Antimicrobial Resistance and One Health: Research Needs

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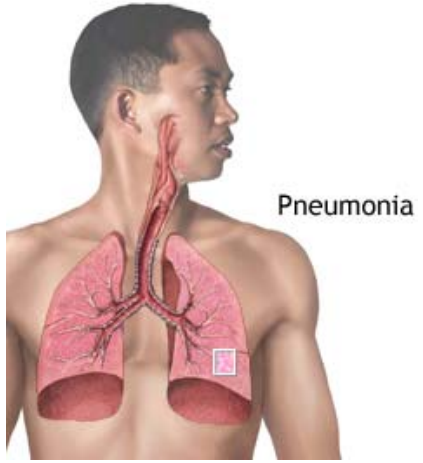
Why do we use antimicrobials? (AM)

- To treat or prevent bacterial infections
  - that can sicken or kill
  - people or animals

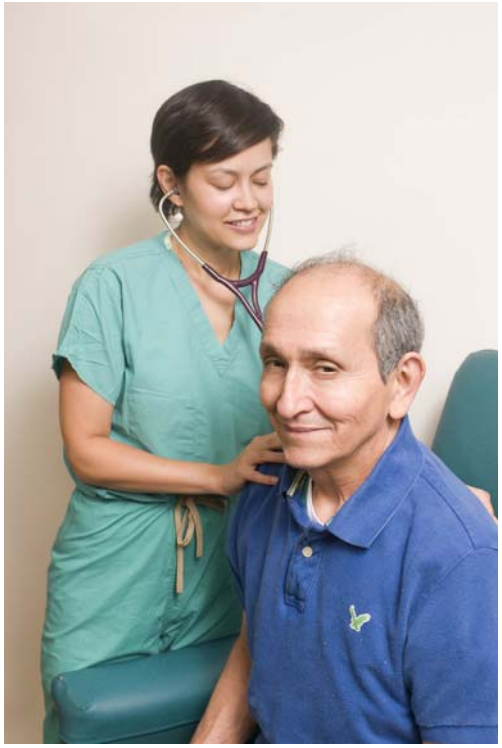
- Plants get AM too

  …for certain infections

- Some bacterial infections that affect people:
  - "strep throat"
  - infected cuts and wounds, and skin infections
  - certain types of
    - sinus infections
    - pneumonia (lung infection)
    - intestinal problems that cause diarrhea
      - e.g. traveller's diarrhea due to *E. coli*



- Some bacterial infections that affect animals:
  - "strep throat" ("strangles" in horses)
  - infected cuts and wounds, and skin infections
  - certain types of
    - sinus infections
    - pneumonia (lung infection)
    - intestinal problems that cause diarrhea
      - e.g. neonatal diarrhea due to *E. coli*



Antimicrobials can cure infections and save lives of people AND animals

- Antimicrobial resistance has been around for a long time

Drug-Resistant Bacteria Found in 4-Million-Year-Old Cave

OPEN ACCESS Freely available online

PLoS one

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

Kirandeep Bhullar[1], Nicholas Waglechner[1], Andrew Pawlowski[1], Kalinka Koteva[1], Eric D. Banks[2], Michael D. Johnston[2], Hazel A. Barton[2], Gerard D. Wright[1]*

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MRSA infection
CDC.gov

MRSP infection
todaysveterinarypractice.navc.com

- BUT: AMR bacteria are becoming easier to find in people and animals
  - Sometimes they cause serious illness or death

What should we do about AMR?

- Stop using AM?
  - Some research: stop using AM: AMR goes down

    Reviewed in Volkova et al., 2016
  - Some research: stop using AM: AMR does NOT go down

    Kassem et al., 2017; Agga et al., 2016
  - Some research: even when AM are used, AMR is sometimes not very common

    Noyes et al., 2015; Smith et al., 2016

- The relationship between AM use and AMR is not as clear as you might expect

- Should we use AM only for the very sick?
  - Waiting to treat disease until the patient is very sick may be too late
  - Untreated patients may spread bacteria to others, making more individuals sick…

