June 15, 2016

Dr. Bruce Gellin
Deputy Assistant Secretary for Health.
Designated Federal Officer, PACCARB

Re: **Joint Comments to the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria**

Dear Dr. Gellin:

We, the undersigned medical, public health, veterinary, consumer, environmental and other groups wish to submit the following comments to the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (herein the Advisory Council) in response to its charge from HHS Secretary Burwell[1], as well as its own Request for Information.[2]

Secretary Burwell asked the Advisory Council to recommend how U.S. investments should be prioritized so as to reduce antibiotic use and antibiotic resistance, including use in both agriculture and in human medicine. *While our groups individually may support other priorities, we collectively urge the Advisory Council to recommend that collection of data on antibiotic usage at the farm level be made a much higher priority*, and that a higher level of current resources be identified reflecting this priority. The imperative to collect data on antibiotic usage at the farm level has long been clear; further delay in doing so is an unaffordable luxury.

Sales data collected by the FDA indicate that 70% of medically important antibiotics in the U.S. are sold for use in animals. Data on actual usage are needed to better understand why antibiotics are used in each animal species, and how in detail they are used. That information in turn will inform key areas where the USDA and FDA should focus to help meet the goals of the National Action Plan to reduce antibiotic use as well as to gauge the impact of current interventions.

No comprehensive, quantitative, representative data are currently available to help track progress in reducing antibiotic use in agriculture. Meaningful data would be:

a) quantitative with information on the actual amounts of each antibiotic used;
b) representative of all the major food animal species and production classes and cover key information about the antibiotics used, the purpose and extent of the use, and the particulars of the use;
c) gathered in an ongoing manner to facilitate trend analysis;
d) not based on voluntary participation to avoid potential selection bias.

The Appendix contains in some detail key elements of a strong, reliable program for monitoring antibiotic use at the farm level, including case studies where such data already are being collected.

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[1] Task Letter from HHS Secretary Burwell to the PACCARB Chair and Vice Chair, dated March 25, 2016. Accessed at http://www.hhs.gov/ash/advisory-committees/paccarb/.

[2] Health and Human Services. Notice of Request for Information by the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. FedReg May 23, 2016.

As antibiotic resistance emerges not only as a health crisis, but as a threat to economic development and national security, the need for an effective U.S. response has never been greater.

As CDC Director Dr. Tom Frieden recently warned, "[T]he end of the road isn't very far away for antibiotics." With plasmid-mediated colistin resistance (mcr-1) having been recently found in bacteria from both humans and pigs in the U.S., there is urgent need to improve antibiotic stewardship and reduce antibiotic overuse, including in animal agriculture.

National investment in data collection to support reductions in antibiotic use and resistance at the farm level is imperative. We look forward to supporting the Advisory Council's work to ensure that investment occurs, is effective and sized appropriately. Thank you for your consideration.

Signed by,

American Academy of Pediatrics

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Food Animal Concerns Trust

Health Care Without Harm

Appendix: Response to the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria's Request for Information (RFI)

The RFI published in the Federal Register dated May 23, 2016, requests information in response to five questions. These comments refer to questions #4 and #5.

4. Please provide information on the best ways to collect data on antibiotic use [and resistance] in animal agriculture through public-private collaborations. Your response can include information on the types of data to be collected, including the method of collection, and the metrics for reporting the data.

Sales of antibiotics considered medically important for use in livestock increased 23% from 2009 to 2014.[3] Approximately 70% of all medically important antibiotics sold in the US are for use in agriculture. The data on U.S. antibiotic sales collected from pharmaceutical companies has been a useful and appropriate proxy for measuring trends in agricultural antibiotic usage since 2009.

However, collection of data on actual usage closer to the farm level is also essential. Antimicrobial use information could be collected from producers, veterinarians, or feed mills, but in any case the reports ought to be broken out by livestock owner and facility. Collection of these data in the U.S. is eminently achievable, as is illustrated by the attached case studies.

Actual data on antibiotic use on the farm are needed to:

1) More fully understand exactly how antimicrobials are used in each of the major livestock species, including trends and risks in that usage, as well as opportunities to reduce the spread of antibiotic-resistant bacteria; and
2) Provide a baseline to gauge the impact of federal interventions to (such as Guidance for Industry #213 and the new Veterinary Feed Directory, which have been put forward as steps to reduce unnecessary uses of animal antimicrobials and to bring remaining uses under veterinary oversight.

