Efforts to Denmark and the Netherlands

The limited data on antibiotic use in U.S. animal agriculture stands in stark contrast to Denmark and the Netherlands. Both countries have robust, profitable meat and poultry industries where they raise animals in intensive, industrial-style operations not unlike those in the U.S. Both have adopted policy and practice changes that have helped to significantly curtail unnecessary antibiotic use in food animal production. In each country, the changes include improved monitoring of antibiotics sold and used in food-producing animals as well as surveillance to identify patterns of resistance in people, retail meat and in food-producing animals. Antibiotic sales, use and surveillance information for each country also are integrated into a single annual report.[123,124] No such integrated report is prepared in the U.S., as is discussed later. The enhanced systems for collecting and integrating data in the two countries have informed additional policy interventions over time by identifying areas in need of improvement. They also have made it possible to benchmark how well veterinarians and/or farms use antibiotics relative to their peers. These systems have been crucial in enabling the countries to reach their antibiotic use goals and reduction targets as well as keep antibiotic resistance in animal populations at low levels. Data, in other words, are central to driving improvements in antibiotic use.

Denmark – Responding to public concern about levels of antibiotic use in food-producing animals, and possible impacts on human health, Denmark began taking a series of important steps in 1995, including improving data collection. It established DANMAP, the Danish Integrated Antimicrobial Resistance Monitoring and Research Program, which: 1) monitors antibiotic use in food-producing animals and people; 2) monitors occurrence of antibiotic resistance in bacteria from food-producing animals, food of animal origin and people; 3) identifies trends and puts together information on associations between antibiotic use and resistance; and 4) identifies routes of transmission and areas for further research.[125] Individual farm level data are collected from veterinarians, pharmacies and feed mills and reported to a centralized system (VETSTAT). VETSTAT information can be accessed by farmers or veterinarians, allowing them to compare their level of use to a national average.

The Netherlands – In 2009, public concern in the Netherlands led the four main livestock sectors (veal, cattle, pigs and poultry), along with other stakeholders, to establish a task force on antibiotic resistance. Later that year, industry and government together set a goal for reducing antibiotic use by 50% within five years. The independent SDa was formed in 2010, and serves as a repository for sales data collected from the pharmaceutical industry, and for prescription data collected by the livestock industry and then provided in an anonymized form to the SDa. SDa is a public–private partnership between government, the Royal Dutch Veterinary Association and the livestock industries.

Box D: What Data Should Be Collected?

Certain minimum data are essential to capture a meaningful picture of how and why antibiotics are being used in animal agriculture. It is critical to know:

- Antibiotic administered;
- Species (pigs, turkeys, chickens, beef and dairy cattle) on which the drug was used;
- Purpose of use and/or indication (disease treatment, disease prevention/control, type of infection such respiratory illness, etc.);
- Route of administration (feed, water, oral, injection, intramammary, topical, other);
- Volume of antibiotic active ingredient;
- Duration of use; and
- Number of animals receiving the antibiotic.

Ideally, the following additional information also would be collected to provide a more complete understanding of use and resistance patterns:

- Dose of the antibiotic administered;
- Production class (dairy cattle vs. beef cattle, etc.);
- Age of animal (sows vs. piglet; if interested in daily dose);
- Region;
- Farm identification (potentially anonymous);
- Veterinarian identification (potentially anonymous)

Data Sources

Data could be collected from several different sources, as described in the Danish and Dutch examples. At the federal level, for example, FDA could collect information from feed mills on antibiotics mixed into animal feed and then sold for use on farms. Currently, it does not do this and feed mills are only required to maintain records and make them available to the FDA, if requested. Similarly, the USDA could implement a yearly survey representative of the food animal production sector to collect information on how and why antibiotics are used.

In absolute terms, especially relative to the enormous potential economic losses if effective antibiotics are no longer available in the future, the near-term costs of building this system are unlikely to be large relative to the magnitude of the threat. For example, experts in Denmark indicate that a recent overhaul of VETSTAT, their comprehensive data collection system, is going to cost an estimated $3.2 million; ongoing operations will cost an additional $450,000 a year.

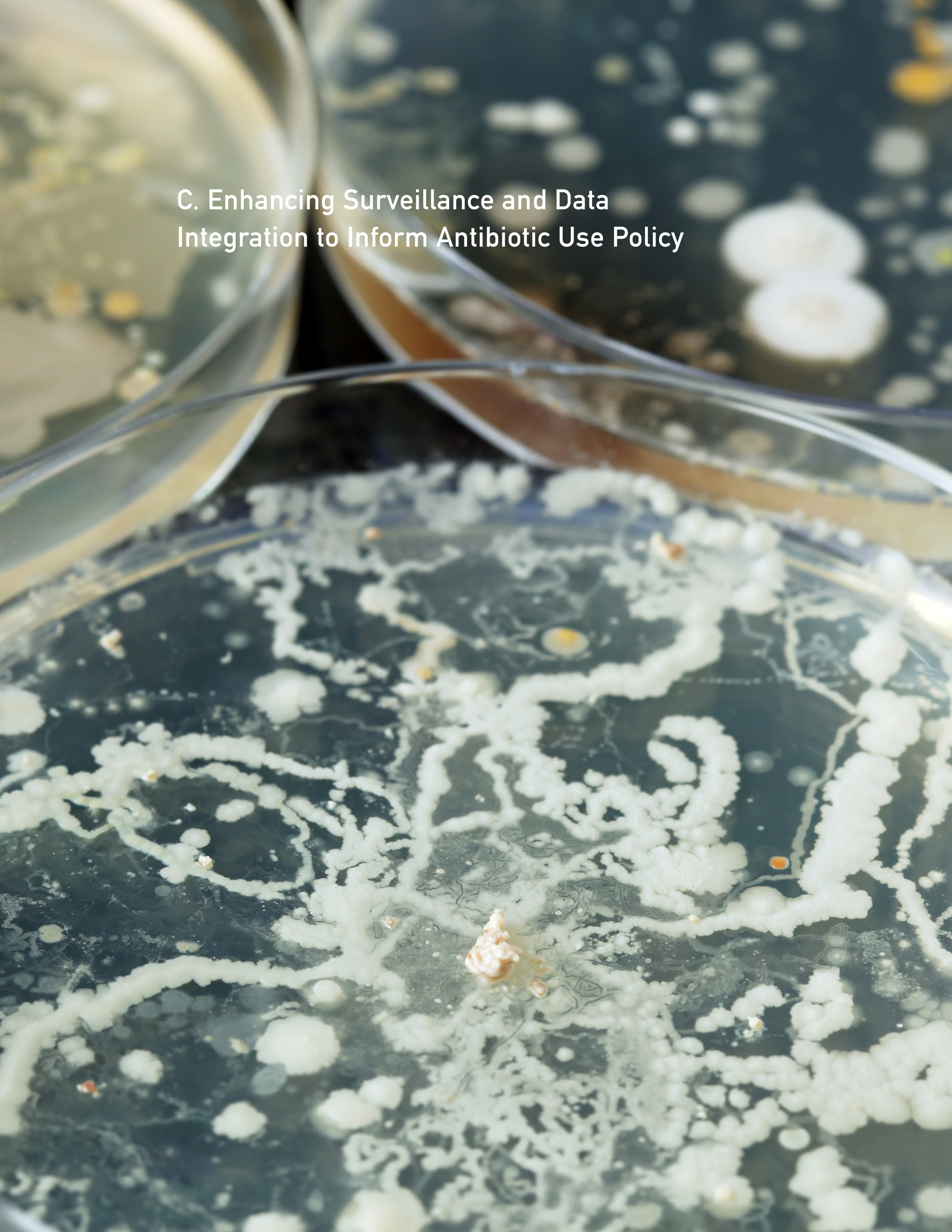
States and private actors in the U.S. also could play significant roles in collecting and reporting data on antibiotic sales and use. For example, California's law addressing antibiotic use in livestock includes a requirement to monitor antibiotic sales and usage. Professional livestock or veterinary associations could collect and report use information to the public, as they do in the Netherlands. Food marketers and buyers also can help increase transparency by requiring suppliers either to report antibiotic use to them directly, or to participate in government or other data collection systems.

Recommendation No. 8: Coordinate with and learn from other countries in developing a comprehensive data collection system.

The most efficient means to develop a U.S. database on antibiotic use is to build on appropriate models currently in place in Europe, modified to accommodate how antibiotics are regulated and distributed at the state and federal levels. The U.S. can take advantage of the fact that several European countries have already spent a decade or more building comprehensive data collection systems, and integrating them with national surveillance of trends in antibiotic resistance. Also, in signing onto the UN declaration, the U.S. signaled its commitment, to cooperate to combat antibiotic resistance and the global public health threat it represents.

Recommendation No. 9: Adopt a metric for reporting data on antibiotic sales or use that better allows trends to be identified, explained, and compared.

Data on antibiotic sales or use are most useful in a policy setting when they are expressed using a metric that facilitates comparisons, such as across time, animal species, or countries. Appendix A describes different metrics in use today. Until a better system is put into place to collect more data (detailed in Box D) the U.S. should employ a metric for reporting on antibiotic use that can inform its efforts to eliminate unnecessary and inappropriate use, as well as to allow for comparisons with other countries. In the near-term, the U.S. can and should employ the mg/PCU metric. This measures the amount of antibiotics sold per amount of livestock raised. The longer-term goal should be to transition to use of an animal defined daily dose metric, a drug and animal species-specific measure that requires the collection of additional data.



C. Enhancing Surveillance and Data Integration to Inform Antibiotic Use Policy

The previous section described three streams of data currently being collected in the U.S. concerning livestock use of antibiotics: FDA's collection of sales data from the animal drug makers; USDA's periodic voluntary surveys of farms; and the NASS collection of data on numbers of animals raised. The National Antimicrobial Resistance Monitoring System (NARMS) represents a fourth stream of data collection. NARMS is a surveillance program that monitors for antibiotic resistance among bacteria isolated from people, retail meat and food-producing animals at the slaughterhouse, and is discussed in greater detail below. Individually, each data stream provides some meaningful information, but the usefulness of the data is shortchanged by a failure to combine the different data streams into an integrated analysis to provide a more comprehensive picture of antibiotic use in food-producing animals. What follows is a more detailed discussion of the NARMS surveillance program, followed by recommendations for better integration of the various streams of data collected by the federal government.

National Antimicrobial Resistance Monitoring System (NARMS)

Since 2003, the NARMS program has been providing surveillance on a national basis for antibiotic resistance in enteric ('gut') bacteria. NARMS surveillance work is conducted by three federal agencies (CDC, FDA and USDA) and studies bacteria collected from people, the retail meat supply, and food-producing animals, respectively.

In short, public health laboratories submit bacteria from cases of human infection to NARMS, where, led by the CDC, they are tested for resistance to antibiotics. FDA receives bacteria from samples of retail chicken, ground turkey, ground beef and pork chops collected each month by laboratories in 14 states. FDA scientists further characterize the bacteria and test them for resistance to antibiotics.[126] USDA scientists conduct similar tests on bacteria obtained from food-producing animals at federally inspected slaughterhouses and processing plants.

NARMS is valuable for monitoring trends in antibiotic resistance in people, food and in food-producing animals. NARMS would be stronger, however, if it reflected emerging research techniques and the latest science. Its failure to do so means that the NARMS program is falling behind in meeting its stated goal to "protect public health by providing information about emerging bacterial resistance".[127] Below are three specific shortcomings of the program, reflecting an outdated approach:

No consistent monitoring of indicator bacterial species. NARMS currently focuses too narrowly on bacteria that are conventionally considered to be foodborne causes of infection, such as *Salmonella* or *Campylobacter*. Other bacteria, such as *Escherichia coli* and *Enterococcus spp.* also are found in the food supply, can cause disease and are considered to be "indicator" species that can signal existence of a broader reservoir of antibiotic resistance. Only four of the 14 state laboratories participating in the NARMS retail meat program collect samples of these so-called indicator bacteria for later testing by FDA for antibiotic resistance. In addition, there is a lack of uniformity between agencies in terms of which indicator species they monitor (see Table 4). Both problems create a significant challenge for NARMS to track antibiotic resistance in a coordinated and complementary manner along the entire food supply chain.

Table 4: Overview of NARMS Testing According to Bacterial Species

Bacterium	Tested by CDC	Tested by FDA	Tested by USDA
Salmonella	✓	✓	✓
Campylobacter spp.	✓	✓	✓
Enterococci spp.	✓	✓	✓
E. coli		✓	✓
E. coli 0157	✓		
Shigella	✓		
Vibrio spp.	✓		

***Does not apply genetic sequencing to indicator bacteria and pathogens other than Salmonella*.** Federal efforts to begin sequencing the entire genome of certain bacteria collected under NARMS have focused almost entirely on *Salmonella*.[128] However, recent studies show that other indicator bacteria, such as *E. coli*, are the most common bacteria in livestock environments found to be carrying genes that easily spread resistance to antibiotics of last resort (such as colistin or carbapenems) to other bacteria.[129] Clinicians rely upon these last resort medicines to treat life-threatening infections when other drugs have failed, or are likely to fail.

There are two key reasons to sequence the genes of bacteria such as *E. coli* or *Enterococcus spp.* and not just *Salmonella*. First, resistance genes found in either one are important because that resistance could subsequently be shared between the two groups of bacteria, in any environment. Second, these bacteria are more commonly found in livestock and other environments so resistance trends are more easily monitored in these bacteria. For both reasons, sequencing only the genomes of *Salmonella* bacteria would be likely to contribute to incomplete identification of and surveillance for antibiotic resistance genes in livestock environments.

