

COMBATING RESISTANCE

a history and where we are headed
with antibiotic regulation in the US

ASI ANIMAL HEALTH COMMITTEE 2022

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Antibiotic Resistance



A global threat to public health and animal health

Consequences:

- Simple infections more difficult to treat
- Longer treatment times
- Increased costs
- Death

Emergence of Resistance

ANTIBIOTIC RESISTANCE

Spatiotemporal microbial evolution on antibiotic landscapes

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A key aspect of bacterial survival is the ability to evolve while migrating across spatially varying environmental challenges. Laboratory experiments, however, often study evolution in well-mixed systems. Here, we introduce an experimental device, the microbial evolution and growth arena (MEGA)-plate, in which bacteria spread and evolved on a large antibiotic landscape (120 × 60 centimeters) that allowed visual observation of mutation and selection in a migrating bacterial front. While resistance increased consistently, multiple coexisting lineages diversified both phenotypically and genotypically. Analyzing mutants at and behind the propagating front, we found that evolution is not always led by the most resistant mutants; highly resistant mutants may be trapped behind more sensitive lineages. The MEGA-plate provides a versatile platform for studying microbial adaption and directly visualizing evolutionary dynamics.

The worldwide increase in antibiotic resistance has motivated numerous studies aimed at understanding the phenotypic and genotypic evolution of antibiotic resistance (1–7). These experiments have shed light on the trade-offs constraining adaptive evolution in single-

and multidrug environments (5, 6, 8, 9). However, most of our current knowledge about the evolution of resistance is based on laboratory setups with well-mixed environments (1–7, 10, 11).

In natural and clinical settings, bacteria migrate between spatially distinct regions of selection