The following are data that should be collected, including identifying information for the veterinarian, facility owner/operator and reporting party, details of which would be redacted prior to publishing of any data summaries. Other data to be included are:

- the antimicrobial used;
- the indication for which it was prescribed, and the dosage;

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[3] Food and Drug Administration. FDA Annual Summary Report on Antimicrobials Sold or Distributed in 2014 for Use in Food-Producing Animals. Accessed June 2, 2016 at http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm476256.htm.

- the duration of use (i.e. number of treatment days);
- the party reporting antimicrobial usage (e.g. veterinarian, feed mill, production facility)
- the veterinarian prescribing the antimicrobial (if not also the reporting party);
- the owner and/or operator the facility where the antimicrobial was used (i.e. the entity that dictates how the animal is raised)[4]
- the facility's location;
- the species and production class of animals receiving the antimicrobial;
- the total number – or best estimate, if necessary – of animals receiving the antimicrobial;
- the total number of animals raised at the facility at the time antibiotics are administered (these data are key to understanding variations in use and benchmarking performance).

Case Study #1: Denmark

For several reasons, Denmark's experience with antimicrobial use reporting provides an important reference point for the U.S. First, Denmark's monitoring system (DANMAP) collects impressively detailed information, down to specific prescriptions for specific herds.[5,6]

Second, data on consumption of veterinary medicines is collected from several different sources including veterinary pharmacies, feed mills and veterinarians. Danish law requires veterinarians to report monthly on all prescriptions and veterinary drug use for production animals; that information is sent electronically to VetStat, which compiles all veterinary drug use into a single database. For each prescription, the data collected include:

- Identity of the pharmacy, feed mill, or veterinarian practice doing the reporting
- Identity of prescribing veterinarian
- Date of sale

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[4] The "owner of the livestock or poultry" should thus include person who has an ownership interest of any kind in the animals or birds, including a right or option to purchase the animals or birds, or a growing arrangement for obtaining and selling or slaughtering animals or birds.

[5] Hammerum AM, Heuer OE, Emborg H-D, et al. Danish Integrated Antimicrobial Resistance Monitoring and Research Program. *Emerging Infectious Diseases*. 2007;13(11):1633-1639. doi:10.3201/eid1311.070421.

[6] N. Dupont and H. Stege, *Vetstat- Monitoring usage of antimicrobials in animals*, Challenges and benefits of health data recording in the context of food chain quality, management and breeding: Proceedings of the ICAR Conference. ed. / C Egger-Danner; O.K. Hansen; K. Stock; J.E. Pryce; J. Cole; N. Gengler; B. Heringstad. 2013. p. 21-35 (ICAR Technical Series; No. 17).

- Package identity code and amount (Relating to information such as active ingredient, # of unit doses, package size, code of the antimicrobial agent in the ATCvet classification system)
- Animal species and age-group
- Disease category
- A code for herd identity (the herd ID code is tied to the geographical coordinates of the herd and also contains data on production type and number of animals present in the herd (animal species, age group) and contact information on the herd owner)

Case Study #2: California Pesticide Use Reporting System

The California Pesticide Use Reporting System[7], or PUR, covers all crop agriculture (and beyond) in California. PUR collects statewide information from thousands of sites, which illustrates how detailed farm-specific data is being collected for large number of participants. The resultant system provides industry, regulatory agencies, scientists and the public with an invaluable data resource, while at the same time preserving confidentiality for reporting individuals. By extension, the same could be accomplished with broad scale collection of antibiotic use data.

As with Denmark's antimicrobial use reporting system, California pesticide use reporting is completed monthly, and includes a variety of specific information:

- month and year of application(s)
- county in which work was done
- geographic location including the section, township, range, base, and meridian
- field location
- operator ID/permit number
- operator name and address
- applicator name and address
- site ID

5. Please provide information on different resources that exist to promote understanding of how antibiotics are being used in humans and animals in different parts of the world.