Metagenomics is a powerful technique, first named in 1998[130], that looks at the DNA recovered from all bacteria in a particular environmental sample. Because the FDA and USDA already have the ability to sequence genes of individual bacteria,[131,132] that capability likely could be easily adapted to detect resistance from all of the bacteria isolated from a particular animal or meat sample. We can and should expect the NARMS program as well to use metagenomics to comprehensively detect emerging resistance in *all* bacteria, and not just in *Salmonella, Campylobacter, E. coli* and *Enterococcus spp*.

Fails to test for resistance to all antibiotics relevant to human medicine. NARMS' limitation is that the panel of antibiotics to which bacteria are tested for resistance will vary according to the species of bacteria being tested, and that these test panels also are too limited in scope to fully assess reservoirs of resistance. NARMS antibiotic susceptibility testing focuses only on classes of antibiotics used in food animal production and/or the classes commonly used to treat human infections. This overlooks other antibiotics of importance to human medicine. Colistin is an example of an antibiotic that has only recently become more common in human medicine, as resistance to other, less toxic agents forced practitioners to return to using it. And now colistin-resistant bacteria, likely enriched by overuse of the drug in pig production (outside of the U.S.), are spreading around the world.[133,134]

Roadmap Recommendations for Enhancing Surveillance and Data Integration

In light of the shortcomings of U.S. surveillance of antibiotic resistance, we propose the following recommendations:

Recommendation No. 10: Integrate available data into a single, comprehensive report

CDC, FDA, and USDA, should publish a joint, integrated report that summarizes the following: antibiotic resistance data (NARMS, NAHMS), antibiotic sales data (ADUFA, IMS Health[135]), antibiotic use data (NAHMS, CDC[136]), and livestock production statistics (USDA/NASS). The report should draw the best connections between the data possible. In the absence of a national report, state policymakers can publish a regional report by requesting state level resistance data from NARMS and livestock production statistics coupled with new surveillance of state-level antibiotic use, such as will soon be collected in California.

The annual DANMAP and NETHMAP/MARAN reports are examples of integrated, comprehensive reports that combine data on antibiotic use/sales and antibiotic resistance.[137] Both serve as foundational documents for effective policymaking in both countries. Reports from both countries also contain additional information such as yearly livestock/production data (such as that available from USDA[138] in the U.S.), and provide a basis for a rough metric that facilitates international comparison of milligrams of antibiotics used or sold per kilogram of animal weight after slaughter.

Recommendation No. 11: Improve surveillance to detect new and emerging resistance threats

The public health goal of any surveillance system should be to detect problems earlier rather than later. Early detection is more likely to result in an intervention that succeeds in addressing problems that arise. Later detection, on the other hand, may result in being able to recognize that a problem exists, but not being able to do anything about it. In order to improve and/or expand upon the scope of NARMS current surveillance, the government agencies responsible for the program should leverage the latest science to elucidate new and emerging health threats from antibiotic resistance.

For example, recent scientific studies clearly indicate that multidrug-resistant *S. aureus* bacteria, including MRSA, are present in food-producing animals and on U.S. retail meats.[139,140] These "livestock associated" antibiotic-resistant bacteria have been found to colonize the nasal passages of swine and poultry workers, and also can cause skin and soft tissue infections in workers, as well as other community members.[141,142,143] In addition, certain strains of disease-causing *E. coli* bacteria (extra-intestinal pathogenic *E. coli*, or ExPEC) that can be transmitted from food-producing animals/retail meat to people have been characterized by several studies as a probable source of human urinary tract infections.[144,145] Some of these EXPEC bacteria produce an enzyme called extended-spectrum beta-lactamase (ESBL) which mediates resistance to a number of important and often-prescribed antibiotics, such as penicillins and cephalosporins.

Finally, transmissible plasmids have been discovered recently on U.S. pigs[146] or on pig farms[147] that carry resistance to colistin or carbapenem, two antibiotics considered to be of last resort for some of the deadliest antibiotic resistant bacteria we face today. When genes that are resistant to both of these medicines eventually land on the same plasmid, and that plasmid spreads to other bacteria, it will mark the emergence of widespread untreatable infections. This discovery on U.S. pig farms lends weight to the conclusion that there are resistance threats in the food supply chain that are not being adequately monitored.[148] Of 15 serious and urgent antibiotic-resistant threats identified in a 2013 CDC report, at least eight are bacteria that have been detected both in U.S. food-producing animals and in retail meat from the U.S. or abroad.[149] Three of these (MRSA, VRSA, and multidrug-resistant Pseudomonas aeruginosa) are not captured by the current surveillance system, and another two are only partially captured (CRE, ESBL Enterobacteriaceae).

As a surveillance system, NARMS suffers because it does not consistently look for antibiotic resistance among newly emerging pathogens or among bacteria where important reservoirs of resistance are first thought to emerge. We therefore recommend the following specific expansions:

11a. Expand surveillance for emerging resistance using next generation sequencing technology.

Both FDA and USDA currently sequence the genomes of traditional foodborne pathogens tested through NARMS. These sequencing efforts should be expanded to a wider array of bacteria, including *E. coli* and *Enterococcus* which can be important reservoirs of resistance that can spread to other bacteria. The agencies should set up a publicly accessible database or make use of existing databases for the timely release of genome sequencing data.[150]

11b. Expand surveillance for important emerging pathogens. Emerging threats from pathogenic bacteria could be better characterized and assessed if NARMS were expanded to include additional surveillance for *S. aureus* and ExPEC *E. coli* from people, retail meat and food-producing animals, as well as testing these bacteria for susceptibility to antibiotics. If sufficient funding from regulatory agencies is not available, a less preferable alternative would be for NIH or CDC to authorize research funding for the proposed expansion of NARMS testing, on a pilot basis.

11c. Pilot test approaches that comprehensively detect resistance in all bacteria in a sample. As noted above, the NARMS program can and should explore the use of metagenomics to detect emerging resistance in *all* bacteria, and not just in *Salmonella, Campylobacter, E. coli* and *Enterococcus spp*. With metagenomics, the resistance information collected also is no longer limited to a few antibiotics; rather, the results from a sample are compared, simultaneously, to a comprehensive database collection of known resistance genes. Again, expanding metagenomic analysis within NARMS could take place as a pilot, if funds couldn't be secured through regular budgetary means.

11d. Expand surveillance at the state level. Beyond the federal level, state veterinary laboratories have an important role to play in improved surveillance by publicly reporting on resistance found among food producing animals. For example, in 2016, the Minnesota Veterinary Diagnostic Laboratory published findings on resistance in *Salmonella* from clinical samples from 2006 to 2015 in swine and cattle.[151] Public reporting on resistance from food animal clinical isolates at the regional level on a yearly basis would help address the important data gap regarding antibiotic resistance on the farm.

Conclusion

Antibiotic resistance is an urgent public health threat that demands immediate action. Drug-resistant infections are on the rise, making antibiotics less effective and putting routine and common and life-saving procedures in jeopardy. Antibiotic resistance is changing the practice of modern medicine by compromising our ability to treat sick people and animals. Additionally, it is a serious threat to economic and national security. It is estimated that by 2050 a person will die every three seconds from a drug-resistant infection and $100 trillion in global economic productivity will have been lost.[152]

Antibiotic use and overuse in people and in food animal production are important drivers of antibiotic resistance. However, this report focuses specifically on antibiotic use in food-producing animals because 70% of medically important antibiotics sold in the U.S. (i.e. those identical or belonging to the same class as antibiotics used in human medicine) are sold for use in food-producing animals, not people. Additionally, the U.S. has taken significant steps in promoting better antibiotic stewardship policies and programs in human medicine, but falls woefully short in doing the same as it relates to food animal production.

This Commission wants to keep the existing arsenal of antibiotics effective for as long as possible. We came together to craft this policy roadmap because we strongly believe the U.S. cannot fully respond to this public health crisis unless it does a better job to address the contribution to antibiotic resistance antibiotic use in food animal production.

Our recommendations are steps that will help ensure that on-farm use of medically important antibiotics is monitored-and reduced, and that there will be adequate surveillance of the development and spread of antibiotic resistant bacteria. Success, we believe, depends on leadership that builds on approaches that have proven successful elsewhere. While state and federal policymakers have important roles to play, action is need from all stakeholders. Health professionals and hospitals, as well as food companies and other major meat and poultry purchasers also have key roles to play. The appendices that follow outline actions for each sector.

We all stand to lose when antibiotics no longer work. Steps must be taken today to help ensure that our existing supply of antibiotics stay as effective as possible, now and for future generations.

Endnotes

1 NARMS – Combating Antimicrobial Resistance with Surveillance. Centers for Disease Control and Prevention website. https://www.cdc.gov/narms/faq.htm. Accessed April 11, 2017.

2 UN General Assembly, Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance., September 2016. http://www.un.org/pga/70/wp-content/uploads/sites/10/2015/08/Antimicrobial-resistance-informal-consultations-8-September-2016.pdf. Accessed March 9, 2017.

3 Paulson JA, Zaoutis TE, The Council on Environmental Health, The Committee on Infectious Diseases. Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics. *Pediatrics.* 2015;3630.

4 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

5 World Health Organization. Antimicrobial Resistance: Global Report on Surveillance, 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1.

6 Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in Antimicrobial Drug Development: Implications for the Future. *Clin Infect Dis.* 2004; 38: 1279-86.

7 World Health Organization. WHO Director-General Addresses UN General Assembly on Antimicrobial Resistance. September 21, 2016. http://www.who.int/dg/speeches/2016/unga-antimicrobial-resistance/en. Accessed March 9, 2017.

8 Gupta SK, Nayak RP. Dry antibiotic pipeline: Regulatory Bottlenecks and Regulatory Reforms. *Journal of Pharmacology & Pharmacotherapeutics.* 2014; *5*(1): 4.

9 Deak D, Outterson K, Powers JH, Kesselheim S. Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of US Food and Drug Administration–Approved Antibiotics, 2010–2015 FDA-Approved Antibiotics, 2010-2015. *Annals of Internal Medicine. 2016;165*(5):363-372.

10 Avorn J. Kesselheim AA. The 21st Century Cures Act—Will It Take Us Back In Time? *New England Journal of Medicine.* 2015; *372*(26): 2473-2475.

11 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

12 Center for Disease Dynamics, Economics and Policy. State of the World's Antibiotics, *2015*. http://cddep.org/sites/default/files/swa_2015_final.pdf. Accessed March 9, 2017.

13 Levy SB, Marshall B. Antibacterial Resistance Worldwide: Causes, Challenges and Responses. *Nat Med*. 2004; 10(12 Suppl): S122-9.

14 Catry B, Laevens H, Devriese LA, et al. Antimicrobial Resistance in Livestock. *Journal of Veterinary Pharmacology and Therapeutics.*2003; 81-93.

15 Review on Antimicrobial Resistance. Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste. https://amr-review.org/Publications.html. Accessed March 9, 2017.

16 World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015. http://www.who.int/antimicrobial-resistance/publications/global-action-plan/

en/. Accessed March 9, 2017.

17 Ibid. All 194 members of the World Health Assembly, including the U.S., voted to adopt the Global Action Plan on May 26, 2015 and by doing so committed to creating National Action Plans in conformance with it.

18 In September 2016 UN member nations declared their commitment to combat antibiotic resistance in a globally coordinated way, especially across human health, animal health, and agricultural sectors. Joint UN/WHO/OIE Press Release. September 21, 2016. http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/. Accessed March 5, 2017.

19 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal*. 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

20 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

21 In this report, medically important antibiotics are those the FDA considers of importance to human medicine. Generally speaking, they are either identical to, or belonging to the same classes as, those drugs actually used in human medicine. The WHO also has a largely overlapping list of antibiotics important to human medicine. World Health Organization. Critically Important Antimicrobials for Human Medicine, 4th Revision, 2016. http://www.who.int/foodsafety/publications/antimicrobials-fourth/en/. Accessed March 16, 2017.

22 Record-High Antibiotic Sales for Meat and Poultry Production. The Pew Charitable Trusts. http://www.pewtrusts.org/en/multimedia/data-visualizations/2013/recordhigh-antibiotic-sales-for-meat-and-poultry-production. Accessed March 16, 2017; Food and Drug Administration 2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf. Accessed February 28, 2017; Food and Drug Administration Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology. Drug Use Review.April 5, 2012. www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf. Accessed February 28, 2017.

23 Van Boeckel TP, Brower C, Gilbert M, et al. Global Trends in Antimicrobial Use in Food Animals. Proceedings of the National Academy of Sciences of the United States of America. 2015; 112(18):5649-54. doi:10.1073/pnas.1503141112.

24 Wegener HC. Antibiotics in Animal Feed and Their Role in Resistance Development. *Current Opinion in Microbiology.* 2003; 6(5):439-445.

25 Wegener HC. Antibiotic resistance — Linking Human and Animal Health. In: Institute of Medicine (US). Improving Food Safety Through a One Health Approach: Workshop Summary. Washington (DC): National Academies Press (US); 2012. A15. https://www.ncbi.nlm.nih.gov/books/NBK114485/. Accessed March 16, 2017.

26 Agersø Y, Aarestrup FM. Voluntary Ban on Cephalosporin Use in Danish Pig Production has Effectively Reduced Extended-Spectrum Cephalosporinase-Producing Escherichia Coli in Slaughter Pigs. *J Antimicrob Chemother* 2013; 68(3): 569–572.