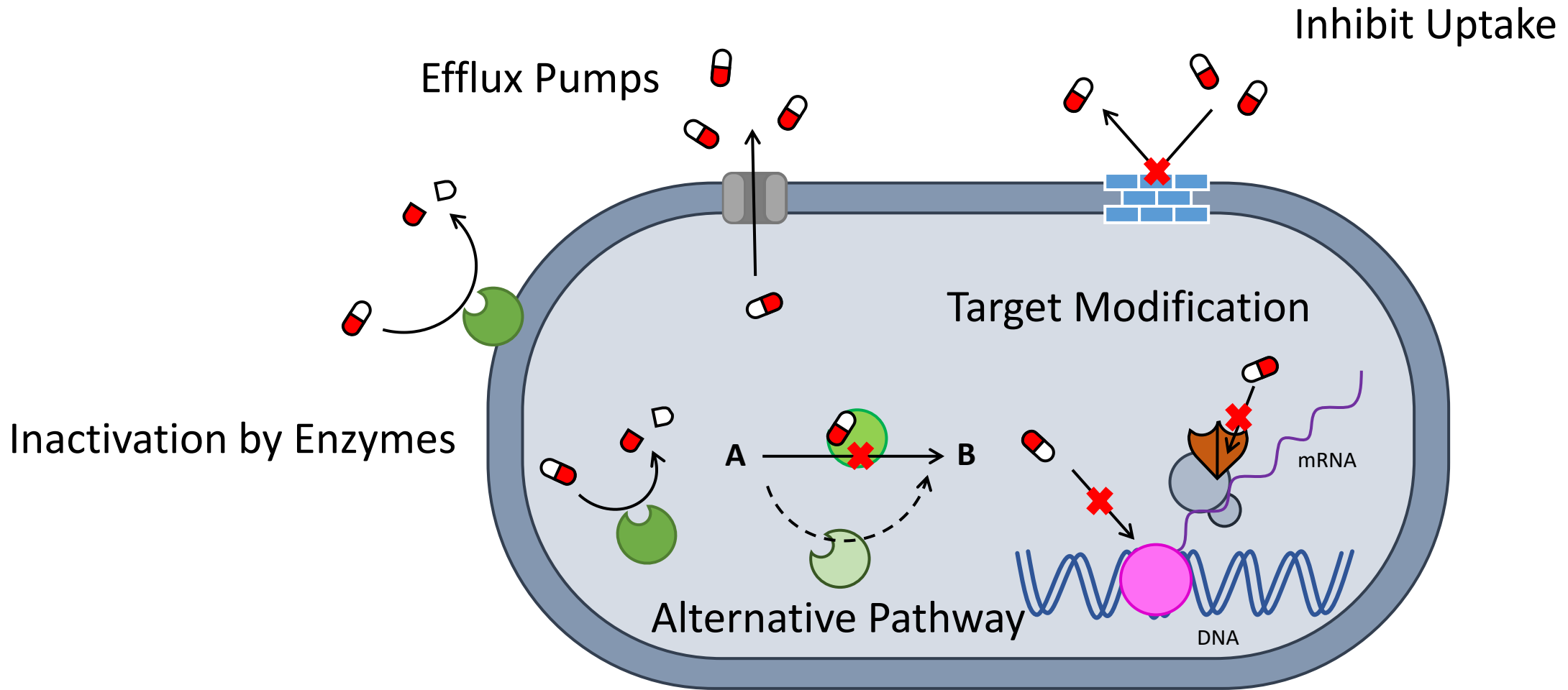
Emergence of Resistance

Natural evolutionary response to exposure

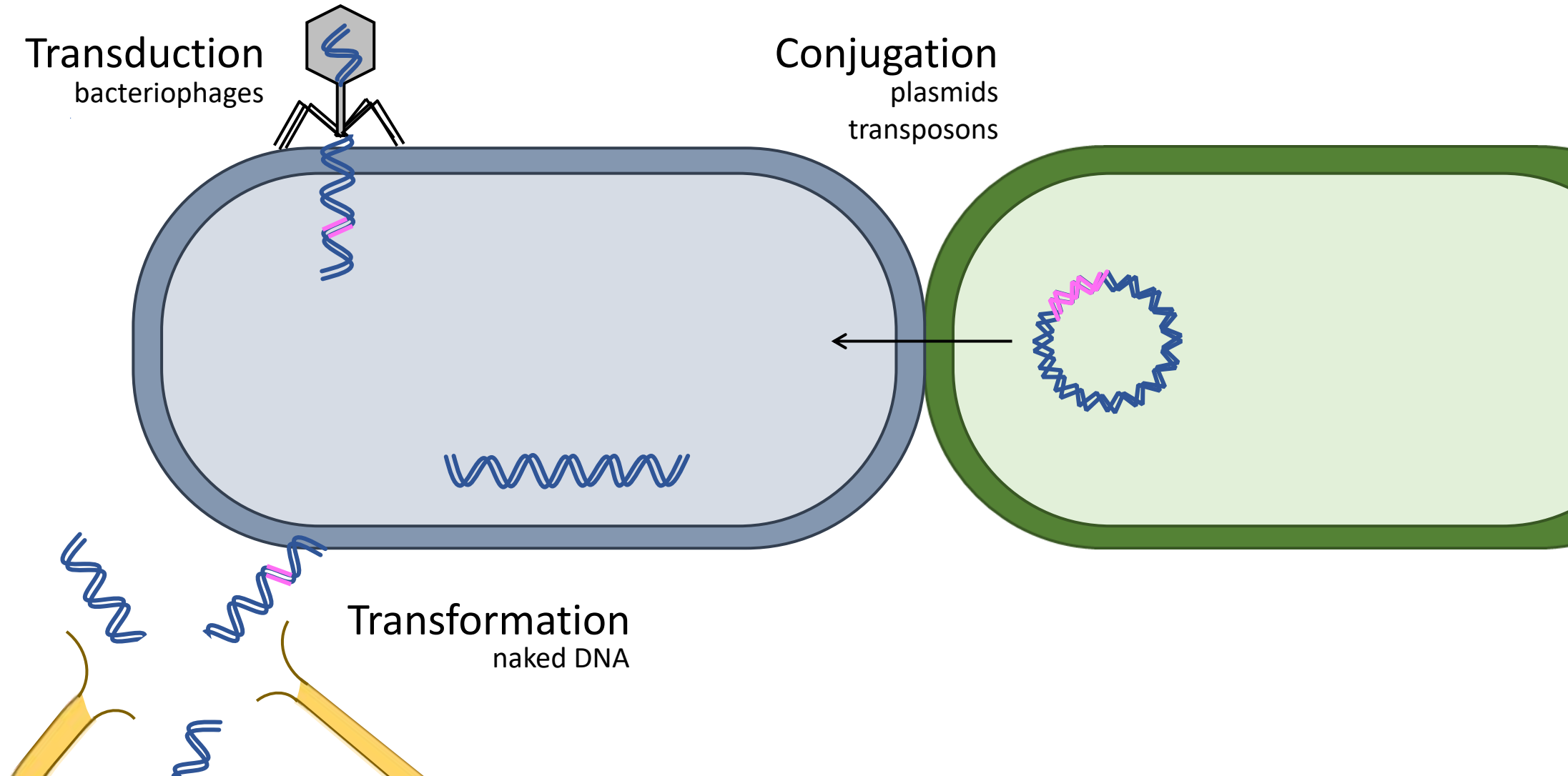
- Selection pressure
 - Intrinsic vs Acquired; Commensal vs Pathogenic
- Rate of de novo resistance development
 - Mutability & fitness
 - Pathogen-drug interactions
 - Pathogen-host interactions
 - Bacterial Population Size



Mechanisms of Resistance



Transmission of Resistance