Many resources exist that can lead to better understanding of how antibiotics are used in humans and animals both inside and outside of the United States. Following are weblinks and brief descriptions of a select number of them:

[7] See http://www.cdpr.ca.gov/docs/pur/purmain.htm

i. **How antibiotics are used in U.S. hospitals**. As a result of the National Action Plan (Sub-Objective 1.1.3), U.S. hospitals will begin reporting to the National Health Safety Network on amounts of specific antibiotics used to treat hospitalized patients, as well as cases of antibiotic-resistant disease. The information to be supplied will includes particulars about each facility where antibiotics are used (size in terms number of beds, number of patients admitted, and total patient days), as well as answers to more than 34 specific questions. The goal of the reporting is to "identify geographic variations and/or variations at the provider and/or patient level that can help guide interventions".

Data on antibiotics used in animal agriculture, and the context for that usage should similarly be collected. Among other benefits, the collection of these data may be the most direct way to identify innovators succeeding in reducing antibiotic usage, and also to identify individuals who could benefit from targeted education on how to reduce usage. In contrast, current information on antibiotic use in animal agriculture in the U.S. relies on piecemeal information, with the NAHMS surveys from USDA providing only an occasional snapshot representing only a regional picture at best, and zero information on broiler chicken or turkey production.

ii. **Europe-wide resources on antibiotic use in food animals.** Various resources exist from the European Commission, the European Food Safety Authority (EFSA) and European Medicines Agency (EMA) and other sources that reflect evolving understanding of how antibiotics are used or should be used in animal agriculture in Europe, including the following.

Grave et al. (2010) was the first attempt to collect and compare veterinary antibiotic usage data for European countries, portrayed in Figure 1. Aarestrup et al. (2010)

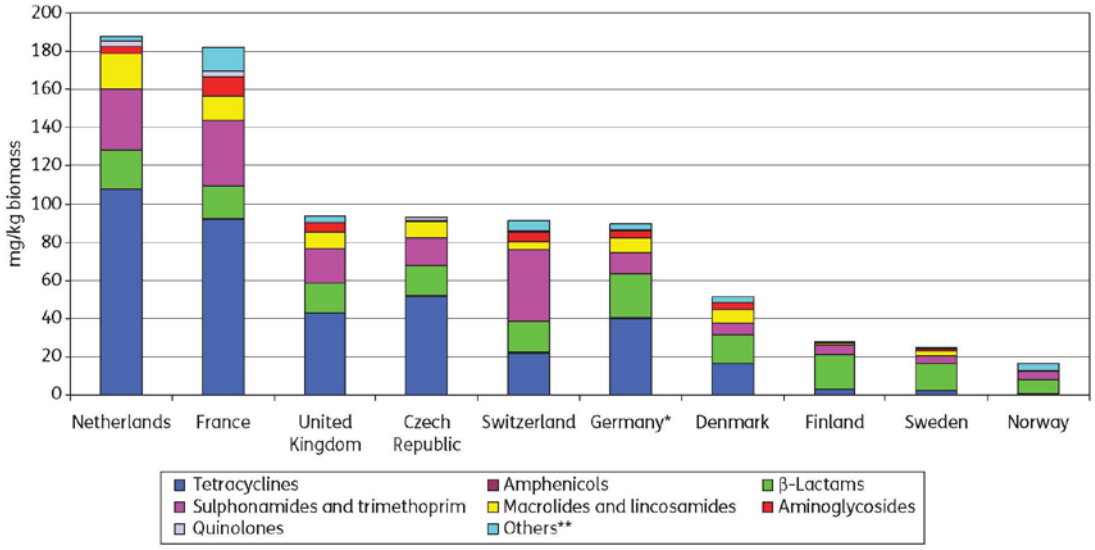


Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

reported that a conservative estimate of the comparable figure for the U.S. was considerably higher than for the Netherlands, approximately 300 mg/kg of biomass.

From the European Medicines Agency, the 2013 ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) report is the latest comparing sales of veterinary antimicrobial agents in 25 EU/EEA countries.