27 van den Bogaard AE, et al. The Effect of Banning Avoparcin on VRE Carriage in the Netherlands. *J Antimicrob Chemother.* 2000. 46(1):146–148.

28 Dorado-García A, Mevius DJ, Jacobs JJ, Van

Geijlswijk IM, Mouton JW, Wagenaar JA, Heederik DJ. Quantitative Assessment of Antimicrobial Resistance in Livestock During the Course of A Nationwide Antimicrobial Use Reduction in the Netherlands. J *Antimicrob Chemother*. 2016;71(12): 3607-3619.

29 NethMap/MARAN Reports, 2016. http://www.wur.nl/upload_mm/0/b/c/433ca2d5-c97f-4aa1-ad34-a45ad522df95_92416_008804_NethmapMaran2016+TG2.pdf. Accessed April 11, 2017.

30 European Commission. Final Report of A Fact-Finding Mission Carried Out in the Netherlands from 13 September 2016 to 20 September 2016 In Order to Gather Information on the Prudent Use of Antimicrobials in Animals. http://ec.europa.eu/food/audits-analysis/act_getPDF.cfm?PDF_ID=12902. Accessed April 11, 2017.

31 Chen L, Todd R, Kiehlbauch J, Walters M, Kallen A. *Notes from the Field:* Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016. *MMWR Morb Mortal Wkly Rep.* 2017; 66:33. DOI: http://dx.doi.org/10.15585/mmwr.mm6601a7. Accessed March 9, 2017.

32 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

33 Ibid.

34 Spellberg B, Hansen GR, Kar A, Cordova CD, Price LB, Johnson JR. Antibiotic Resistance in Humans and Animals National Academy of Medicine Discussion Paper, June 22, 2016. https://nam.edu/antibiotic-resistance-in-humans-and-animals/. Accessed March 9, 2017.

35 The Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. December 2014. https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf. Note that many, but not all of the estimates refer to infections due to resistant bacteria. They include deaths due to resistant infections caused by viruses (HIV) and parasites (malaria), as well. Accessed March 9, 2017.

36 The Atlantic Council. Antimicrobial Resistance as an Emerging Threat to National Security. 2014. http://www.atlanticcouncil.org/publications/reports/antimicrobial-resistance-as-an-emerging-threat-to-national-security. Accessed March 16, 2017.

37 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

38 Silbergeld E, Graham J, and Price L. Industrial Food Animal production, Antimicrobial Resistance, and Human Health. *Annual Review of Public Health*. 2008; 29: 151-169.

39 Fleming A. Penicillin's Finder Assays its Future. *The New York Times*. June 26, 1945, as cited by Spellberg B et al. 2016.

40 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

41 FDA. 2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf. Accessed February 28, 2017; FDA, Center for Drug Evaluation and Research. Drug Use Review. April 5, 2012. www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf. Accessed February 28, 2017.

42 FDA. 2015 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Table 3. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf. December 2016. Accessed February 28, 2017.

43 Of the roughly 130 medically important antibiotics actively marketed for use in food animals, 12 are also FDA-approved for use in pets. Sales data from pharmaceutical companies are not broken out by individual animal species, so the FDA's annual reports as a rule do not report on the proportion sold for use in pets. Collectively, however, these 12 antibiotics accounted for only about 1.5% of all sales of medically important antibiotics in 2014, and presumably pets account for only a portion of them (and maybe a small portion). See FDA website. Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. https://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm236149.htm. December 22, 2016. Accessed February 14, 2017.

44 The White House. National Action Plan for Combating Antibiotic-Resistant Bacteria. https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf. March 2015. Accessed March 9, 2017.

45 Wegener HC. Antibiotic Resistance - Linking Human and Animal Health. Institute of Medicine (US). Improving Food Safety Through a One Health Approach: Workshop Summary. Washington (DC): National Academies Press (US); 2012. A15. https://www.ncbi.nlm.nih.gov/books/NBK114485/. Accessed March 9, 2017.

46 Lammie SL, Hughes JM. Antimicrobial Resistance, Food Safety, and One Health. The Need for Convergence. *Annu Rev Food Sci Technol*. 2016;7:287-312.

47 OIE. One Health at a Glance. http://www.oie.int/en/for-the-media/onehealth/. 2017. Accessed March 11, 2017.

48 CDC. Zoonotic Diseases. https://www.cdc.gov/onehealth/basics/zoonotic-diseases.html. October 16, 2016. Accessed March 7, 2017.

49 Ibid. Personal communication with CDC identified the underlying source for this statement as: Taylor LH, Latham SM, Woolhouse MEJ. Risk Factors for Human Disease Emergence. Philosophical Transactions of the Royal Society B. *Biological Sciences*. 2001;356(1411):983-9. DOI: 10.1098/rstb.2001.0888.

50 Grøntvedt CA, Elstrøm P, Stegger M, et al. Methicillin-Resistant *Staphylococcus aureus* CC398 in Humans and Pigs in Norway: A "One Health" Perspective on Introduction and Transmission. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2016;63(11):1431-1438. doi:10.1093/cid/ciw552.

51 Levy SB. Factors Impacting on the Problem of Antibiotic Resistance. *J Antimicrob Chemother* 2002; 49(1):25-30.

52 Marshall B M & Levy SB. Food Animals and Antimicrobials: Impacts on Human Health. *Clinical Microbiology Reviews*. 2011;*24*(4):718–733.

53 Meek RW, Vyas H., Piddock LJV. Nonmedical Uses of Antibiotics: Time to Restrict Their Use? *PLoS Biology*. 2015. *13*(10): e1002266.

54 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

55 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal*.

2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

56 Paulson JA, Zaoutis TE, The Council on Environmental Health, The Committee on Infectious Diseases. Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics. *Pediatrics.* 2015;2015-3630.

57 Ibid.

58 CDC. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

59 Review on Antimicrobial Resistance: Tackling Drug-Resistant Infections Globally: Final report and recommendations. May 2016. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed April 5, 2017.

60 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal.* 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

61 EFSA Panel on Biological Hazards (BIOHAZ) Scientific Opinion on thePpublic Health Risks of Bacterial Strains Producing Extended-spectrum --lactamases and/or AmpC --lactamases in Food and Food-Producing Animals. *EFSA J.* 2011;9:2322.

62 WHO. Global Strategy for Containment of Antimicrobial Resistance. http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_2001_2_EN/en/ Accessed April 12, 2017.

63 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal.* 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

64 Lammie SL, Hughes JM. Antimicrobial Resistance, Food Safety, and One Health. The Need for Convergence. *Annu Rev Food Sci Technol.* 2016;7:287-312.

65 Bell BG, et al. A Systematic Review and Meta-Analysis of the Effects of Antibiotic Consumption on Antibiotic Resistance. *BMC Infectious Diseases.* 2014;14:13. doi: 10.1186/1471-2334-14-13.

66 Levy SB. Antibiotic Resistance: An Ecological Imbalance. Ciba Foundation Symposium 207 - Antibiotic Resistance: Origins, Evolution, Selection and Spread. Chichester, UK. 2007.

67 Levy SB. Antibiotic Resistance: Consequences of Inaction. *Clin Infect Dis* 2001; 33(3):S124-S129. https://doi.org/10.1086/321837.

68 Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of Beta-Lactam: Risk Factors for Carriage of Penicillin-Resistant Streptococcus Pneumoniae. *JAMA.* 1998;279(5):365-70.

69 Valiquette L & Laupland KB. Get Shorty! *Can J Infect Dis Med Microbiol.*2015;26(4):174-7.

70 Zilahi G, McMahon MA, Povoa P, Martin-Loeches I. Duration of Antibiotic Therapy in the Intensive Care Unit. *Journal of Thoracic Disease.* 2016; 8(12):3774–3780. doi.org/10.21037/jtd.2016.12.89

71 Kaziani K, Sotiriou A, Dimopoulos G. Duration of Pneumonia Therapy and the Role of Biomarkers. *Curr Opin Infect Dis.* 2017;30(2):221-225. doi: 10.1097/QCO.0000000000000351.

72 WHO. The National Action Plan for Combating Antibiotic Resistant Bacteria. March 2015. http://www.who.int/antimicrobial-resistance/national-action-plans/library/en/. Accessed January 30, 2017.

73 Marshall BM, Ochieng DJ, Levy SB. Commensals: Underappreciated Reservoir of Antibiotic Resistance. *ASM News.* 2009;4(5):231-238.

74 Andremont A. Commensal Flora May Play Key Role in Spreading Antibiotic Resistance. *ASM News.* 2003;69(12): 601-607.

75 Stecher B, Denzler R, Maier L, et al. Gut Inflammation Can Boost Horizontal Gene Transfer Between Pathogenic and Commensal Enterobacteriaceae. *PNAS.* 2012;109 (4):1269-1274.

76 Levy SB, Marshall BM. Honeybees and Tetracycline Resistance. *MBio*. 2013;4(1): e00045-13..

77 University of Utah. Antibiotic Resistance. http://learn.genetics.utah.edu/content/microbiome/resistance/. Accessed February 14, 2017.

78 Van Boeckel TP, Brower C, Gilbert M, et al. Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(18):5649-5654. doi:10.1073/pnas.1503141112.

79 Ibid.

80 Review on Antimicrobial Resistance. Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste. December 2015. http://amr-review.org/Publications Accessed March 16, 2017.

81 Ibid.

82 Netherlands Veterinary Medicines Authority (SDa). 2017. Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2016. Published May 29, 2017. Accessed (Dutch language only) at https://www.rijksoverheid.nl/documenten/rapporten/2017/05/29/het-gebruik-van-antibiotica-bij-landbouwhuisdieren-in-2016.

83 Martijn van Dam, Minister for Agriculture. Opening Speech to the EU Ministerial Conference on Antimicrobial Resistance. Amsterdam, the Netherlands: 10 February 2016. http://bit.ly/2p91h9C. Accessed April 7, 2017.

84 Government of the Netherlands. Good Practices (Use of Antibiotics). https://www.government.nl/documents/reports/2016/01/27/good-practices-use-of-antibiotics. January 27, 2016. Accessed April 7, 2017.

85 FDA. 2015 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Table 11b. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf. Published December 2016. Accessed February 28, 2017.

86 Of the roughly 130 medically important antibiotics actively marketed for use in food animals, 12 are also FDA-approved for use in pets. Sales data from pharmaceutical companies are not broken out by individual animal species, so the FDA's annual reports as a rule do not report on the proportion sold for use in pets. Collectively, however, these 12 antibiotics account for about 1.5% of all sales of medically important antibiotics in 2014, and presumably pets account for only a portion of them (and maybe a small portion). See FDA website. Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. https://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm236149.htm. December 22, 2016. Accessed February 14, 2017.

87 FDA. FDA Seeks Public Input on Next Steps to Help Ensure Judicious Use of Antimicrobials in Animal Agriculture. https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm520110.htm. November 28, 2016. Accessed February 28, 2017.

88 United Nations. At UN, Global Leaders Commit to Act on Antimicrobial Resistance. September 21, 2016. http://www.un.org/pga/71/2016/09/21/press-release-

hl-meeting-on-antimicrobial-resistance/. Accessed March 16, 2017.

89 Penicillin-Containing Premixes, 42 Fed. Reg. 43,772, 43,772 (Aug. 30, 1977); Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. 56,264, 56,288 (Oct. 21, 1977).

90 Ibid.

91 GAO. More Information Needed to Oversee Use of Medically Important Drugs in Food Animals. GAO-17-192. https://www.gao.gov/products/GAO-17-192. Published March 2, 2017. Accessed April 7, 2017.

92 FDA. Guidance for Industry #213 . New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209. December 2013. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf. Accessed March 16, 2017.

93 Hoffman H. New FDA "Rules" Not Likely to Reduce Antibiotic Use on Farm. *Forbes* (Dec. 13, 2013); Flynn, William. Statement to a hearing of the Maryland General Assembly. November 2, 2015.

94 FDA's Efforts Fail to End Misuse of Livestock Antibiotics. Natural Resources Defense Council website (Table, page 4). https://www.nrdc.org/resources/fdas-efforts-fail-end-misuse-livestock-antibiotics. Accessed April 25, 2017.

95 GAO. Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals, GAO-11-801. Washington, D.C.: Sept. 7, 2011. http://www.gao.gov/new.items/d11801.pdf. Accessed April 6, 2017.

96 Ibid.

97 GAO. More Information Needed to Oversee Use of Medically Important Drugs in Food Animals. GAO-17-192. https://www.gao.gov/products/GAO-17-192. Published March 2, 2017. Accessed April 7, 2017.

98 Paulson JA, Zaoutis TE, The Council on Environmental Health, The Committee on Infectious Diseases. Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics. *Pediatrics.* 2015;3630. doi: 10.1542/peds.2015-3630.

99 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal*. 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

100 SB-27 Livestock: Use of Antimicrobial Drugs, Cal. Food & Ag Code § 14400 et seq. http://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB27. Accessed March 16, 2017.

101 EMA and EFSA. Joint Scientific Opinion on Measures to Reduce the Need to Use Antimicrobial Agents in Animal Husbandry in the European Union, and the Resulting Impacts on Food Safety (RONAFA). [EMA/CVMP/570771/2015]. *EFSA Journal*. 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666.

102 Kansas State University. Management Practices to Reduce the Need for Antibiotics. http://www.asi.k-state.edu/research-and-extension/antibiotics/Management_practices.html. November 4, 2016. Accessed March 14, 2017.