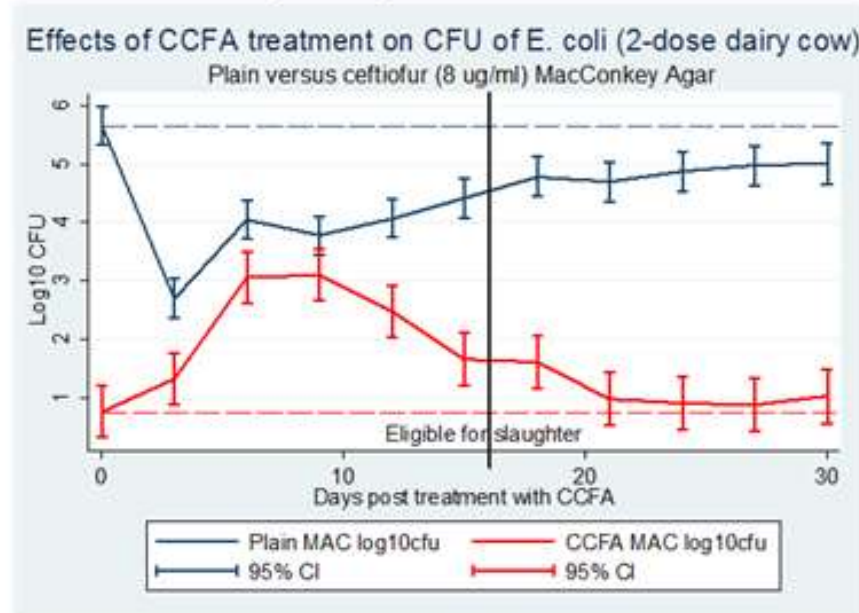
A Complex Web: Everything is Connected

Antibiotic resistance, when germs defeat the antibiotics designed to kill them, can develop and spread across settings. It can affect our progress in health care, food production, and life expectancy.

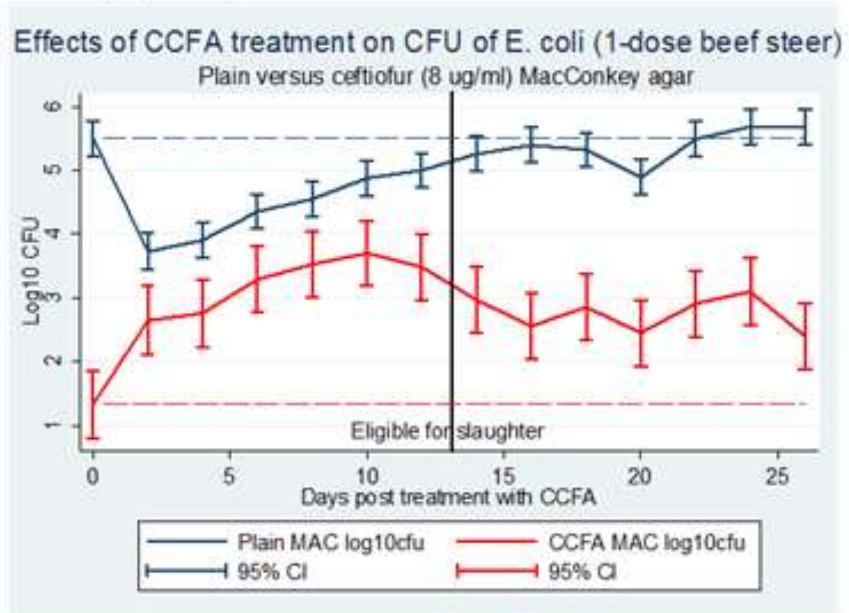
Antibiotic resistance is a One Health problem—the health of people is connected to the health of animals and the environment (soil, water).