From the previously mentioned reports, and other sources, the Review of Antimicrobial Resistance in its December 8, 2015 report compiled a broader comparison that includes estimates of antimicrobial use in the U.S. Van Boeckel et al. (2015) is the first attempt to model antimicrobial use in food animal production at a global scale. More recently, Krishnasamy et al. (2015) focus on antimicrobial use in China, which has been estimated to consume nearly a quarter of all antimicrobials used in food animal production globally.

ECDC (European Centre for Disease Prevention and Control), EFSA and EMA. 2015. ***ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals.*** Stockholm/Parma/ London: ECDC/EFSA/EMA, 2015. *EFSA Journal* 2015;13(1):4006, 114 pp. doi:10.2903/j.efsa.2015.4006.

> This 115 page joint report, prepared in response to a 2012 request from the Europe Food Safety Authority (EFSA), explores associations between consumption of antimicrobials in humans and food-producing animals, and antimicrobial resistance in bacteria from humans and food producing animals, using 2011 and 2012 data currently available from their relevant five EU monitoring networks.

European Medicines Agency. 2012. ***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.*** EMA/286416/2012-Rev.1. Accessed at http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500136456&mid=WC0b01ac058009a3dc.

> The main aim of this paper is to discuss how to establish systems for the collection of reliable and standardized data on consumption of antimicrobial agents by animal species for the ESVAC database and to report the data taking into account the differences in dosing between the various antimicrobial agents as well as the animal population at risk for treatment.

Commission Notice, 2015 O.J. C 299/04 [hereinafter ***Guidelines for Prudent Use of Antimicrobials***. Accessed 12 March 2016 at http://ec.europa.eu/health/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf.

These European Commission guidelines on the prudent use of antimicrobials in veterinary medicine have been drafted with the support of the European Union (EU) Member States, also taking into account consultations with the relevant EU agencies (EMA, EFSA and ECDC), international organizations (OIE, FAO and WHO) and various stakeholders (e.g. Animal Health Advisory Committee and Advisory Group on the Food Chain). They address principles of prudent use, and set out measures to be considered by Member States when developing and implementing national strategies to combat AMR. A separate ***Staff Working Document*** (see http://ec.europa.eu/health/antimicrobial_resistance/docs/2015_prudent_use_guidelines_annex_en.pdf) provides a number of practical examples of approaches used in various Member States for implementing each of the principles in the above Notice.

Upcoming (end of 2016). In 2015 the European Commission requested a joint *scientific opinion* from the European Medicines Agency (EMA) and the European Food Safety Authority (EFSA) on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety. The opinion is to be rendered by 20 December 2016.

iii. **The Netherlands**. Similar to Denmark, the Netherlands has a system where antimicrobial use in food animal production takes place under a strict set of rules. See https://www.government.nl/topics/antibiotic-resistance/ contents/ antibiotic-resistance-in-livestock-farming. Key characteristics of the system are:

- Antibiotics may only be prescribed by a veterinarian, and the latter must inspect and assess a farm before prescribing antibiotics to sick animals.
- Farmers must register all the antibiotics they use, to show how much each animal receives. The independent Netherlands Veterinary Medicines Authority (SDa) collects and analyzes this information.
- Last-resort antibiotics for humans, like colistin, may only be administered to sick livestock under strict conditions.