    …leading to the need for more AM use

- Should we use AM only when we KNOW an infection is due to bacteria?
  - For most infections, confirmation of diagnosis takes at least 2- 3 days
    - Time waiting for diagnosis before we give AM may harm patients with true bacterial infections
    - Testing adds cost to care

- Physicians and veterinarians have some ideas about how to decrease AMR
  - Use vaccines and other approaches to prevent disease, so AM aren't needed
  - Use AM only when we are (pretty) sure a disease is due to bacterial infection
  - Make sure patients take AM long enough, but not too long
  - Choose AM that should kill the bad bacteria while not killing (too many) good bacteria

Guidelines from veterinary professional organizations support these approaches

AABP GUIDELINES

PRUDENT ANTIMICROBIAL USE GUIDELINES FOR CATTLE

AVMA
Our Passion. Our Profession.

Judicious Use of Antimicrobials for Treatment of Aquatic Animals by Veterinarians

AAHA
The Standard of Veterinary Excellence

American Association of Feline Practitioners/American Animal Hospital Association Basic Guidelines of Judicious Therapeutic Use of Antimicrobials

American Association of Swine Veterinarians
Increasing the knowledge of swine veterinarians

Basic Guidelines of Judicious Therapeutic Use of Antimicrobials in Pork Production

AAEP

American Association of Equine Practitioners

Prudent Drug Usage Guidelines

aaap

Guidelines for Judicious Therapeutic Use of Antimicrobials in Poultry

Perhaps surprisingly:

- Little research has been done to test whether recommended practices actually decrease AMR

  Reviewed in Weese et al., 2015

- Available research studies often provide conflicting answers

- Right now we're often guessing we're doing the right thing, when we follow these guidelines
  - guessing wrong **may not be helpful**
  - guessing wrong **may be harmful**

Other questions needing more research:

- In clinical settings, how often does one type of bacteria **transmit resistance** to other types?
  - How does this work in the “microbiome”?
- How does a **patient’s immune system function** impact their susceptibility to developing AMR?
- How often do AMR bacteria **harbored by healthy individuals** spread to others, and make them sick?
- Which situations are most likely to lead to AMR that causes the most serious disease?

Research needs:

- Inter-disciplinary teams of
  - physicians and nurses
  - veterinarians and veterinary technicians
  - animal scientists
  - pharmacists and pharmacologists
  - microbiologists and immunologists

….working together to answer these questions

Research needs:

- Field studies
  - in hospitals and veterinary clinics
  - on farms and in homes

  ….to confirm that recommended approaches actually decrease AMR while maintaining health

- We need research that confirms

  …the best ways to prevent bacterial infections so AM aren't needed

  - through hygiene, vaccination, and preventive health management

- And research that tells us

  …which AM use practices give the best outcomes?

  – does AM **drug choice** matter?

  – does the **duration of therapy** matter?

  – does **patient underlying health** status matter?

March 2017 GAO Report

Antibiotic Resistance: More Information Needed to Oversee Use of Medically Important Drugs in Food Animals

"Since 2011, HHS and USDA agencies have taken actions to increase veterinary oversight of medically important antibiotics used in the feed and water of food animals…However, these actions do not address long-term and open-ended use of medically important antibiotics because some antibiotics do not have defined durations of use on their labels. **Without developing a process to establish appropriate durations of use on labels of all medically important antibiotics, FDA will not know whether it is ensuring judicious use of medically important antibiotics in food animals."** (p. 45)

http://www.gao.gov/products/GAO-17-192

- On March 24, 2017, a PubMed search on the terms "([cattle OR cow OR calf"] AND antimicrobial AND therapy AND duration)" yielded 24 papers
- 2 described primary research testing different durations of therapy on disease outcomes

N Z Vet J. 2014 Jan;62(1):38-46. doi: 10.1080/00480169.2013.830350. Epub 2013 Sep 20.

Effect of prolonged duration therapy of subclinical mastitis in lactating dairy cows using penethamate hydriodide.

Steele N[1], McDougall S.

Can J Vet Res. 2014 Jan;78(1):31-7.

Efficacy of extended intramammary ceftiofur therapy against mild to moderate clinical mastitis in Holstein dairy cows: a randomized clinical trial.