Persistence of Resistance

Treatment of single dairy cow 2-dose CCFA



Metaphylaxis pen of steers 1-dose CCFA



Unpublished data courtesy: Norby, Loneragan, Scott, Halbert

Acknowledgements

Professional colleagues, staff, and trainees in my laboratory group

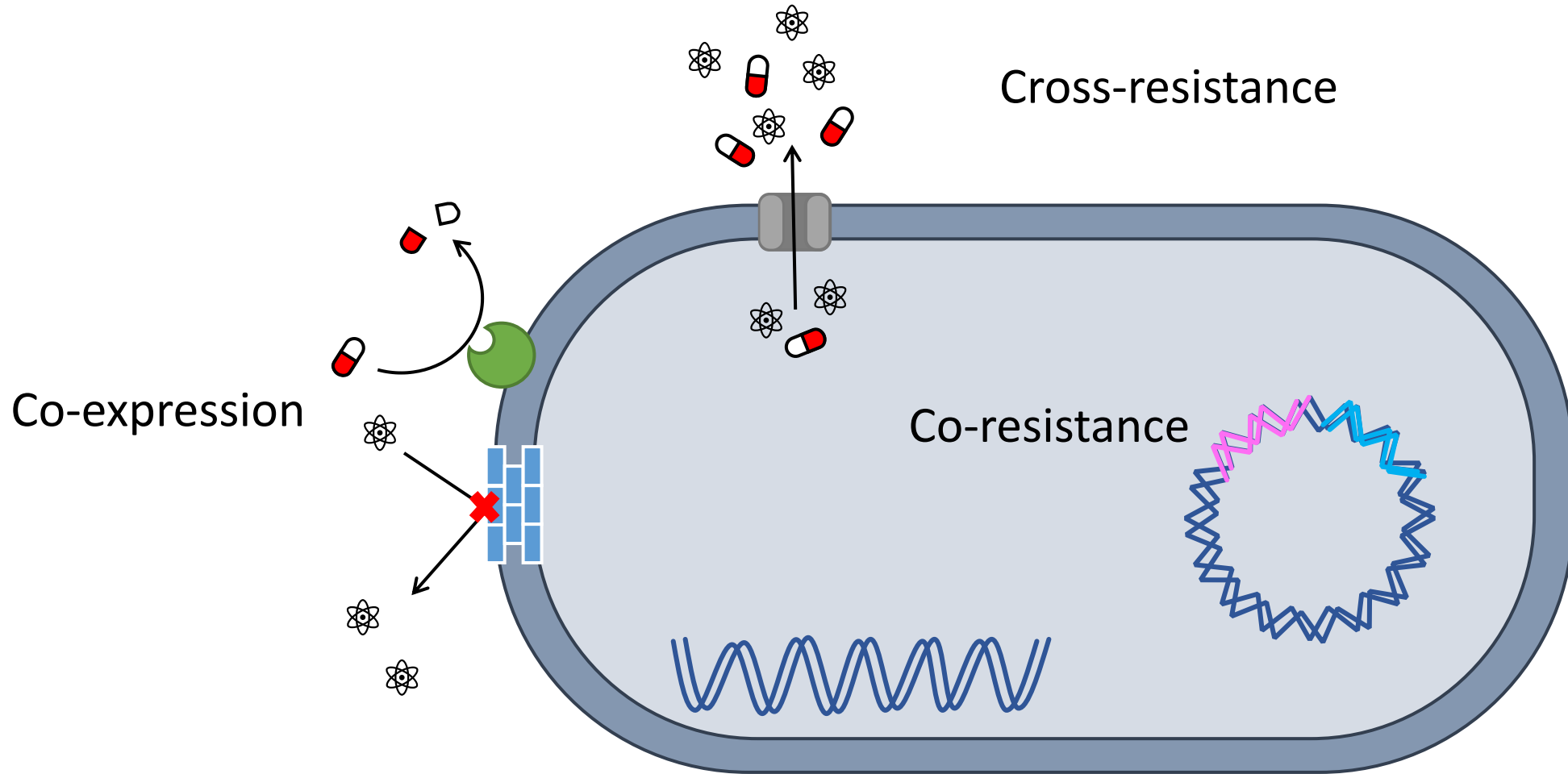
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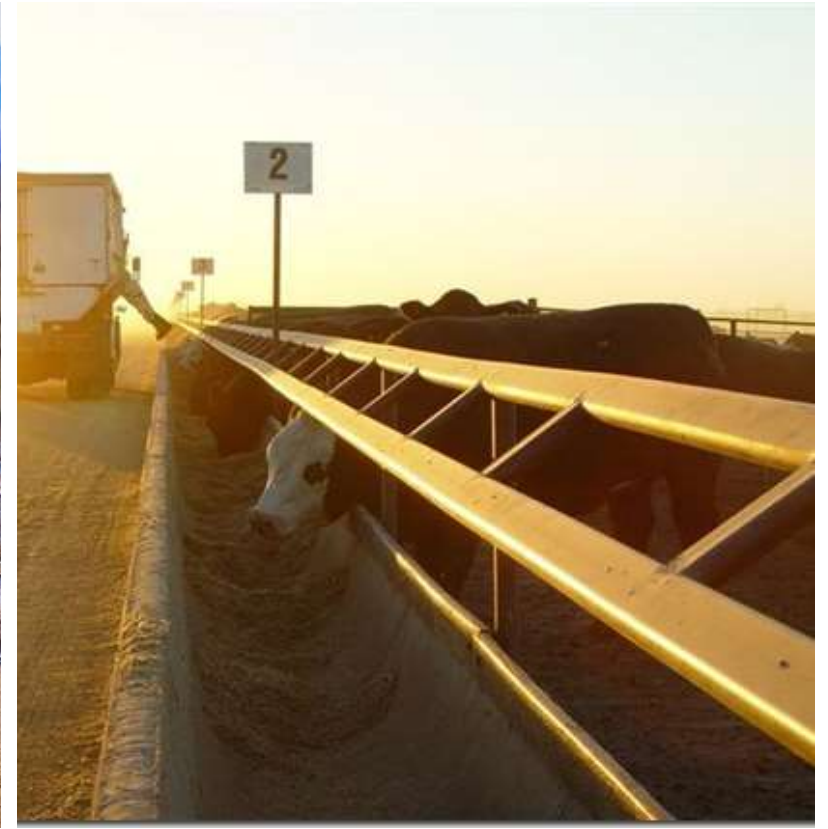
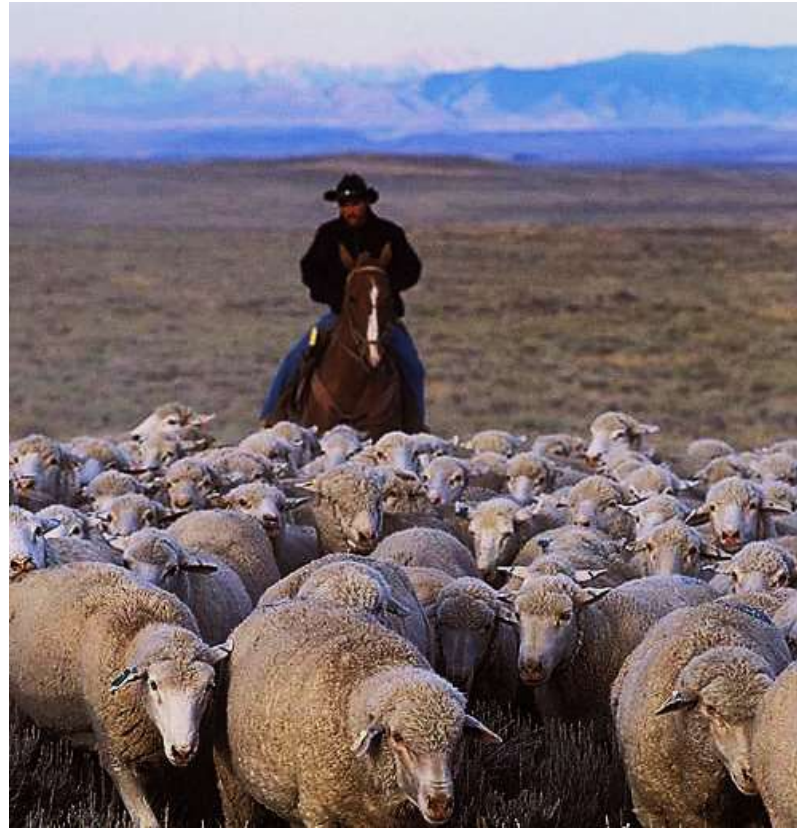
Slide posted with permission by H. Morgan Scott DVM, PhD
Norby et al, unpublished data (left graphic of dairy cow with two treatments)
Ohta et al (in preparation) right graphic of steers in pens with all treated)