103 Weese JS, Giguère S, Guardabassi L, et al. (2015), ACVIM Consensus Statement on Therapeutic Antimicrobial Use in Animals and Antimicrobial Resistance. *J Vet Intern Med*. 2015;29: 487–498. doi:10.1111/jvim.12562.

104 National Pork Board. Responsible Antibiotic Use on Today's Pig Farms Protects People, Pigs and Planet. http://www.porkcdn.com/sites/all/files/documents/Anitbiotics/Get-Smart-ABX-Infographic.pdf. Published 2016. Accessed March 20, 2017.

105 Vision for Antimicrobial Stewardship for Food Animals. McDonald's website. Accessed May 21, 2017 at http://corporate.mcdonalds.com/mcd/sustainability/sourcing/animal-health-and-welfare/issues-we-re-focusing-on/vision-for-antimicrobial-stewardship-for-food-animals.html

106 Since first publishing a list of antibiotics "critically important" to human medicine 2007, the WHO has revised the list in 2009, 2011, 2013 and 2016. WHO List of Critically Important Antimicrobials (CIA). http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/. 2017. Accessed April 13, 2017. In addition, a WHO Guideline for the use of these antibiotics in food producing animals is currently under development.

107 It should be noted that while a limited number of animal polymxin products are FDA-approved in the U.S. they are not being actively marketed. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211080.pdf

108 The FDA compiled its own list of "critically important" antibiotics in 2003, but that list has not been updated since. Guidance for Industry No. 152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern, App. A. https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936pdf. Published Oct. 23, 2003. Accessed March 6, 2017.

109 The list "highest priority" critically important antibiotics includes: cephalosporins (3rd, 4th and 5th generation); glycopeptides; macrolides and ketolides; polymyxins; and quinolones. WHO List of Critically Important Antimicrobials (CIA). http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/. 2017. Table 3, page 24.

110 European Commission, Directorate General for Health and Food Safety. Final Report of a Fact-finding Mission Carried Out in the Netherlands from 13 September 2016 to 20 September 2016 in order to Gather Information on the Prudent Use of Antimicrobials in Animal. Published January 3, 2017. Accessed at http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3753.

111 American Medical Association. Opinion 8.063 - Sale of Health-Related Products from Physicians' Offices. http://journalofethics.ama-assn.org/2015/08/coet1-1508.html. Accessed March 16, 2017.

112 American Medical Association website. Physician Financial Transparency Reports (Sunshine Act). Accessed July 7, 2017 at https://www.ama-assn.org/practice-management/physician-financial-transparency-reports-sunshine-act.

113 GAO. More Information Needed to Oversee Use of Medically Important Drugs in Food Animals. GAO-17-192. March 2, 2017. https://www.gao.gov/products/GAO-17-192. Accessed April 7, 2017.

114 OIE. Monitoring of the Quantities and Usage Patterns of Antimicrobial Agents Used in Food Producing Animals. 2015. http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_antibio_monitoring.htm. Accessed November 12, 2016.

115 WHO. Integrated Surveillance of Antimicrobial Resistance. 2013. http://apps.who.int/iris/bitstream/10665/91778/1/9789241506311_eng.pdf. Accessed October 6, 2015.

116 Collineau L, Belloc C, Stärk KD, Hémonic A, Postma M, Dewulf J, Chauvin C. Guidance on the

Selection of Appropriate Indicators for Quantification of Antimicrobial Usage in Humans and Animals. *Zoonoses Public Health*. 2016; doi: 10.1111/zph.12298.

117 GAO. Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals: Report to the Ranking Member, Committee on Rules, House of Representatives. 2011. http://www.gao.gov/new.items/d11801.pdf. Accessed April 6, 2017.

118 Animal and Plant Health Inspection Service, U.S. Department of Agriculture. Antimicrobial Use 2017. Updated April 27, 2017. Accessed June 20, 2017.

119 Ibid.

120 New NAHMS Survey to Measure Antibiotic Use, Stewardship. National Pork Board press release, dated April 27, 2017. Accessed May 22, 2017 at http://www.pork.org/new-nahms-survey-measure-antibiotic-use-stewardship/.

121 USDA. Agricultural Resource Management Surveys. https://www.fda.gov/downloads/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/UCM464312.pd. Updated March 2, 2017. Accessed April 4, 2017.

122 Stege H, Bager F, Jacobsen E, Thougaard A. VETSTAT-the Danish System for Surveillance of the Veterinary Use of Drugs for Production Animals. *Prev Vet Med*. 2003; 57(3): 105–115.

123 The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. DANMAP 2015 - Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark. 2016. http://www.danmap.org/Downloads/Reports.aspx. Accessed March 9, 2017.

124 Central Veterinary Institute of Wageningen University and Research Centre. MARAN 2016 Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2015. http://www.rivm.nl/bibliotheek/rapporten/2016-0060.pdf. Accessed January 17, 2017.

125 Danish Veterinary and Food Administration. Risk Management of Antimicrobial Use and Resistance from Food Producing Animals in Denmark. June 14, 2007. https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/05kontor/Risk_management_antimicrobia_%20use_and%20resistance_Denmark_E.pdf. Accessed April 7, 2017.

126 Additionally, FDA scientists analyze bacteria from cattle intestinal samples collected by USDA inspectors at processing plants.

127 FDA. The National Antimicrobial Resistance Monitoring System. http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/. Accessed February 3, 2017.

128 Bacterial strains collected to date as part of the NARMS retail meat program, and then whole genome-sequenced have mostly been Salmonella. Public health laboratories receive CDC funding to sequence all human isolates of *Salmonella* as well. For more information: https://www.cdc.gov/narms/about/index.html. Accessed March 9, 2017.

129 Mollenkopf DF, et al. Carbapenemase-Producing Enterobacteriaceae Recovered from the Environment of A Swine Farrow-to-Finish Operation in the United States. *Antimicrob Agents Chemother*. 2017; 61:e012198-16.

130 Handelsman J, Rondon MR, Brady SF, Clardy J, Goodman RM. Molecular Biological Access to the Chemistry of Unknown Soil Microbes: A New Frontier for Natural Products. *Chemistry & Biology*. 1998; 5(10):R245–R249.

131 Hoffmann M, Zhao S, Pettengill J, et al. Comparative Genomic Analysis and Virulence Differences in Closely Related Salmonella Enterica Serotype Heidelberg Isolates from Humans, Retail Meats, and Animals. *Genome Biol Evol*. 2014:(5)1046-1068;

132 USDA Food Safety and Inspection Service Strategic Plan, 2017-2021. https://www.fsis.usda.gov/wps/wcm/connect/317d14d6-1759-448e-941a-de3cbff289e5/Strategic-Plan-2017-2021.pdf?MOD=AJPERES. Published October 2016. Accessed February 2, 2017.

133 Liu YY, Wang Y, Walsh TR, et al. Emergence of Plasmid-Mediated Colistin Resistance Mechanism MCR-1 in Animals and Human Beings in China: A Microbiological and Molecular Biological Study. *Lancet Infect Dis*. 2016; 16:161–8.

134 Mollenkopf DF et al. Carbapenemase-Producing Enterobacteriaceae Recovered from the Environment of a Swine Farrow-to-Finish Operation in the United States. *Antimicrob Agents Chemother*. 2017; 61:e012198-16.

135 IMS Health. Global Prescription Sales Information. http://www.imshealth.com/en/about-us/news/top-line-market-data.

136 CDC. National Healthcare Safety Network: Surveillance for Antimicrobial Use and Antimicrobial Resistance Options. https://www.cdc.gov/nhsn/acute-care-hospital/aur/index.html. Accessed March 20, 2017.

137 Denmark releases a single report combining antibiotic use and resistance information relevant to both the human and livestock sectors. In contrast, the Netherlands report is divided into two parts: 1) data on antibiotic use and surveillance primarily associated with human medicine and 2) use and surveillance data more closely associated with the livestock sector.

138 USDA. Economics, Statistics and Market Information System. http://mannlib.cornell.edu/projects/usda-esmis. Accessed March 20, 2017.

139 Thapaliya D, Forshey BM, Kadariya J, et al. Prevalence and Molecular Characterization of Staphylococcus aureus in Commercially Available Meat Over A One-year Period in Iowa, USA. *Food Microbiol. 2017. 65:122-129*.

140 Ge B, Mukherjee S, Hsu CH, Davis JA, et al.. MRSA and Multidrug-Resistant Staphylococcus aureus in U.S. Retail Meats, 2010-2011. *Food Microbiol*. 2017; 62:289-297. [doi: 10.1016/j.fm.2016.10.029](https://doi.org/10.1016/j.fm.2016.10.029).

141 Casey JA, Kim BF, Larsen J, et al. Industrial Food Animal Production and Community Health. *Curr Envir Health Rpt*. 2015;2:259.

142 Wardyn SE, Forshey BM, Farina SA. Swine Farming Is a Risk Factor for Infection With and High Prevalence of Carriage of Multidrug-Resistant Staphylococcus aureus. *Clin Infect Dis*. 2015; 61(1): 59-66.

143 Nair R, Wu J, Carrel M, et al.Prospective Multicenter Surveillance Identifies Staphylococcus aureus Infections Caused by Livestock-Associated Strains in An Agricultural State. *Diagnostic Microbiology and Infectious Disease.* 2016; 85(3):360-366. doi: 10.1016/j.diagmicrobio.2016.04.014.

144 Nordstrom L, Liu CM, Price LB. Foodborne Urinary Tract Infections: A New Paradigm for Antimicrobial-Resistant *Foodborne* Illness. *Frontiers in Microbiology.* 2013; 4(29):1-6.

145 Johnson JR, Porter SB, Johnston B, et al. Extraintestinal Pathogenic and Antimicrobial-Resistant Escherichia coli, Including Sequence Type 131 (ST131), from Retail Chicken Breasts in the United States in 2013. *Appl Environ Microbiol.* 2017 Mar 2;83(6). pii: e02956-16. doi: 10.1128/AEM.02956-16.

146 National Geographic *Phenomenon*. Long-Dreaded Superbug Found in Human and Animal in U.S. May 26, 2016. http://phenomena.nationalgeographic.com/2016/05/26/colistin-r-9/. Accessed February 28 2017.

147 Mollenkopf DF, Stull JW, Mathys DA, et al.. Carbapenemase-Producing Enterobacteriaceae Recovered from the Environment of a Swine Farrow-to-Finish Operation in the United States. A*ntimicrob Agents Chemother.* 2017;61(2):pii: e01298-16. doi: 10.1128/AAC.01298-16.

148 HHS. Proactive Efforts by U.S. Federal Agencies Enable Early Detection of New Antibiotic Resistance. May 26, 2016. https://www.hhs.gov/blog/2016/05/26/early-detection-new-antibiotic-resistance.html. Accessed February 28, 2017.

149 NRDC. Cordova C. New WHO List Underscores Need for Maryland Antibiotics Bill. https://www.nrdc.org/experts/carmen-cordova. Accessed February 27, 2017.

150 See the databases maintained by the National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/home/about/programs.shtml.

151 Hong S. et al. Serotypes and Antimicrobial Resistance in Salmonella enterica Recovered from Clinical Samples from Cattle and Swine in Minnesota, 2006 to 2015. *PloS One*. 2016;11(12):e0168016.

152 Review on Antimicrobial Resistance. Tackling Drug Resistant Infections Globally: Final Report and Recommendations. May 2016. http://amr-review.org/Publications. Accessed April 12, 2017.

Appendix A: Metrics for Reporting on Antibiotic Use in Food-Producing Animals

Use of antibiotics in food-producing animals is an important contributor to the selection and spread of antibiotic resistance. As a result, many countries have established national programs to monitor and report on the sales and/or consumption of antibiotics in this sector. Comparing results from different places or authorities is complicated. They may use completely different metrics. Even when using the same basic metric, the methodology used to calculate it may differ. Two countries may differ in the dosages they authorize for a certain antibiotic, or in the correction factor they employ for long-acting antibiotic products.[1] This appendix describes different metrics that the U.S. might employ in reporting its data on antibiotic sales and use, as well as examples of how different countries calculate those metrics.

What Metrics Should Be Used?

In the near-term, the U.S. has data sufficient to report on antibiotics sales/use using the metric of milligrams/population corrected unit (mg/PCU), although it does not currently do so. The mg/PCU metric compares the amount of antibiotics used, or sold for use, in food production to the total weight of animals being produced. The denominator, the population correction unit (PCU), is a calculated estimate of animal weight; it is a surrogate for the animal population at risk, one that normalizes antibiotic sales by animal population in individual countries.