Truchetti G[1], Bouchard E[1], Descôteaux L[1], Scholl D[1], Roy JP[1].

- In both papers the longer duration of therapy tested had a significantly improved effect by at least one measure
- We need a lot more research like this, for different diseases and different antimicrobials in different animal populations

- ALSO: how do we most effectively teach people who prescribe AM to adopt the safest and most effective uses?

- More collaborative research between those working in human health and in animal health should
  - ensure a “One Health” approach
  - decrease finger pointing?
  - **avoid duplication of effort and optimize synergies**

Final thoughts

- AMR is a complicated problem affecting people, animals, and environments in the U.S. and around the world

Final thoughts

- Scientists working together can improve this situation through research if they are given
  - Adequate resources
  - Opportunities and encouragement to work in collaborative multidisciplinary teams
  - Channels to effectively communicate their findings to the public
  - Assistance getting the public to follow their guidance

References cited

Agga GE et al. Effects of in-feed chlortetracycline prophylaxis in beef cattle on animal health and antimicrobial-resistant *Escherichia coli.* Appl Environ Microbiol 2016; 82:7197.

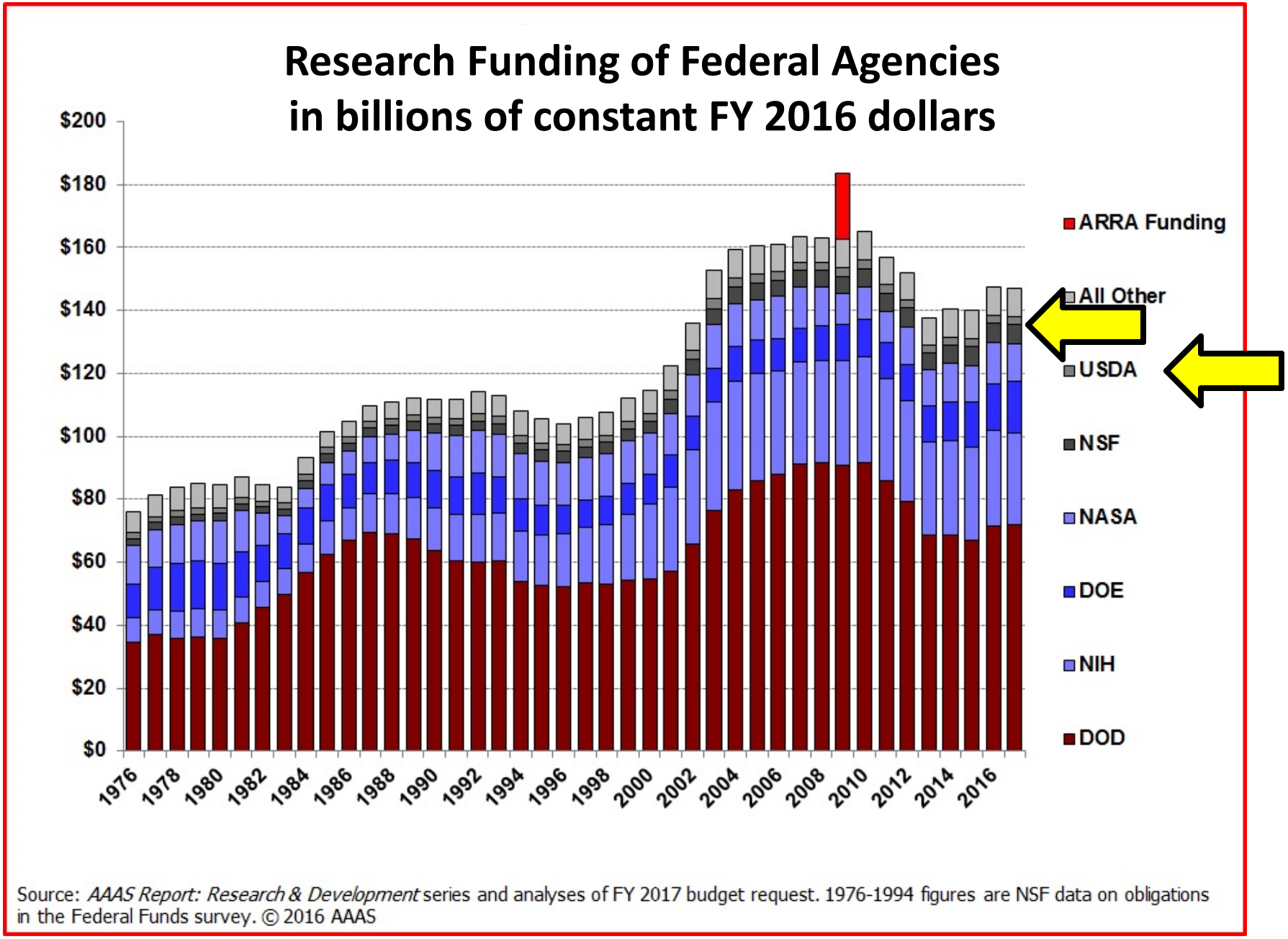
Kassem II et al. Antimicrobial-resistant Campylobacter in organically and conventionally raised layer chickens. *Foodborne Pathogen Dis* 2017; 14:29.