Persistence of Resistance





Any time an antibiotic is used (regardless of the indication) there is potential for adverse effects or development of antibiotic resistance.



“The consequences of antibiotic resistance in bacteria of animal origin are not limited to public health.”

International Policies



United States

Animal Medicinal Drug Use Clarification Act (1994)

- Permits licensed veterinarians to use FDA approved drugs extra-label
 - under certain conditions per federal regulations (21 CFR 530).
- FDA can prohibit extra-label use of specific drugs in food-producing animals



Prohibited Drugs (21 CFR 530.41)

Carcinogenic

- Diethylstilbesterol (DES), Nitroimidazoles, Nitrofurans, Sulfonamide class antibiotics (adult lactating dairy cattle, >20 months of age)

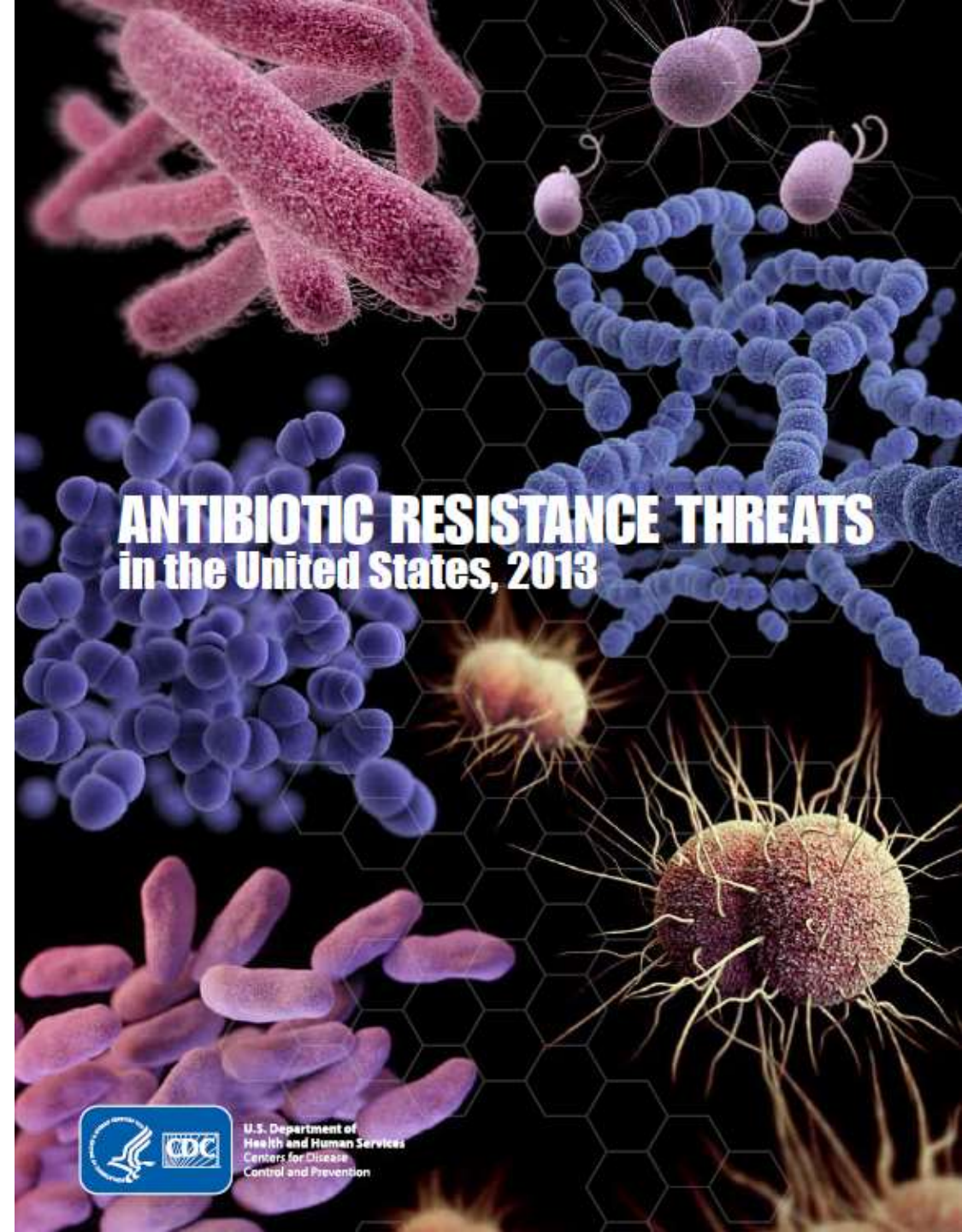
Toxic Reaction

- Clenbuterol, Chloramphenicol, Phenylbutazone (adult lactating dairy cattle, >20 months of age)

Antimicrobial Resistance

- 1997: Fluoroquinolone class antibiotics, Glycopeptide class antibiotics
- 2012: Cephalosporins (except Cephapirin) in MAJOR food animal species – cattle swine, chickens, and turkeys – is permissible only for therapeutic indications not listed on the label

Global and National Action demanded



ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

FDA Guidance for Industry

GFI #152 (2003)

- Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern

GFI #209 (2012)

- The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

GFI #213 (2013)

- 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

FDA Guidance for Industry

GFI #263 (2021)

- Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter

Draft GFI #273

- Recommendations for Sponsors of Medically-Important Antimicrobial Drugs Approved for Use in or on Medicated Feed of Food-Producing Animals for Establishing Appropriately Defined Durations of Use Where None Currently Exist

Revision of GFI #152 (Appendix A - MIADs)

National VFD Final Rule

Veterinary Feed Directive

- Antibiotics in livestock feed
- Written statement issued by a licensed veterinarian
- VCPR
- According to label (CPG 625.115)