In essence, the PCU for each animal category is calculated by multiplying numbers of slaughtered animals (cattle, pigs, lambs, poultry and turkeys) and other livestock animals (dairy cows, sheep, sows and horses) by the theoretical weight at the time most likely for treatment. Adjustments are made for the numbers of animals exported or imported for fattening or for slaughter (cattle, pigs and poultry) multiplied by a standardized weight.[2]

The independent European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project already collects such data from 29 countries across Europe. Its 2014 report, for example, demonstrates that 68.4 mg / per population corrected unit (PCU) of antibiotics were sold for use in food animals in the Netherlands, in the midrange of 3.10 mg/PCU (Norway) to 418.8. mg/PCU (Spain).[3] We believe data for calculating both numerator and denominator of this metric also are currently available in the U.S. The FDA issues annual reports on antibiotic sales for use in food producing animals.[4] Meanwhile, the USDA collects and maintains livestock and poultry production data, including the pounds produced,[5]as well as data on imports of meat and poultry products, and in the live animals from which those products are derived.[6]

An alternate metric, once more detailed data are available

A more desirable metric for reporting antibiotic use information in the U.S. would be one based on animal defined daily dose[7], a numerical measure of drug consumption that indicates the daily maintenance dose needed for a particular use and active ingredient in a particular species (and age group, if relevant). This metric already is widely used within the European Union; its adoption by the U.S. would allow for the future comparison of the U.S. and other important food animal-producing countries. Its use in the U.S. would first require collection of detailed and comprehensive antibiotic use data down to the farm level that is not currently done in the U.S., nor is yet under consideration. There are several advantages to using this metric, rather than mg/PCU.

This second metric adds another layer of important information – namely, the potency of the particular antibiotic used is built into the metric.[8] This metric also can facilitate the comparison of trends in antibiotic use over time, even if the potency of the antibiotics used varies over that time period.[9] Finally, it allows for a more meaningful comparison of antibiotic use in food animal production and in human medicine. Different European entities use variations on this second metric that differ depending on the methodologies used to calculate them (see Table A).[10]

Table A: Variations on an Animal Defined Daily Dose metric.

Metric	Explanation	Metric used in
ADD_{DK} Animal Daily Dose (Denmark)	The ADD_{DK} is the assumed average maintenance dose needed to treat one kilogram of animal during one day for the main indication in the target species, in accordance with Denmark's authorizing document for that product.[1]	DANMAP, 2009-2011
$DADD_{DK}$ Defined Animal Daily Dose (Denmark)	The $DADD_{DK}$ is specified for a particular animal species. It is the average maintenance dose (in mg/kg) per day for a drug used for its main indication in the appropriate animal species.[12] The $DADD_{D}K$ is not defined at product level but for each antibiotic agent, administration route and animal species and when appropriate, also age group.	DANMAP, 2012 – present
$DDDA_{NAT}$ Defined Daily Dose Animal (Netherlands)	Based on national antibiotic usage data, the 'Defined Daily Dose Animal' is a metric used to determine the amount of antibiotics used within a particular livestock sector, irrespective of any differences between farms in the sector; it is expressed as DDDA/animal year.[13] The DDDANAT is determined by first calculating the total number of treatable kilograms within a particular livestock sector for a specific year, and then dividing this number by the average number of kilograms of animal present within that sector.	Maran/ NethMAP Reports

Endnotes

1 Taverne F, Jacobs J, Heederik D, et al. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. BMC Veterinary Research. 2015;11:250. doi:10.1186/s12917-015-0566-7.

2 European Medicines Agency. Trends in the sales of veterinary antimicrobial agents in nine European countries (2005-2009) (EMA/238630/2011). 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf. Accessed April 6, 2017.

3 European Medicines Agency. Sales of veterinary antimicrobial agents in 29 European countries in 2014. 2016. www.ema.europa.eu/docs/en_GB/document_library/Report/2016/10/WC500214217.pdf. Accessed April 6, 2017.

4 ADUFA Reports. U.S. Food and Drug Administration website. Updated December 22, 2016. https://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm. Accessed March 23, 2017.

5 Statistics by Subject. United States Department of Agriculture, National Agricultural Statistics Service website. Updated April 29, 2016. https://www.nass.usda.gov/Statistics_by_Subject/index.php?sector=ANIMALS%20&%20PRODUCTS. Accessed March 23, 2017.

6 Livestock and Meat International Trade Data. Economic Research Service, USDA website. https://www.ers.usda.gov/data-products/livestock-and-meat-international-trade-data/. Accessed April 5, 2017.

7 Dewulf J, Moulin G, Catry B, et al. Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals. 2013. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf. Accessed March 20, 2017.

8 Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. Prev Vet Med. 2004;64: 201–215.

9 Chauvin C, Madec F, Guillemot D, Sanders P. Vet Res. 2001;32(6):533-543. DOI: https://doi.org/10.1051/vetres:2001145

10 Taverne F, Jacobs J, Heederik D, et al. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. BMC Veterinary Research. 2015;11:250. doi:10.1186/s12917-015-0566-7.

11 Statens Serum Institut, National Veterinary Institute and National Food Institute, Technical University of Denmark. DANMAP Reports. http://www.danmap.org/Downloads/Reports.aspx. Accessed May 1, 2017.

12 Ibid.

13 The Netherlands Veterinary Medicines Authority (SDa). Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2015. September 2016. http://www.autoriteitdiergeneesmiddelen.nl/en/home. Accessed July 5, 2017.

Appendix B: Tools for Health Professionals To Improve Use of Medically Important Antibiotics in Livestock

Health professionals, their institutions and professional organizations are on the front lines of the antibiotic resistance crisis. Each should be fully committed to antibiotic stewardship to preserve the effectiveness of existing antibiotics for as long as possible, and ultimately to better protect the public against rising rates of antibiotic resistant infections.

Healthcare professionals around the world are leading antibiotic stewardship efforts in hospitals and outpatient settings. There is also an opportunity for health leaders to help end the overuse and misuse of antibiotics in food animal production. Of all medically important antibiotics sold for use in the U.S., 70% of them go to food animals, not people. Most of those antibiotics are mass-administered to groups of animals where there is neither a diagnosed disease, nor a working diagnosis. Antibiotics are routinely fed to flocks and herds as a quick fix, often in place of better hygiene, nutrition, animal husbandry or management practices – all of which can help prevent the need for antibiotics in the first place.

In May 2017, a panel of experts in human and veterinary medicine, infectious diseases, epidemiology, public health and microbiology issued a Policy Roadmap to Reduce Antibiotic Use in Livestock http://battlesuperbugs.com/PolicyRoadtrip. While the recommendations in the document mainly pertain to leadership needed from state and federal policymakers, there also is much that can be accomplished by clinicians, their professional groups and institutions.

Using Existing Toolkits

A toolkit[1] recently released by the Clinician Champions in Comprehensive Antibiotic Stewardship (CCCAS) collaborative – a joint initiative of the Pediatric Infectious Diseases Society (PIDS), Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS), the Pediatric Infectious Diseases Society (PIDS) and Health Care Without Harm (HCWH) – specifically addresses the role of clinicians and healthcare facilities in promoting comprehensive stewardship of antibiotics in both food production and clinical practice alike. It states:

"It is imperative that antibiotic stewardship programs seeking to preserve the effectiveness of existing antibiotics in human health also consider strategies that reduce overuse of antibiotics in the agricultural sector. This module provides the tools to incorporate this important aspect of stewardship into your program. In addition to bringing this to the forefront of hospital- based care, we aim for this comprehensive approach to translate to the community setting as well, via patient education in ambulatory settings."

Here we highlight just a few of the strategies and resources covered by that Toolkit. They track some of the seven *core elements* of successful antibiotic stewardship programs outlined by the CDC[2]. Committed Leadership; Accountability; Drug Expertise; Action; Tracking; Reporting; and Education.

Next Steps for Hospitals, Health Organizations, Health Professional Groups

Leadership Commitment

- Make a strong statement by your institution in support of antibiotic stewardship that includes the phase-out of medically important antibiotics being routinely used in food animal production, and the importance of health organizations and facilities making purchasing decisions consistent with that goal.

Action, beyond your facility

- Endorse hospitals associations, medical schools and universities making their own statements to support phase-out of medically important antibiotics for routine use in food animals.

- Expand your modeling and leadership of antibiotic stewardship organization-wide by passing policy guiding your procurement of meat and poultry products.

Next Steps: Individual Champions for Antibiotic Stewardship

Nurture Committed Leadership

- Be prepared to explain to your leadership why buying meat raised where medically important antibiotics have not been routine used is clinically relevant, doable and important.

- Make sure you know which antibiotics are used in food animal production, and be familiar with mechanisms of plasmid transferability, cross-selection and co-selection, so as to explain how antibiotic use on farms can spur development and spread of resistance to antibiotics from both related and unrelated classes.

- To make your best case, anticipate questions about costs, and options for forward steps. The CCCAS Toolkit links to such presentations.

Accountability / Expertise

All health professionals should:

- Embrace a *One Health* approach to antibiotic resistance, meaning that misuse or inappropriate use of medically important antibiotics, whatever the setting, is a shared responsibility.

- Hold your profession responsible for making antibiotic resistance, and the fight to keep antibiotics effective, a priority policy, especially including taking strong policy positions on antibiotic use in non-human settings.

- Hold yourself accountable for understanding how the meat and other food products served in your facility, or at your lunches, meetings and conferences, is purchased.

For those leading Antibiotic Stewardship Programs (ASPs):

- Incorporate strategies to reduce antibiotic use in food animal production into your ASPs.
- Invite facility food service leaders and dietitians onto your antibiotic stewardship team.

Action

- Help draft and be a champion for your hospital/clinic, institution, or professional society to pass a policy resolution to phase-out the procurement of meat and poultry produced with the routine use of medically important antibiotics, perhaps modeled on the following draft.

DRAFT Resolution

Ending Medically Important Antibiotic Use for Routine Disease Prevention

SUBJECT: No Routine Use of Antibiotics Important to Human Medicine in Food Animal Production

INTRODUCED BY:

WHEREAS, the World Health Organization warns that unless we act urgently, the world will enter a 'post-antibiotic era' where even common infections will again kill patients[3];

WHEREAS, The Centers for Disease Control and Prevention (CDC) estimates conservatively at least 23,000 patients in the U.S. already die each year from antibiotic-resistant infections[4];

WHEREAS, Antibiotic use and overuse are principal drivers for the emergence and spread of antibiotic resistance;

WHEREAS, Of all U.S. sales of medically important antibiotics (e.g. those from classes important to disease treatment in humans), about 70% are products for use in food animals, and the remainder for use in human medicine, according to the Food and Drug Administration (FDA)[5];

WHEREAS, The FDA's National Antibiotics Resistance Monitoring System reports that antibiotic-resistant bacteria have become a common fixture in retail meat[6];

WHEREAS, An ever-larger, but already compelling body of evidence demonstrates that this large-scale use of medically important antibiotics in food animals contributes to the development and spread antibiotic resistance, including to human populations[7];

WHEREAS, In January 2017, and after approximately seven decades of use, the FDA finally effected the end of medically important antibiotics being mass-administered to flocks and herds in animal feed or water, specifically for the purposes of growth promotion or increased feed efficiency[8];

WHEREAS, FDA continues to allow the routine administration of medically important antibiotics to flocks and herds for 'disease prevention' in the absence of a disease diagnosis, and at dosages identical or similar to those used for growth promotion.[9]

WHEREAS, Improved collection and public reporting of data on sales of antibiotics for use in agriculture – including parsed out data to illuminate in which animal species and for what particular purpose such antibiotics are used – is fundamental to efforts by health officials and researchers to both better understand development and spread of antimicrobial resistance, and to assess the efficacy of any steps taken to address it.

Be it resolved that: Our [insert your professional organization] supports federal and state efforts to phase-out or ban routine or regular addition of antibiotics to animal feed or water for the purpose of disease prevention.

Be it resolved that: Our [insert your professional organization] recognizes that to model antibiotic stewardship, and to do our part to help keep existing antibiotics more effective for longer, it's important to set a goal of purchasing meat and poultry products from operations that only allow use of medically important antibiotics for animals that are sick with diagnosed disease, and never mass administered to herds or flocks for [routine] disease prevention.

Endnotes

1 Pediatric Infectious Disease Society and Health Care Without Harm. Antimicrobial Stewardship through Food Animal Agriculture Toolkit Module. March 2017. https://noharm-uscanada.org/sites/default/files/documents-files/4603/CCCAS%20Toolkit%20Module_FINAL_3-2-2017.pdf. Accessed February 28, 2017.

2 Core Elements of Hospital Antibiotic Stewardship Programs. Centers for Disease Control and Prevention. May 25, 2016. https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed February 28, 2017.

3 World Health Organization Press Release. 2014. http://www.who.int/mediacentre/news/releases/2014/amr-report/en/. Accessed May 1, 2017.

4 CDC. Antibiotic Resistance Threats in the United States. 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed March 9, 2017.

5 Record-High Antibiotic Sales for Meat and Poultry Production. The Pew Charitable Trusts. 2013. http://www.pewtrusts.org/en/multimedia/data-visualizations/2013/recordhigh-antibiotic-sales-for-meat-and-poultry-production. Accessed March 16, 2017; 2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. U.S. Food and Drug Administration. 2017. www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf. Accessed February 28, 2017; Food and Drug Administration Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology. Drug Use Review. April 5, 2012. www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf. Accessed February 28, 2017.

6 U.S. Food and Drug Administration, National Antimicrobial Resistance Monitoring System. 2014 NARMS Integrated Report. 2016. https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059103.htm. Accessed July 07, 2017.

7 Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C. http://battlesuperbugs.com/PolicyRoadmap. Accessed August 19, 2017.

8 FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance. U.S. Food and Drug Administration . 2017. https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm. Accessed May 1, 2017.

9 Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C. http://battlesuperbugs.com/PolicyRoadmap. Accessed August 19, 2017.

Appendix C: Tools for State and Local Governments to Improve Use of Medically Important Antibiotics in Livestock

While federal action is important in order to make progress on reducing unnecessary antibiotic use and addressing antibiotic resistance, many other actors have essential roles to play, particularly when it comes to uses of the drugs in food animal production. State and local governments can take considerable action to ensure that antibiotics are not overused in the livestock sector.