Noyes NR et al. *Mannheimia haemolytica* in feedlot cattle: prevalence of recovery and associations with antimicrobial use, resistance, and health outcomes. *J Vet Intern Med* 2015; 29:705.

Smith AB et al. Prevalence and quinolone susceptibilities of Salmonella isolated from the feces of preharvest cattle within feedlots that used a fluoroquinolone to treat bovine respiratory disease. *Foodborne Pathogen Dis* 2016; 13:303.

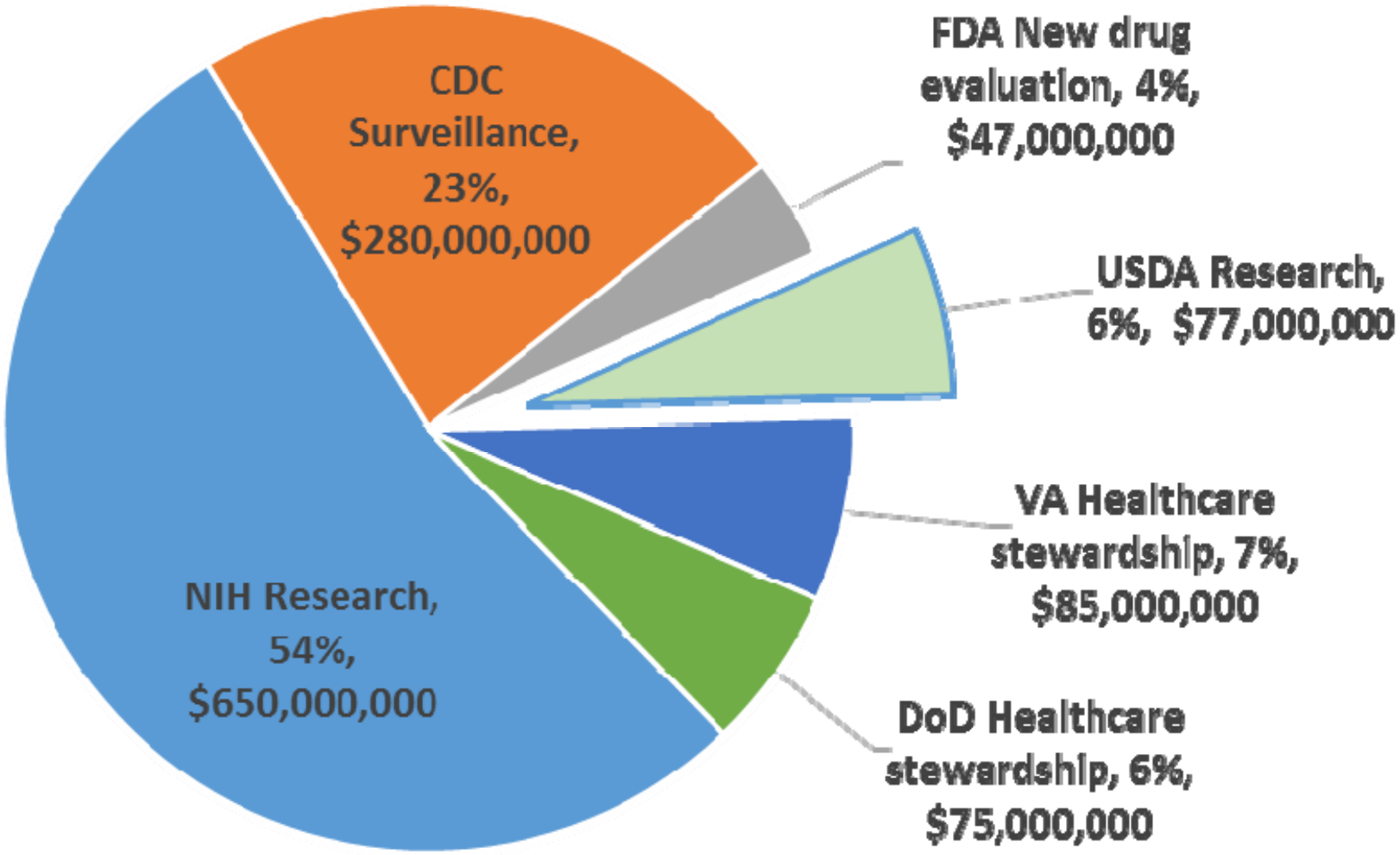
Volkova VV et al. Exploring post-treatment reversion of antimicrobial resistance in enteric bacteria of food animals as a resistance mitigation strategy. *Foodborne Pathogen Dis* 2016; 13:610.