Antibiotics in water → Prescription





FDA

U.S. FOOD & DRUG
ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

2017

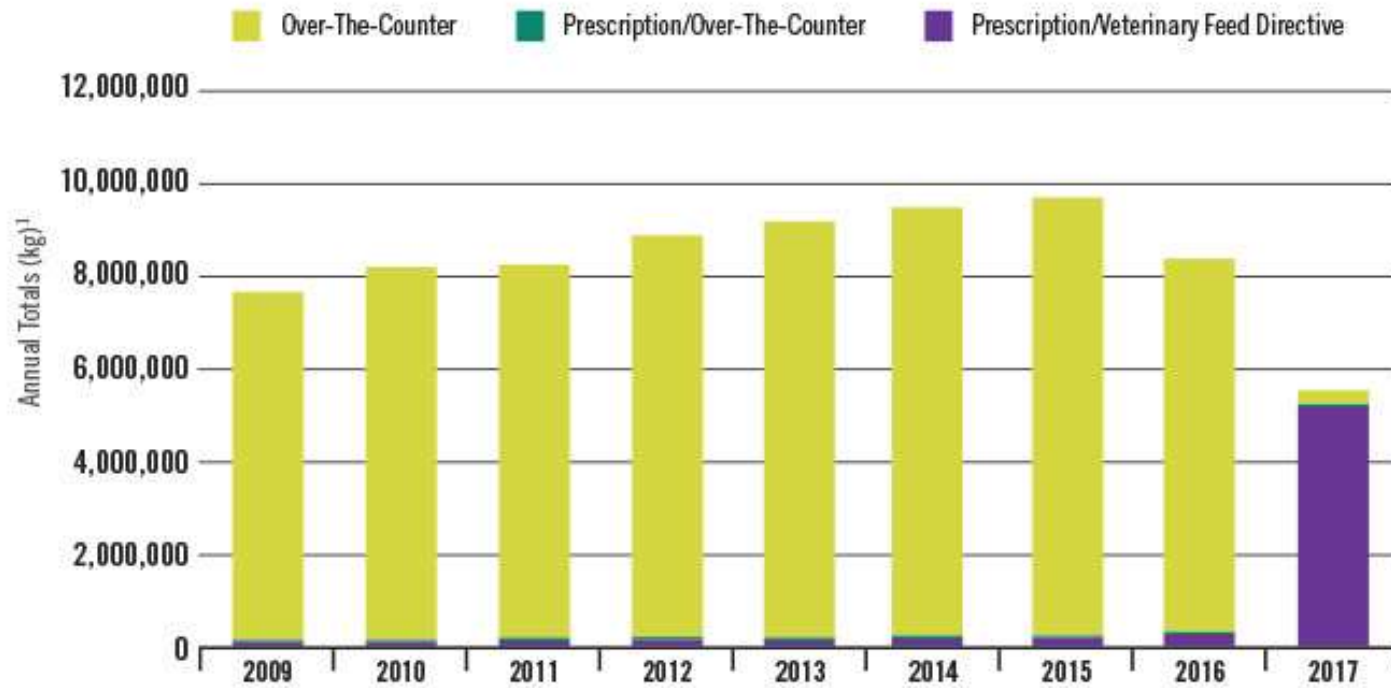
Summary Report

On

*Antimicrobials Sold or Distributed for
Use in Food-Producing Animals*

December, 2018

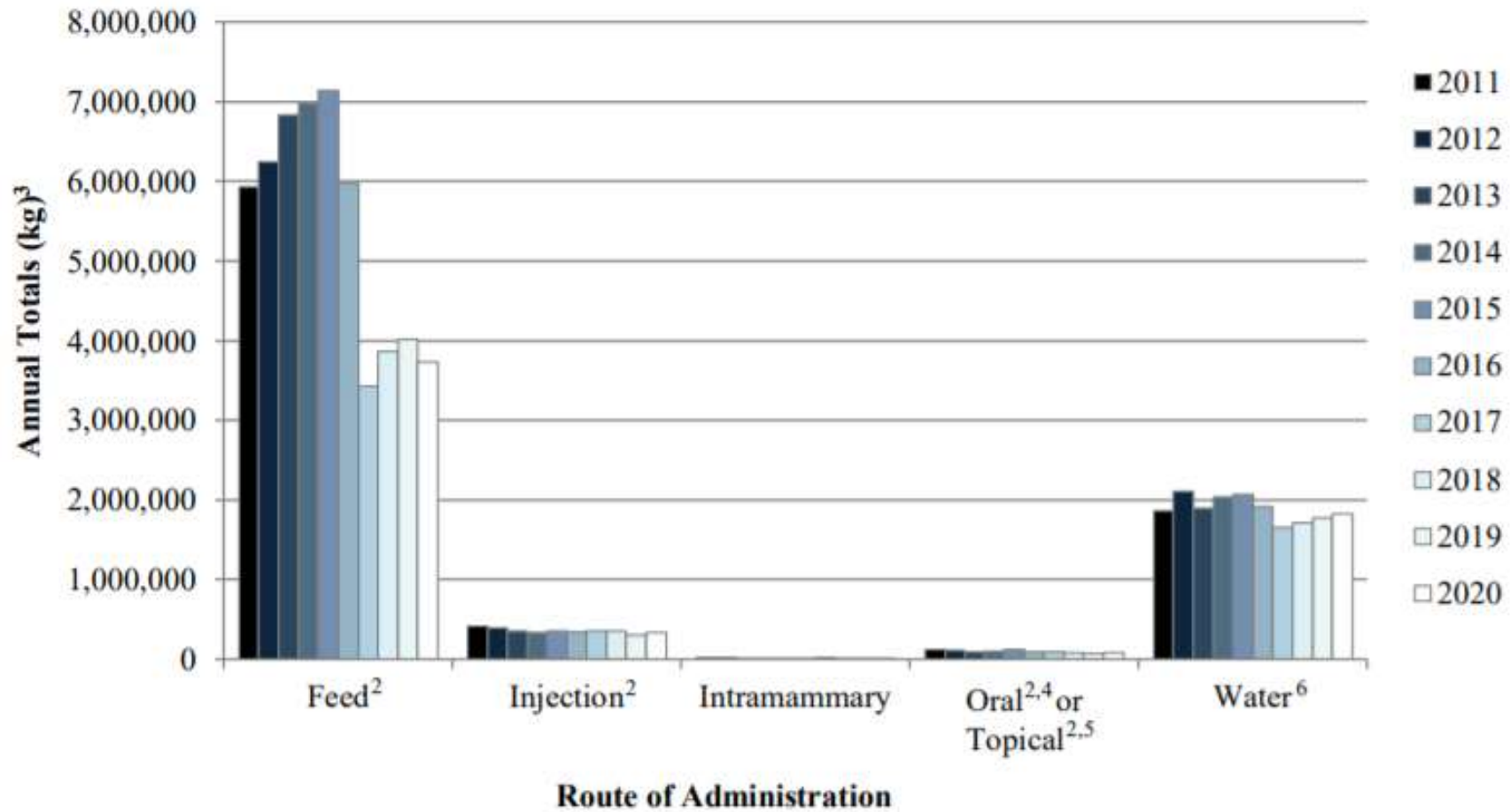
Antibiotics Sales Report



“FDA Cites Progress”

<https://www.bovinevetonline.com/article/antibiotic-stewardship-fda-cites-progress>

Since 2017?



A flock of sheep is grazing in a lush green field under a bright blue sky with scattered white clouds. The sheep are positioned across the horizon line, with some in the foreground and others further back. The overall scene is peaceful and rural.

California and Maryland State Laws

Since **Jan. 1st, 2018**, over-the-counter injectable and all other forms of antibiotics have required a prescription or VFD ordered by a licensed veterinarian.