State action can move the market and drive improved antibiotic use practices while reducing risk for their citizens, demonstrating the feasibility of alternative approaches, and laying the groundwork for eventual action at the national level. California has shown early leadership on the issue, passing legislation to curtail the routine use of antibiotics and institute monitoring of antibiotic use and sales.

In addition to laws that address how antibiotics are used, state and local actors can also make procurement choices to prioritize and increase the purchase of meat and poultry raised without the routine use of antibiotics in the absence of diagnosed disease and support producers that are using antibiotics responsibly.

The California Model: Legislation[1] to Reduce and Monitor Livestock Antibiotic Use

California provides a model for other states to draw on for their own efforts to reduce unnecessary use of medically important antibiotics in food animal production. Key features of California's legislation include:

- Requires veterinary authorization for use of medically important antibiotics.
- Prohibits routine disease prevention use of medically important antibiotics.
- Allows use for:
  - Treatment of sick animals;
    - When necessary for surgery or medical procedures;
  - To control the spread of disease outbreaks; or
    - For prophylaxis to address an elevated risk of contraction of particular disease or infection (as long as the use does not constitute a "regular pattern of use"
- Requires the California Department of Food and Agriculture to monitor sales and usage to help producers improve antibiotic use practices
- Requires the development of guidance on antimicrobial stewardship to help producers improve antibiotic use practices
- Requires a report to the legislature on progress made

Other Options for State Action to Reduce Livestock Antibiotic Use

- Establish targets for reducing the sale or use of antibiotics in food-producing animals in the state (e.g. a 50% reduction relative to a benchmark year).

- Phase out all use in food-producing animals of certain antibiotics that are critically important to human medicine.

Procurement by State and Local Government Agencies

States and local governments could set targets for procurement of meat and poultry produced without the routine use of antibiotics. A large portion of the chicken industry has already made commitments to eliminate the routine use of medically important antibiotics and progress towards those commitments. State and local governments could prioritize meat and poultry purchases from producers with such commitments, particularly those that adhere to third-party verified standards such as the Certified Responsible Antibiotic Use (CRAU) (add link) standard for poultry or otherwise require that the suppliers refrain from the use of medically important antibiotics for growth promotion and prevention. Other standards and claims with strong antibiotic use provisions include Organic, Humane Certified, Animal Welfare Approved, Raised Without Antibiotics (Process Verified Program), and Global Animal Partnership (GAP).

State or Local Legislation on Reporting of Antibiotic Use Practices in Meat Supply Chain

States or cities also could enact legislation to require grocery stores in their jurisdictions to report to the city or state the antibiotic use practices associated with the meat or poultry they sell. The city or state could then analyze this data and make information and guidance available to the public.

Endnotes

1 A copy of the bill, Senate Bill 27 (SB 27), is available here: http://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB27. The bill also bans growth promotion use of medically important antibiotics, but that simply replicates FDA regulations.

Appendix D: Tools for Restaurants, Food Retailers and Food Management Companies to Improve Antibiotics Use in their Meat and Poultry Supply Chains

Consumer demand for meat and poultry raised with responsible antibiotics use practices continues to rise. People are rightfully concerned that antibiotic overuse in livestock and poultry exacerbates the public health crises of antibiotic resistance. By preferentially choosing meat raised with responsible antibiotic practices, the public is sending a clear signal to the livestock industry that they need to reform current practices. Major buyers of meat and poultry are sending a similar signal to the livestock industry. The 2016 *Chain Reaction II* Antibiotics Scorecard, released by several NGO groups, ranked the antibiotic policies and practices of the top 25 restaurants in the United States.[1] Nine of 25 chains earned passing grades, thanks in large part to strong policies for chicken supplies. The number of companies with passing grades doubled from 2015 to 2016. Similarly, leading health systems throughout the U.S. have set impressive goals around responsible meat and poultry procurement; in some cases, up to 60% of a health system's purchases are comprised of meat raised without routine use of antibiotics.[2,3]

The good news for major buyers throughout the food sector is that availability of supply is growing to meet demand, especially in the chicken industry. Major chicken suppliers like Tyson, Perdue, and Foster Farms have either made commitments to phase out routine antibiotics use of medically important antibiotics in their supply chains or have already done so.[4,5,6] Pilgrim's Pride committed 25% of its vast chicken supply to be raised without antibiotics by 2020.[7]

There are signs of progress in the pork industry as well. Since 2016, Smithfield (the largest pork producer and processor in the world) and Tyson have launched product lines of raised-without-antibiotics pork that are meant for retail and food service sectors.[8,9] Positive signs are also beginning to emerge from the beef industry: Cargill announced in April 2016 that it would cut its use of medically important antibiotics by 20% in 1.2 million cattle.[10] This is a virtuous cycle: the more consumers, foodservice, and institutional buyers ask for responsibly raised meat, the more the industry responds.

Responsible Antibiotics Use Procurement Toolkit

We encourage all major buyers – whether at a grocery chain, a restaurant, or a foodservice operation – to set clear antibiotic use policies governing meat and poultry procurement decisions at their company, school, and/or hospital. These policies should have three key components and be integrated into bidding processes and contracts:

1. A time-bound commitment to phase out routine use of medically-important antibiotics, i.e. for disease prevention; use of antibiotics for treatment of sick animals or to control identified disease outbreaks need not be limited.
2. A requirement that production claims be verified by a 3rd-party auditor to provide assurance that antibiotics use practices match company policies. Verified standards and claims with strong antibiotics use provisions include the Certified Responsible Antibiotic Use (CRAU) standard for poultry; Certified Organic; Certified Humane; Animal Welfare Approved; Raised Without Antibiotics or No Antibiotics Ever (if compliant with USDA Process Verified Program), and Global Animal Partnership.[11,12,13,14,15,16] A producer could also work with the USDA to develop a company-specific Process Verified Program that complies with an antibiotics policy that bans medically important antibiotics for growth promotion and routine disease prevention uses.
3. A publicly available, annually updated progress report to ensure that customers and investors (if applicable) are informed.

We also encourage institutional and foodservice purchasers to do the following:

1. Ask their meat and poultry suppliers about their antibiotic use practices to improve transparency about which antibiotics are being used by supplying farms, in what quantities, and for what species. Even if this information is kept confidential, it sends an important signal to producers.

2. Engage in public policy to contribute to solutions at federal, state and local levels.

Endnotes

1 2016 Chain Reaction Antibiotics Scorecard (NRDC.org): https://www.nrdc.org/resources/chain-reaction-how-top-restaurants-rate-reducing-antibiotics-their-meat-supply

2 Health Care Sector Demands Sustainable Meat and Poultry (Health Care without Harm): https://noharm-uscanada.org/articles/press-release/us-canada/health-care-sector-demands-sustainable-meat-and-poultry

3 Extensive information for major buyers in the health-care sector interested in purchasing meat and poultry raised without routine antibiotics is available via Health Care Without Harm: https://noharm-uscanada.org/purchasing

4 Antibiotic Use –Statement (Tyson Foods): http://www.tysonfoods.com/media/position-statements/antibiotic-use.aspx

5 Antibiotics Position Statement (Perdue Farms): https://www.perdue.com/perdue-way/no-antibiotics/

6 Antibiotics Stewardship Statement (Foster Farms): https://www.fosterfarms.com/because-we-care/antibiotic-stewardship/

7 Pilgrim's Expects 25% of Its Chicken Will Be Antibiotic-Free by 2019 (Wall Street Journal): https://www.wsj.com/articles/pilgrims-expects-25-of-its-chicken-will-be-antibiotic-free-by-2019-1429564675

8 Smithfield Foods Introduces Pure Farms™ Antibiotic-Free Product Line (Smithfield Foods): http://www.smithfieldfoods.com/newsroom/press-releases-and-news/smithfield-foods-introduces-pure-farms8482-antibiotic-free-product-line

9 Cleaner Meat; Just months after Big Pork said it couldn't be done, Tyson is raising up to a million pigs without antibiotics (Quartz.com): https://qz.com/624270/just-months-after-big-pork-said-it-couldnt-be-done-tyson-is-raising-up-to-a-million-pigs-without-antibiotics/

10 Cargill eliminates 20% of shared-class antibiotics used for beef cattle (Cargill.com): https://www.cargill.com/news/releases/2016/NA31934263.jsp

11 Certified Responsible Antibiotic Use (CRAU).Poultry that supports health from farm to fork (BattleSuperbugs.org): http://battlesuperbugs.com/crau-standard

12 Animal Welfare Approved: https://animalwelfareapproved.us/

13 National Organic Program. United States Department of Agriculture (USDA.gov) https://www.ams.usda.gov/about-ams/programs-offices/national-organic-program

14 Certified Humane: http://certifiedhumane.org/

15 Official Listing of Approved USDA Process Verified Programs (USDA.org): https://www.ams.usda.gov/sites/default/files/media/Official%20ListingPVP.pdf

16 Global Animal Partnership: http://www.globalanimalpartnership.org/

Appendix E: Policies Leading to Reduced Antibiotic Use in Two Countries

Denmark and the Netherlands are two European livestock-producing countries that have made significant efforts to reduce antibiotic use in the production of food animals. Both countries have robust and profitable livestock sectors. They offer many lessons for the U.S. to draw upon in its own efforts to reduce antibiotic use in food animal production.

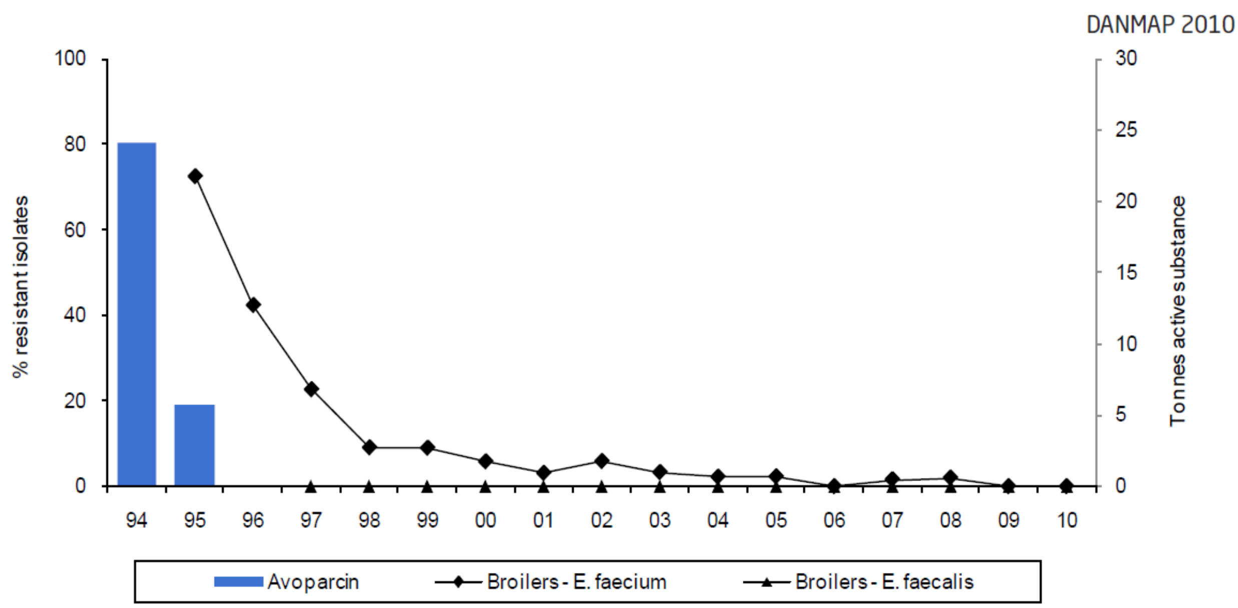
Denmark

Denmark (along with Sweden and Norway) emerged as an early model for how the adoption of new policies and practices could quickly and effectively reduce use of antibiotics in food animal production.

Establishment of DANMAP

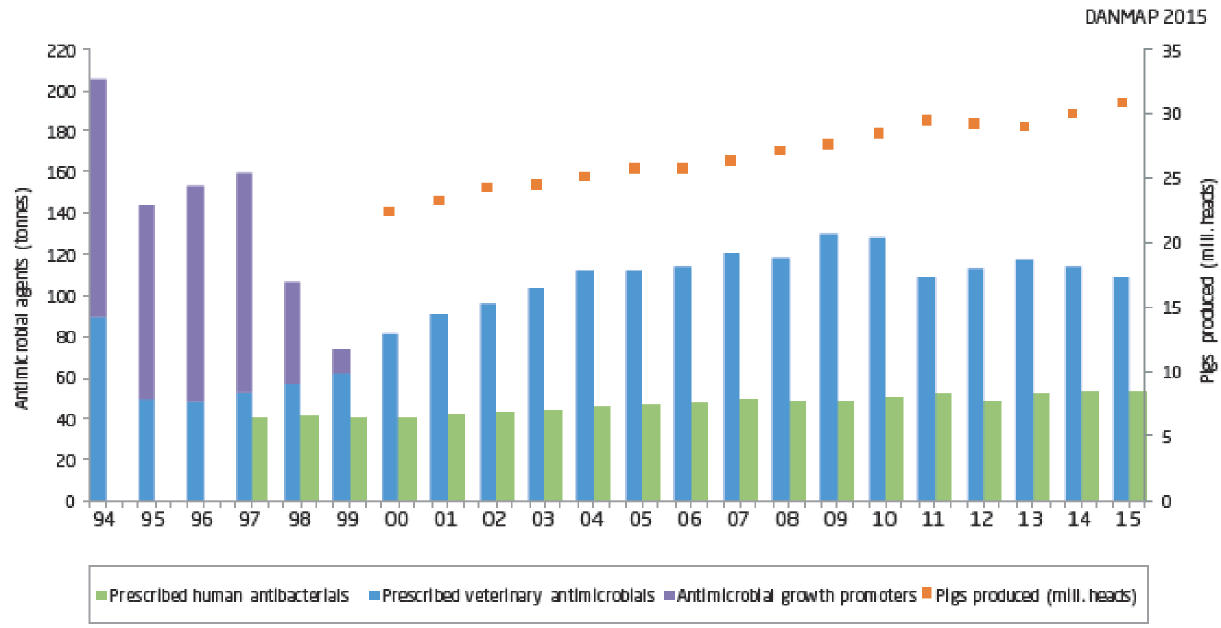
The establishment of DANMAP, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, in 1995 provided a platform to document the effect of different actions taken. Figure 1, for example, shows the impact of declining avoparcin use on the prevalence of avoparcin/vancomycin-resistant *Enterococcus faecium* in Danish broilers.[1]

Figure 1. Avoparcin consumption and resistance (%) to avoparcin/vancomycin in *E. faecium* from broilers.