Weese JS et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. *J Vet Intern Med* 2015; 29:487



Source: www.aaas.org

President's 2016 $1.2B Budget to Combat Antibiotic-Resistant Bacteria to Protect Public Health



https://www.whitehouse.gov/the-press-office/2015/01/27/fact-sheet-president-s-2016-budget-proposes-historic-investment-combat-a

From CDC report: *Antibiotic Resistance Threats in the United States, 2013*

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS[1]
ACTIVELY MARKETED IN 2015
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE AND ROUTE OF ADMINISTRATION

	Route	Annual Totals (kg)[2]	% Subtotal	% Grand Total
Medically Important[3]	*Feed*[1]	7,139,853	74%	46%
	Injection[1]	353,297	4%	2%
	Intramammary	16,049	<1%	<1%
	Oral[5] *or Topical*[1]	121,288	1%	1%
	Water[6]	2,071,492	21%	13%
	Subtotal	***9,701,978***	***100%***	***62%***
Not Currently Medically Important[4]	*All Routes*[7]	5,874,997		38%
	Grand Total	***15,576,975***		***100%***

1 Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals (e.g., cattle and swine) and nonfood-producing animals (e.g., dogs and cats).

2 kg = kilogram of active ingredient. Antimicrobials which were reported in International Units (IU) (e.g., Penicillins) were converted to kg. Antimicrobial class includes drugs of different molecular weights, with some drugs reported in different salt forms.

3 Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered "medically important" in human medical therapy.

4 Not Currently Medically Important refers to any antimicrobial class not currently listed in Appendix A of FDA's Guidance for Industry #152.

5 Orally administered, excluding administration by means of feed and water.

6 Water includes when the drug is administered either through drinking water, as a drench, through the immersion of fish, or as a syrup or dusting for honey bees.

7 This category includes the following: Feed, Intramammary, and Water. In order to protect confidential business information, the routes of administration for the "not currently medically important" antimicrobial drugs are not separately presented.

https://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS[1]
ACTIVELY MARKETED IN 2012
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE AND ROUTE OF ADMINISTRATION

	Route	Annual Totals (kg)[2]	% Subtotal	% Grand Total
Medically Important[3]	*Feed*[1]	6,246,451	70%	43%
	Injection[1]	393,422	4%	3%
	Intramammary	25,979	<1%	<1%
	Oral[1,5]	113,409	1%	<1%
	Water[6]	2,113,840	24%	14%
	Subtotal	***8,893,101***	***100%***	***61%***
Not Currently Medically Important[4]	*All Routes*[7]	5,725,327		39%
	Grand Total	***14,618,428***		***100%***

http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM416983.pdf