FDA's Five-Year Plan

SUPPORTING ANTIMICROBIAL STEWARDSHIP IN
VETERINARY SETTINGS

GOALS FOR FISCAL YEARS 2019 – 2023

FDA CENTER FOR VETERINARY MEDICINE

September 2018

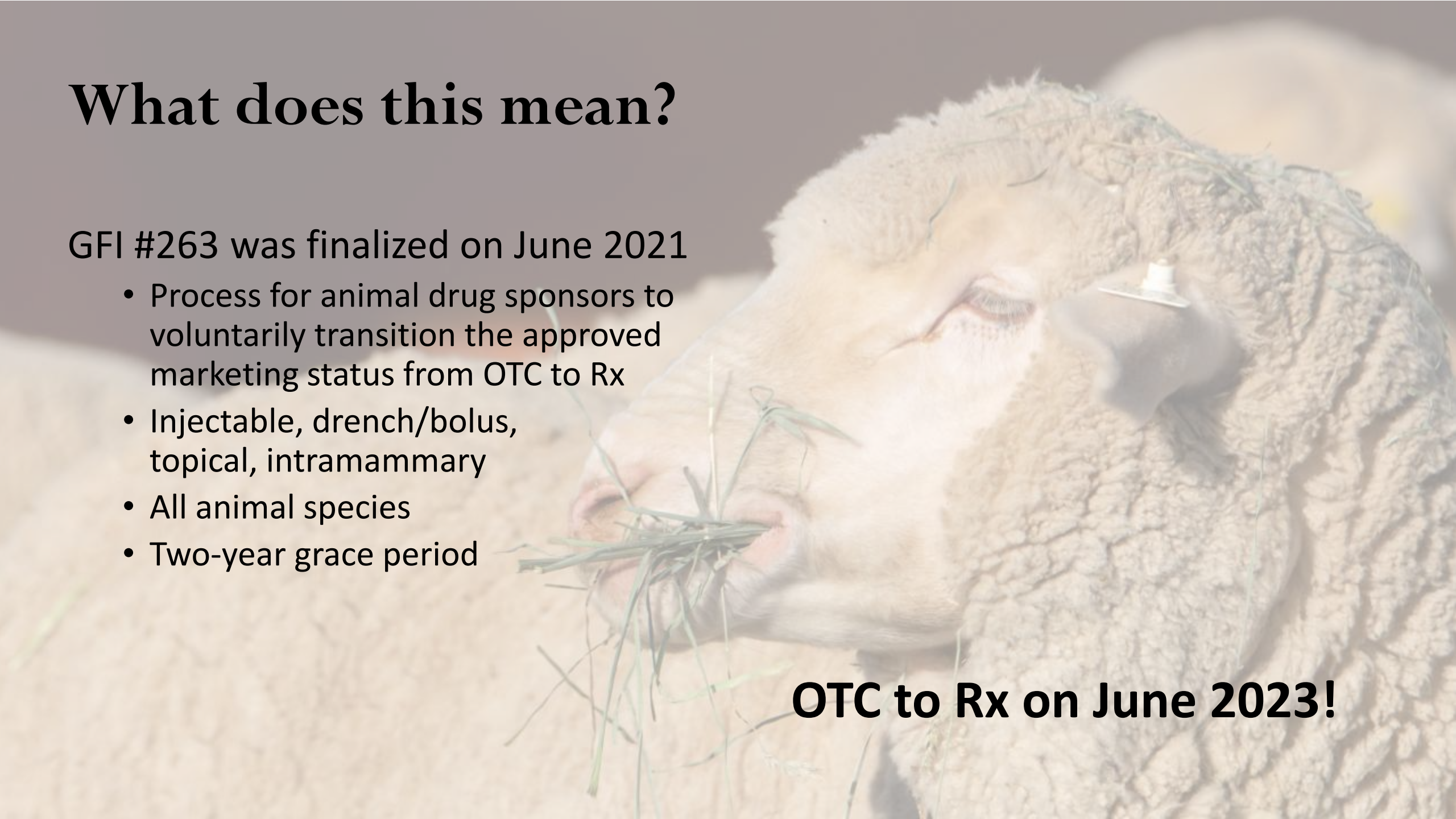
<https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-progress-fdas-support-antimicrobial-stewardship-veterinary-settings>

What does this mean?

GFI #263 was finalized on June 2021

- Process for animal drug sponsors to voluntarily transition the approved marketing status from OTC to Rx
- Injectable, drench/bolus, topical, intramammary
- All animal species
- Two-year grace period

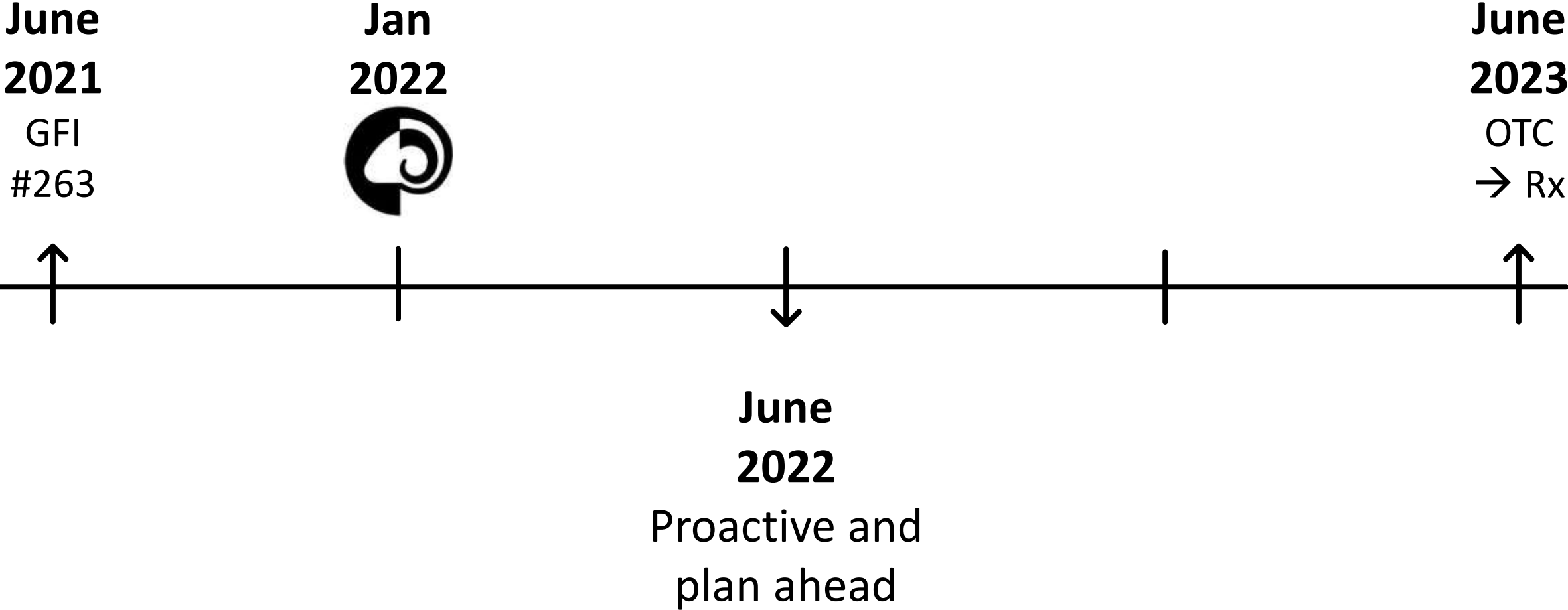
OTC to Rx on June 2023!



What does this mean?