Similarly, Figure 2 shows that total antibiotic consumption in animals in Denmark, relative to 1994 levels, dropped 43% by 2013 and 47% by 2015. Meanwhile, the number of pigs produced rose 15% from 1994 to 2015.[2]

Figure 2. Antibiotic consumption and millions of pigs produced in Denmark, 1994-2015.



Data collection on veterinary use of antibiotics

As stated, DANMAP collects data on veterinary use of antibiotics. In Denmark, antibiotics are prescription-only drugs. By law, veterinarians are required to report each month on all prescriptions written and drugs used for production animals to the VETSTAT database[3]; for most of them, the registration of data is automatically linked to their writing of invoices. In addition to veterinary drug sales, data also are sent electronically from pharmacies, private companies and feed mills to VETSTAT. For each prescribed item, VETSTAT holds detailed information about its source and consumption, its date of sale, the prescribing veterinarian, source ID (identity of the pharmacy, feed mill, or veterinarian practice reporting), package identity code and amount, animal species, age-group, disease category and code for farm-identity (Central Husbandry Register).[4] At pharmacies, the electronic registration of sales data is linked to stock reports and the billing process, ensuring the data are accurate with respect to the identity and amounts of antibiotics listed there.

Box A: Timeline of select Danish initiatives

Pre-1970s	All veterinary medical products are made available only by prescription.
1994	Central Husbandry Register is created to register and identify all herds.
1994/95	Prophylactic antibiotic use is prohibited.
1995	Veterinarian profits directly from sales of prescribed drugs are limited to 5-10% of income.
1995	DANMAP is created to research/monitor antibiotic use and resistance in humans, animals, food.
1995	Government bans growth promotion use of avoparcin.
1996	Pharmacies and the pharmaceutical industry are barred from increasing sales by offering economic incentives to veterinarians or others.
1998	Government bans growth promotion use of virginiamycin. The EU bans growth promotion uses of virginiamycin, bacitracin, tylosin, spiramycin.
2000	VETSTAT database established to record (by animal age group, herd and veterinarian) all antibiotics prescribed for production animals.
2002	Fluoroquinolones intended for injection are restricted to use by veterinarians only.
2002	EU extends its earlier growth promotion ban to all antibiotics. Effective 2006.
2003	Mandatory susceptibility testing that documents the need for fluoroquinolones prior to their use in production animals, and mandatory notification of authorities with that use as well.
2005	Action plan issued for reducing swine antibiotic use, including development of swine prudent use guidelines, and outreach to veterinarians with a high prescription rate.
2007	Action plan issued for also reducing antibiotics in cattle and poultry, including: (1) new treatment guidelines; (2) biennial audit of veterinarians; and, (3) new oversight to ensure no financial conflicts of interest between antibiotic makers and veterinarians.
2010	"Yellow card" control of antibiotic use begins in pig production, imposing preventive measures in the herds with highest consumption per pig.
2010	Use of cephalosporins in pig production is voluntarily ended.
2010	Evidence-based treatment guidelines are issued for swine veterinarians.
2010	Joint AMR action plan established by Ministries of Health, Food and Agriculture.
2010	One veterinarian/one farmer herd health agreements are mandated for swine and cattle, with an emphasis on welfare and disease prevention not using antibiotics.
2010	Thresholds are established for antibiotic use, mortality and welfare parameters in swine, cattle.
2014	Differentiated taxes implemented on antibiotics for veterinary use.
2014	New and tighter rules on antibiotic treatment of groups of pigs.
2015	Action plan to control livestock-associated MRSA in pigs.
2016	"Yellow card" controls are differentiated to focus on prevention of fluoroquinolones and cephalosporins use, and on limiting tetracycline use in pig production.

Danish initiative

Over the years, many initiatives have been undertaken in Denmark to reduce veterinary use of antibiotics while maintaining a high level of animal production and welfare. Close cooperation between Denmark's scientists and policymakers, as well as the Danish livestock industry, allowed new initiatives to be continuously developed and implemented that further reduced antibiotic use.

Box A lists the initiatives by both governmental interventions and voluntary actions taken by industry. In brief, they include a ban on the use of antibiotics that are critically important to human medicine and measures to remove incentives for farmers and veterinarians to use antibiotics as a management tool. While some initiatives have been evidence-based, others were grounded more in common sense – sometimes necessary to expeditiously address new problems. Though some of the biggest changes in food animal production took place two decades ago, the industries continue to thrive. Denmark exports 60% of its poultry meat[5], and remains among the top three pork-exporting nations in the European Union.[6]

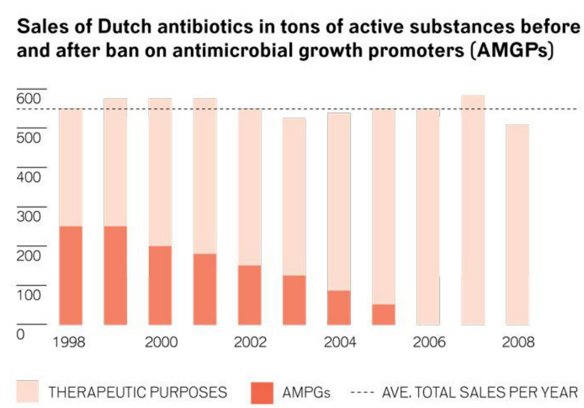
Yellow card initiative

Denmark's enhanced surveillance of both antibiotic use and resistance in its pig production also facilitated implementation of a warning (yellow card) system. In 2005, large differences in antibiotic use on farms were observed in VETSTAT. As a result, authorities adopted treatment guidelines and began auditing prescription patterns and usage.[7] These measures eventually led to a yellow card initiative targeting the pig producers with the highest use of antibiotics. Pig producers found to be using antibiotics above one or more of the government-established thresholds within a nine-month period face penalties that include limitations on usage and/or storage of antibiotics, unannounced inspections and increased veterinary supervision. A pig producer may be required to reduce stocking density, but only in the case of continued excessive use of antibiotics.[8] Using the yellow card system, Denmark has lowered overall antibiotic use by iteratively setting new thresholds, and then targeting top antibiotic users.

The Netherlands

Before 2008, high antibiotic use in the Netherlands' livestock sector persisted, despite an earlier end to antibiotic use for growth promotion (See Figure 3)[9]. Combined with public concern about the potential for drug-resistant bacteria to spread from animals to people, the persistently high usage led to additional measures described in Box B, and instituted after 2008.[10] These latter measures (See Box B) succeeded in greatly reducing overall antibiotic use in the sector (Figure 4).

Figure 3: Persistence of sales of antibiotics (in tons of active substances) in the Netherlands before and after a 2006 ban on antibiotic growth promoters (AMGPs) (adapted)



** Therapeutic use included antibiotics for treatment, control and prevention until 2011, after which prevention uses were no longer allowed.*

Because the Netherlands had successfully controlled MRSA in hospitals through strict measures, reports in 2005 of widespread livestock-associated MRSA in pigs – and their potential transmission to livestock workers – caused immediate concern.[11] A multi-stakeholder task force was then formed to reduce antibiotic use in food animal production.[12] Officials felt additional pressure after retail poultry was discovered to be widely contaminated with bacteria producing extended-spectrum beta-lactamase (ESBL) enzyme. These bacteria were also potentially linked to the death of a Dutch patient.[13]

The ESBL enzyme breaks down commonly used antibiotics making the bacteria producing the enzyme resistant to treatment by the affected antibiotics.

Policies and framework

Setting targets. Using 2009 as a baseline, the government set clear targets for reducing antibiotic use in livestock production as a whole: 20% by 2011, and 50% by 2013. Both of these targets were agreed to by the animal sector. In 2012, a reduction target of 70% by 2015 was set by government decree without agreement by the animal sector.[14]

Public-private partnership. The program in the Netherlands has been set up as a public-private partnership. Stakeholders in pig, broiler, veal and cattle production, along with the Royal Netherlands Veterinary Association (KNMvD), took responsibility for putting in place effective measures, while the national government provided facilitation, legislation and inspection. Implementation plans for meeting the above targets, for example, were developed by the industry members.

Surveillance of antibiotic usage. Various livestock sectors collect data on antibiotic use from 40,000 farms, anonymize it to protect the identity of individuals, and then share it with the independent Netherlands Veterinary Medicines Authority (SDa). The SDa, the government and the public have access only to the anonymized data. An independent panel of experts from medicine, veterinary science, epidemiology and pharmacy, convened by the SDa, analyzes these data and prepares annual reports on antibiotic use, the most recent being from 2016.[15]

Veterinary oversight. Farms must have only one veterinarian per herd, who does periodic inspections and who must prescribe any antibiotics administered. Generally, the veterinarian inspects and assesses the farm before doing so, except in very well-defined instances. Farms also must have herd treatment and health plans (mostly including resistance profiling of the farm and tailored management practices) in place. Antibiotics are tiered for farm use according to their importance to human medicine. Farms are allowed to treat up to 15% of their animals using so-called first choice, non-critical antibiotics, based on the yearly veterinary consultation and the development of the aforementioned farm treatment plan that includes treatment protocols for common diseases on a particular farm. The second and third tiers include certain critical drugs that may only be administered by the consulting veterinarian.[16] Third-tier antibiotics (e.g. fluoroquinolones and 3rd and 4th generation cephalosporins) also are only allowed if susceptibility testing has demonstrated there to be no available alternative antibiotic, and are typically not used for herd or flock treatment. This tiering system also applies to antibiotic use in pets.

Box B: Timeline of Select Initiatives and Events in the Neatherlands

1998	Health Council recommends ending antimicrobial growth promoters (AGPs) in animal feed.
2005	Discovery of livestock-associated MRSA transmitted to livestock workers and families. Strict infection control procedures for this LA-MRSA at hospitals put pressure on livestock industry.
2006	Based on EU legislation, the Netherlands completes the previously-recommended AGP ban.
2009-2010	Discovery of ESBL-producing bacteria on meat and possible association with a human death raises concerns in the public sphere.
2010	Government sets a 50% reduction target for 2013 using 2009 levels as a benchmark.
2011	The independent Netherlands Veterinary Medicines Authority (SDa) becomes active, overseeing antimicrobial usage and assessing improvements in various animal sectors.
2011	Dutch Health Council makes recommendations on use reduction recommendations to combat antibiotic resistance including reserving fluoroquinolones and aminoglycosides for treatment of animals after diagnostic tests.
2009-2012	Abandoned preventative use. Restricted duration of therapy. Increased use of single substance 2012 therapy in place of combination drug therapy. Also replaced herd-wide treatment with treatment of partial herds or individual animals.
2012	Livestock, Meat & Eggs industry groups impose new requirement for farm health plans and farm treatment plans, and central registration of all prescribed antimicrobials on farms.
2014	Legislation is introduced dictating that all antimicrobials should be administered by veterinarians except in cases that meet specific conditions.
2015	Key report of the Dutch Health Council updated[a].
2016	Minister of Health & Economic Affairs sends Letter to Parliament outlining actions to come to further reduce antibiotic use in food animal production[b].

[a] Health Council of the Netherlands. Advisory letter Tightening up on antibiotic use in animals. The Hague: Health Council of the Netherlands, 2015; publication no. 2015/31E. Accessed April 5, 2015 at https://www.gezondheidsraad.nl/en/task-and-procedure/areas-of-activity/prevention/advisory-letter-tightening-up-on-antibiotic-use-in.

[b] https://www.government.nl/binaries/government/documents/parliamentary-documents/2015/06/24/letter-to-parliament-about-the-approach-to-antibiotic-resistance/en-kamerbrief-aanpak-antibioticaresistentie.pdf.

