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

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Rosie Busch, DVM
Sheep and Goat Veterinary Medicine Extension Specialist
UC Davis School of Veterinary Medicine
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

Michael Baym,1 Tamir D. Lieberman,2,3 Eric D. Kelsoe,3 Yenny Chait,1† Rotem Gross,3 Idan Yelin,3 Roy Kishony1,2,3,†

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 evolve on a large antibiotic landscape (120 x 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 resistances (7-9). However, most of our current knowledge about the evolution of resistance is based on laboratory setups with well-mixed environments (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

- Inhibit Uptake
- Efflux Pumps
- Inactivation by Enzymes
- Target Modification
- Alternative Pathway
Transmission of Resistance

- **Transduction**
  - bacteriophages

- **Conjugation**
  - plasmids
  - transposons

- **Transformation**
  - naked DNA
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

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

Co-expression

Cross-resistance

Co-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
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
2017

Summary Report

On

Antimicrobials Sold or Distributed for Use in Food-Producing Animals

December, 2018
“FDA Cites Progress”

https://www.bovinevetonline.com/article/antibiotic-stewardship-fda-cites-progress
Since 2017?
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

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

June 2021
GFI
#263

Jan 2022

June 2022
Proactive and plan ahead

June 2023
OTC → Rx
Veterinarian-Client-Patient Relationship (VCPR)

VCPR requirements: State vs federal

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)
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
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!

Rosie Busch, DVM
rcbusch@ucdavis.edu
@ucce.sheepngoat