Timeline



Veterinarian-Client-Patient Relationship (VCPR)

VCPR requirements: State vs federal

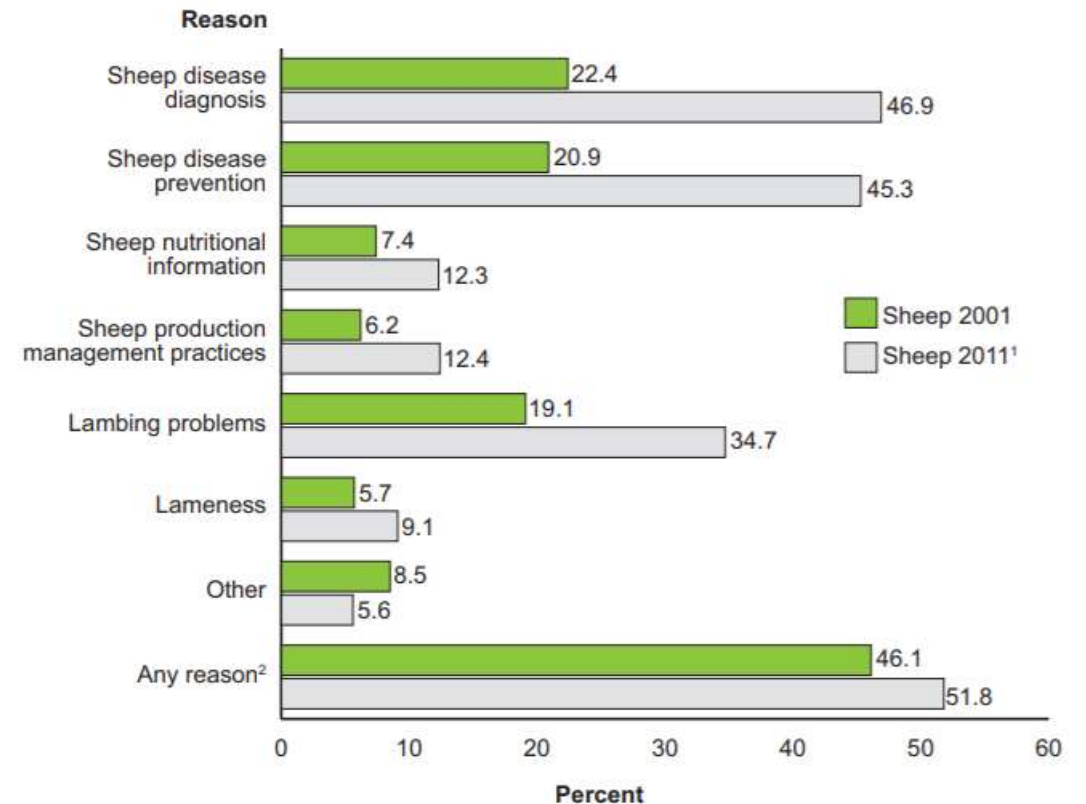
- <https://www.fda.gov/animal-veterinary/development-approval-process/does-state-or-federal-vcpr-definition-apply-lawful-vfd-my-state>



VCPR

- Veterinary shortage
- Veterinary usage according to NAHMS 2011
 - 28% of operations visited by a veterinarian in 2010
 - 52% of operations consulted with a veterinarian in 2010
 - (compared to 46% in 2001)

Percentage of operations that had consulted a private veterinarian during the previous year, by reason and by study



¹In 2011, additional reasons listed and not included here were "interstate health certificate," "breeding soundness exam," and "pregnancy check."

²Includes all reasons listed as options in 2011.

VCPR

- Licensed veterinarian
- Local vs consultant



Herd Health Plan

- Routine visits
- Treatment protocols
 - Common conditions
 - All drugs used
 - Dose, route, frequency, duration
 - Meat and milk withdrawals
 - When to seek veterinary assistance
- Treatment records
- Review



AASRP GUIDELINES

ESTABLISHING AND MAINTAINING THE VETERINARIAN-CLIENT-PATIENT RELATIONSHIP IN SMALL RUMINANT PRACTICE

The veterinarian-client-patient relationship (VCPR) underpins veterinary oversight and appropriate drug use in small ruminants. The VCPR is typically codified in state and federal regulations and is also defined by the AVMA, with minor differences in each version. A VCPR can exist with an individual animal that presents for veterinary care or with a herd or flock managed in consultation with a herd veterinarian. The guidelines below provide non-legally-binding recommendations on the critical components of establishing and maintaining a VCPR at the herd level.

- Maintain written agreements with clients about who is accountable for drug use and treatments administered on the farm or premises. The written agreement (see draft template below) should include a Veterinarian-of-Record (VOR). The VOR is responsible for timely visits to the premises, treatment protocols, treatment record review and regular communication with the client.
 - The written VCPR should include the responsibilities of any other veterinarians who have working relationships or consulting agreements with a client. Consultants and other veterinarians who are not the VOR are responsible for communicating with the VOR about medical care, protocols and drug use recommendations.
- Provide written treatment protocols for commonly occurring easily recognized conditions when clients will be directly responsible treating animals in their herd. The protocols should include all drugs recommended for use including over-the-counter, feed additive and prescription drugs. The protocols should clearly define when to stop treatment and seek veterinary assistance. The protocols should include appropriate dose, route, frequency and duration of drug therapy as well as applicable milk and meat drug withdrawal intervals.
- Ensure written or electronic treatment records are maintained. Treatment records of individual animals or groups of animals are essential to maintaining the VCPR, and regular and timely review of treatment records is an important role for the VOR.
- Provide drugs, prescriptions or Veterinary Feed Directives (VFD) for specific periods and for specific protocols. These drugs should only be provided for the animals over which the VOR has oversight under the existing VCPR; failure to follow treatment protocols or drug labels is a violation of the VCPR by the client. A VCPR should not be established for the sole purpose of drug sales.

Approved by the AASRP Board of Directors December 2020



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AASRP.ORG

Telemedicine

- Phone calls
- Video chats
- Email exchange

VCPR → diagnose, prescribe medications or treat animals



How can you get prescription antibiotics?

- Dispensed by your veterinarian
- Licensed pharmacies
- In California, Veterinary Food Animal Drug Retailors



Thanks!

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