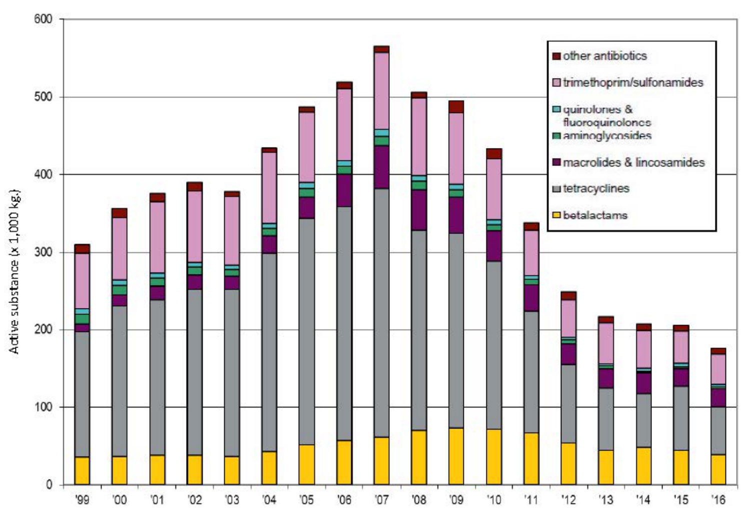
Benchmarking and Transparency. Critical to the program's success has been establishing and clearly communicating expectations. The goal of improved herd health is made clear, as are expected responsibilities in antibiotic delivery and herd management. The independent panel of experts advising SDa proposes veterinary benchmarks regarding the quantity of antibiotics to be used within each livestock (sub)sector. SDa can then make comparisons between data collected from farms and veterinarians, although those data have been anonymized. A 2014 SDA report, for example, contains the first analysis of prescription patterns by Dutch veterinarians.[17]

Surveillance of antibiotic resistance. MARAN (the Monitoring of Antibiotic Resistance and Antibiotic Usage in Animals in the Netherlands), the country's chief program for monitoring antibiotic resistance in animals, also tracks resistance trends in animals and retail meat.[18] Monitoring programs across the country randomly take samples from animals at slaughter; retail samples also are collected from chicken, pork, beef, and turkey and other products, and reflect both domestic and imported products. Parallel to MARAN is NethMap, which annually publishes yearly trend data for major pathogens affecting humans, based on robust antibiotic susceptibility data collected from hospitals and held in the centralized repository, called ISIS-AR. Resistance profiles of Enterococci, Salmonella spp., E. coli and Campylobacter spp. in food animals and retail meat are presented in the NethMap-MARAN reports.

Reduction in antibiotic sales and antibiotic resistance

Figure 4 shows the rapid drop in antibiotic sales (the metric used to measure success) after various measures were implemented starting in 2008. By 2012, total sales had dropped 49% relative from the 2009 baseline, reaching the target originally set for 2013 a year early. Sales of 3rd and 4th generation cephalosporins, antibiotics critically important to human health and also used in animals, dropped more than 90% over the same period. By 2016, total sales had shown a further drop of more than 64%, relative to the 2009 baseline.[19]

Figure 4: Dutch sales of antibiotic agents, 1999 to 2016. By year and by 1,000s of kg. of active substances sold [*not including antibiotic growth promoters*][20]



Among the different animal species and four bacterial groups tested, antibiotic resistance has plateaued or trended downward in recent years (with the exception of fluoroquinolone resistance in Campylobacter spp.).[21] These trends coincide with reduced antibiotic use in food animals. See Figures 5 and 6.

Figure 5: Trends in resistance (%) of C. jejuni bacteria isolate from broiler chickens and poultry meat in the Netherlands

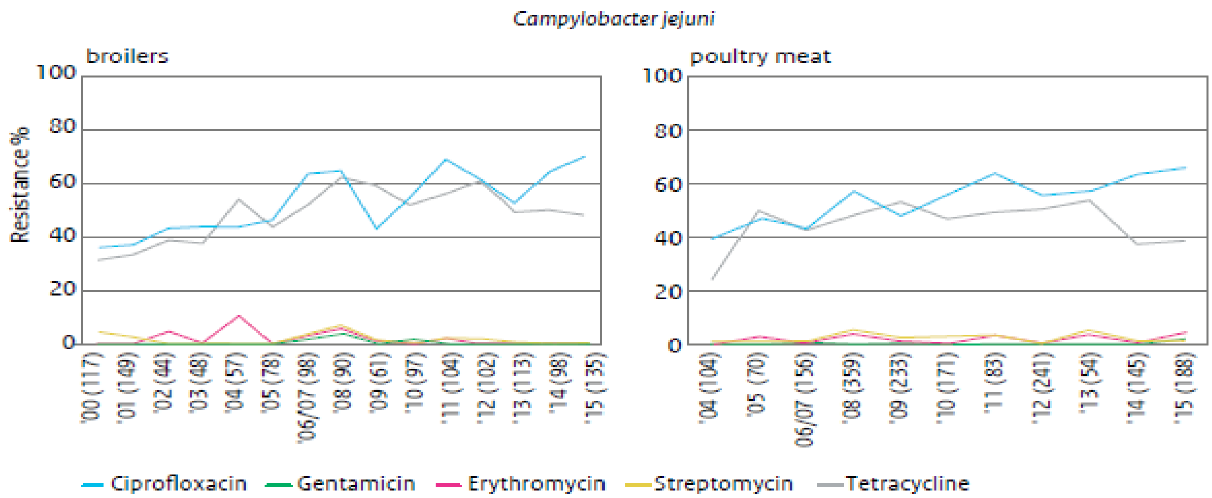
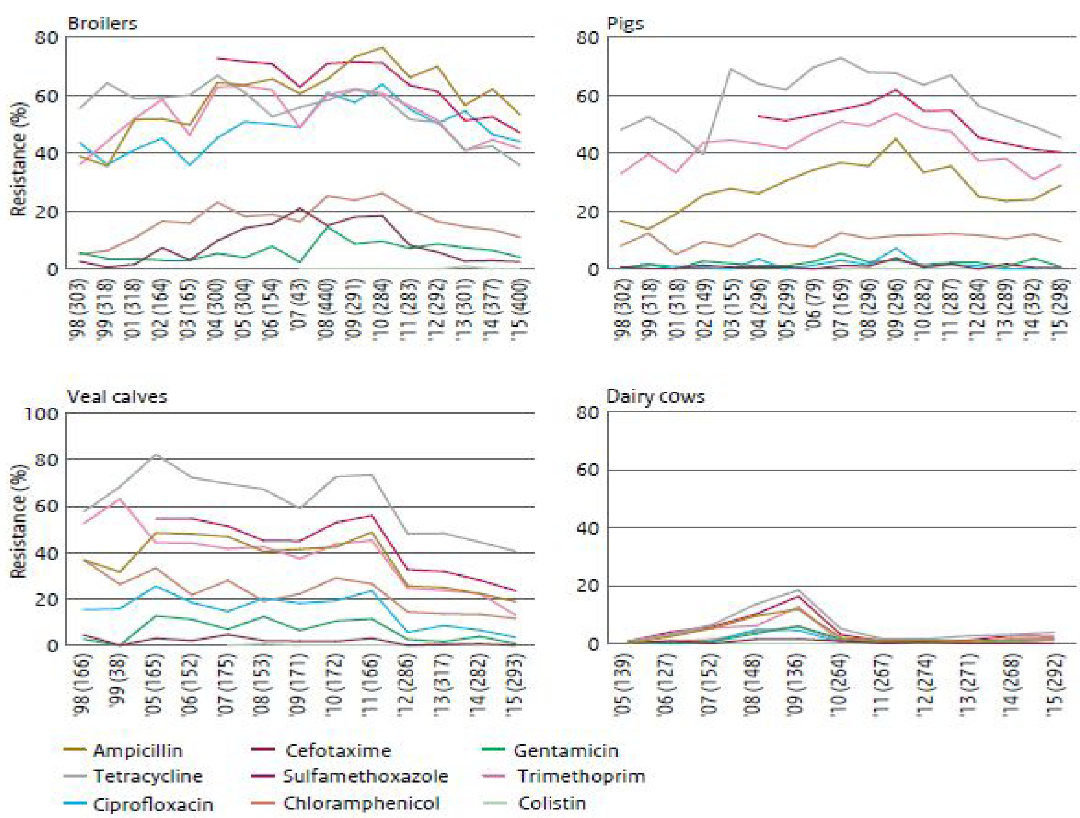


Figure 6: Trends in resistance (%) of E. coli isolated from broilers, slaughter pigs, veal calves and dairy cattle in the Netherlands. Similar favorable trends have been observed for Enterococci spp. and Salmonella spp. in animal samples. (Adapted from MARAN 2016)[22]



Endnotes

1 Statens Serum Institut, Danish medicines Agency, National Veterinary Institute and National Food Institute, Technical University of Denmark. DANMAP 2010 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. September 2010. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2010.ashx. Accessed May 1, 2017.

2 Statens Serum Institut, National Veterinary Institute and National Food Institute, Technical University of Denmark. DANMAP 2015 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. September 2015.http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%20%202015/DANMAP%202015.ashx. Accessed May 1, 2017.

3 Stege H, Bager F, Jacobsen E, Thougaard A. VETSTAT – the Danish system for surveillance of the veterinary use of drugs for production animals. 2003. http://orbit.dtu.dk/en/publications/vetstat--the-danish-system-for-surveillance-of-the-veterinary-use-of-drugs-for-production-animals(184762f4-87cc-42a2-b7de-f1c53513ce39).html. Accessed May 1, 2017.

4 Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. 2014. http://www.danmap.org/~/media/projekt%20sites/danmap/danmap%20reports/danmap%202014/danmap_2014.ashx. Accessed May 1, 2017.

5 DanHatch company website. The Danish Industry. http://www.danhatch.dk/the-danish-industry.

6 Denmark No Longer Europe's Top Pork Exporter. CPH Post. 2016. http://cphpost.dk/news/business/denmark-no-longer-europes-top-pork-exporter.html. Accessed May 1, 2017.

7 Nielsena AC, Aarestrup F, Myginda J. Danish Food and Veterinary Administration. Risk Management of Antimicrobial Use and Resistance from Food Producing Animals in Denmark. 2007. https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/05kontor/Risk_management_antimicrobia_%20use_and%20resistance_Denmark_E.pdf. Accessed May 1, 2017.

8 Ministry of Environment and Food of Denmark; Danish Veterinary and Food Administration. The Yellow Card Initiative on Antibiotics. 2017. https://www.foedevarestyrelsen.dk/english/Animal/AnimalHealth/Pages/The-Yellow-Card-Initiative-on-Antibiotics.aspx. Accessed May 1, 2017.

9 Government of the Netherlands. Reduced and Responsible: use of antibiotics in food-producing animals in the Netherlands. 2014. https://www.government.nl/documents/leaflets/2014/02/28/reduced-and-responsible-use-of-antibiotics-in-food-producing-animals-in-the-netherlands. Accessed May 1, 2017.

10 Wagenaar J. Personal Communication, July 26, 2016.

11 Voss A, Loeffen F, Bakker J, et al. Methicillin-resistant Staphylococcus aureus in Pig Farming. *Emerg Infect Dis*. 2005;11(12):1965-1966. doi:10.3201/eid1112.050428..

12 Speksnijder DC, Mevius DJ, Bruschke CJM, Wagenaar JA. Reduction of veterinary antimicrobial use in the Netherlands. The Dutch success model. *Zoonoses Public Health*. 2015;62:79–87. doi: 10.1111/zph.12167.

13 Ibid.

14 Ibid.

15 Netherlands Veterinary Medicines Authority (SDa). 2017. Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2016 (Dutch language only). May 29, 2017. https://www.rijksoverheid.nl/documenten/rapporten/2017/05/29/het-gebruik-van-antibiotica-bij-landbouwhuisdieren-in-2016. Accessed June 15, 2017.

16 Netherlands Veterinary Medicines Authority (SDa). Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2015, Table 4. September 2016. http://www.autoriteitdiergeneesmiddelen.nl/en/home. Accessed June 15, 2017.

17 Netherlands Veterinary Medicines Authority (SDa). The Veterinary Benchmark Indicator. August 2014. http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/pdf/SDa-rapporten/sda-report-the-veterinaire-benchmark-indicator-(vbi).pdf. Accessed June 15, 2017.

18 Wageningen University and Research website. MARAN Reports. 2017. http://www.wur.nl/nl/Expertises-Dienstverlening/Onderzoeksinstituten/Bioveterinary-Research/Publicaties/MARAN-Rapporten.htm. Accessed June 15, 2017.

19 Netherlands Veterinary Medicines Authority (SDa). 2017. Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2016 (Dutch language only). 2017. https://www.rijksoverheid.nl/documenten/rapporten/2017/05/29/het-gebruik-van-antibiotica-bij-landbouwhuisdieren-in-2016. Accessed June 15, 2017.

20 Ibid.

21 Dorado-García A, Dohmen W, Bos ME, et al. Dose-response relationship between antimicrobial drugs and livestock-associated MRSA in pig farming. *Emerg Infect Dis.* 2015; 21: 950–59. doi: 10.3201/eid2106.140706

22 Wageningen Bioveterinary Research (WBVR). NethMap MARAN-2016; Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2014; NethMap: Consumption of antimicrobial agents and antimicrobial resistance among bacteria medically Important in the Netherlands. http://www.wur.nl/nl/Expertises-Dienstverlening/Onderzoeksinstituten/Bioveterinary Research/Publicaties/MARAN-Rapporten.htm. Accessed June 15, 2017.

The Expert Commission convened at the George Washington University Milken Institute School of Public Health (GWSPH) on November 13, 2016. The Commission's efforts have been supported by staff at the Antibiotic Resistance Action Center at GWSPH and the Natural Resources Defense Council.

Suggested citation:
Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. *COMBATING ANTIBIOTIC RESISTANCE A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017.* Washington, D.C.