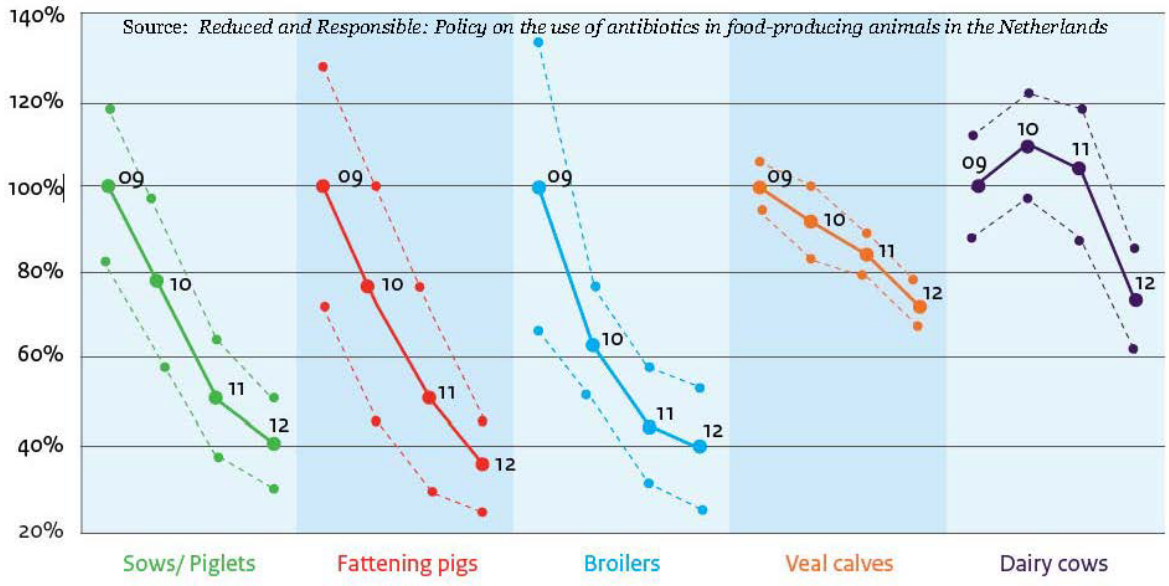
While the governmental Food and Consumer Product Safety Authority (NVWA) monitors the registration and use of antibiotics by farmers, the Netherlands Veterinary Medicines (SDa) was established in 2010 as an independent agency to promote responsible drug use in livestock production generally, and especially usage of antibiotics. SDa convenes an independent panel of expert scientists from human medicine, veterinary science and epidemiology and is considered a neutral and trusted group. The panel analyzes data collected by SDa on antibiotic usage from 40,000 Dutch livestock farms, and issues annual reports on that usage. It also

defines *benchmarks* regarding the quantity and the types of therapeutics to be used within each livestock sector. In August 2014, the expert panel released an English language report on Veterinary Benchmark Indicators, as well as its first analysis of prescription patterns among Dutch veterinarians. Other reports include:

- The Veterinary Benchmark Indicator (VBI) (August 2014)
- Antibiotics in Agricultural Livestock in the Netherlands in 2014; Trends and benchmarking of livestock farms and veterinarians (October 2015 revision)
- Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2013
- Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2012
- Consumption of Antimicrobials in Pigs, Veal Calves, and Broilers in the Netherlands: Quantitative Results of Nationwide Collection of Data in 2011 (October 2013)

The SDa's website links to presentations from a March 2014 SDa-sponsored symposium offering additional information on the thinking behind the Dutch approach and its particulars, including the use of Veterinary Benchmark Indicators.

Netherlands antibiotic use per animal species, 2009-2012
(as % of animal-defined-daily doses/yr, relative to 2009)



From 2008-2011, the Netherlands outlined a policy for successful reduction of agricultural use of antibiotics. The program proved to be extremely successful. By 2012, the sales of veterinary antimicrobials (the metric used to measure success) had already dropped by 49% – the 2013 target having been reached a year ahead of schedule; as the above figure shows, sales of antimicrobials for individual animal

species dropped across the board. In addition, sales of 3rd and 4th generation cephalosporins – critically important human classes of antibiotics also used in animals – had dropped by more than 90% over the same period.

The Dutch plan was a reaction to persistently high levels of antibiotic use in the livestock sector prior to launch of the plan, combined with public concern about potential transfer of antimicrobial resistance from livestock to humans. The program was 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 being facilitated and supervised by the national government. (A program without this level of private sector support might be presumed to carry a lower likelihood of success.) Key elements of the program included:

- The government set clear targets for reductions in antibiotic usage for livestock production as a whole: 20% reduction by 2011 and 50% by 2013, with reference as a baseline to the amount of antibiotic active ingredient sold in 2009. (By a 2012 government decree, the reduction target for 2015 was set at 70%).
- Implementation plans for meeting those targets, however, were devised and agreed upon by the industry members in the industry;
- Transparency and benchmarking of antibiotic use per herd and per veterinarian;
- Improved herd health, clear responsibilities in herd health management and in prescription/delivery of antibiotics by:
    - mandatory herd health plans
    - one contracted veterinarian per herd
    - mandatory periodic veterinary herd inspections
- A program of government enforcement.