Antibiotics in the future tense: The Application of Antibiotic Stewardship in Veterinary Medicine

Mike Apley
Kansas State University

Changes in Food Animal Antibiotic Use

- How the uses of antibiotics in food animals are authorized

Veterinary Authorization

- **Veterinary Feed Directive (VFD)** for all uses of medically important antibiotics in feed for food animals
  - No extralabel use allowed in major species
  - No use for growth promotion
  - Next step is critical evaluation of in-feed antibiotics with no specified duration of administration
- **Prescription** required for all water uses of medically important antibiotics
- **Prescription** required for majority of medically important antibiotics administered to individual animals
  - The rest are slated to be reviewed and added to prescription status (e.g., penicillin G, oxytetracycline, tylosin)

With the VFD and Prescription changes, veterinarians are not only going to be responsible for essentially all antimicrobial use in food animals…

They are going to be accountable.

A Veterinarian's VFD Checklist

- ✓ Do I have a valid VCPR to authorize this use?
- ✓ Is there a reason to use the product, or is it just habit?
- ✓ Is it legal?
- ✓ Is it effective?
- ✓ Are there any residue issues to consider?
- ✓ Are there any issues with antibiotic resistance?

FIGURE 2

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS[1]
ACTIVELY MARKETED IN 2015
SALES AND DISTRIBUTION DATA
REPORTED BY DRUG CLASS

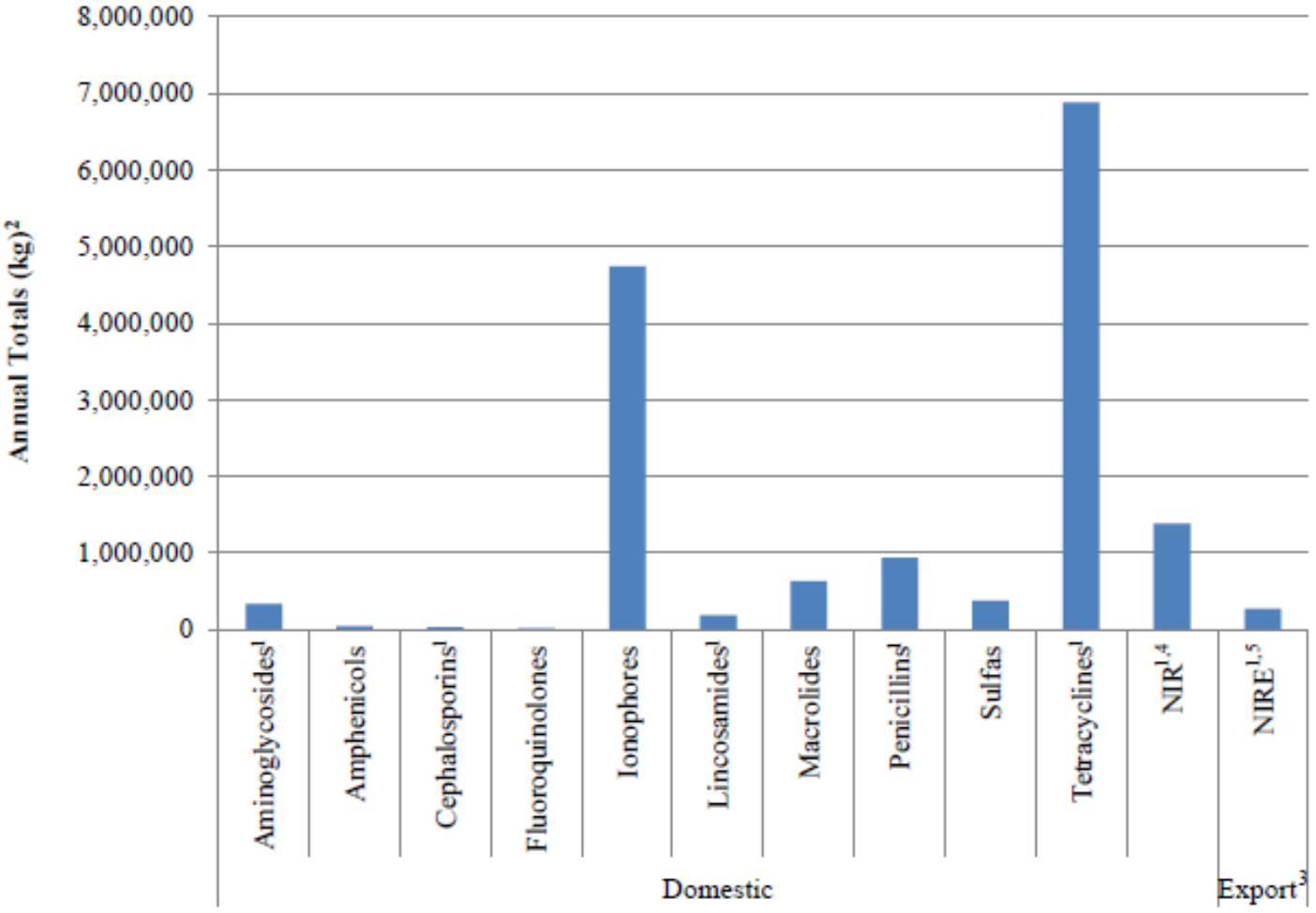


TABLE 3

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

	Drug Class	Annual Totals (kg)[2]	% Subtotal	% Grand Total
Medically Important[3]	*Aminoglycosides*[1]	344,120	4%	2%
	Amphenicols	44,968	<1%	<1%
	Cephalosporins[1]	32,341	<1%	<1%
	Fluoroquinolones	20,063	<1%	<1%
	Lincosamides[1]	182,543	2%	1%
	Macrolides	627,770	6%	4%
	Penicillins[1]	936,669	10%	6%
	Sulfas	380,186	4%	2%
	Tetracyclines[1]	6,880,465	71%	44%
	NIR[1,5]	252,854	3%	2%
	Subtotal	***9,701,978***	***100%***	***62%***
Not Currently Medically Important[4]	*Ionophores*	4,740,615	81%	30%
	NIR[6]	1,134,382	19%	7%
	Subtotal	***5,874,997***	***100%***	***38%***
	Grand Total	***15,576,975***		***100%***

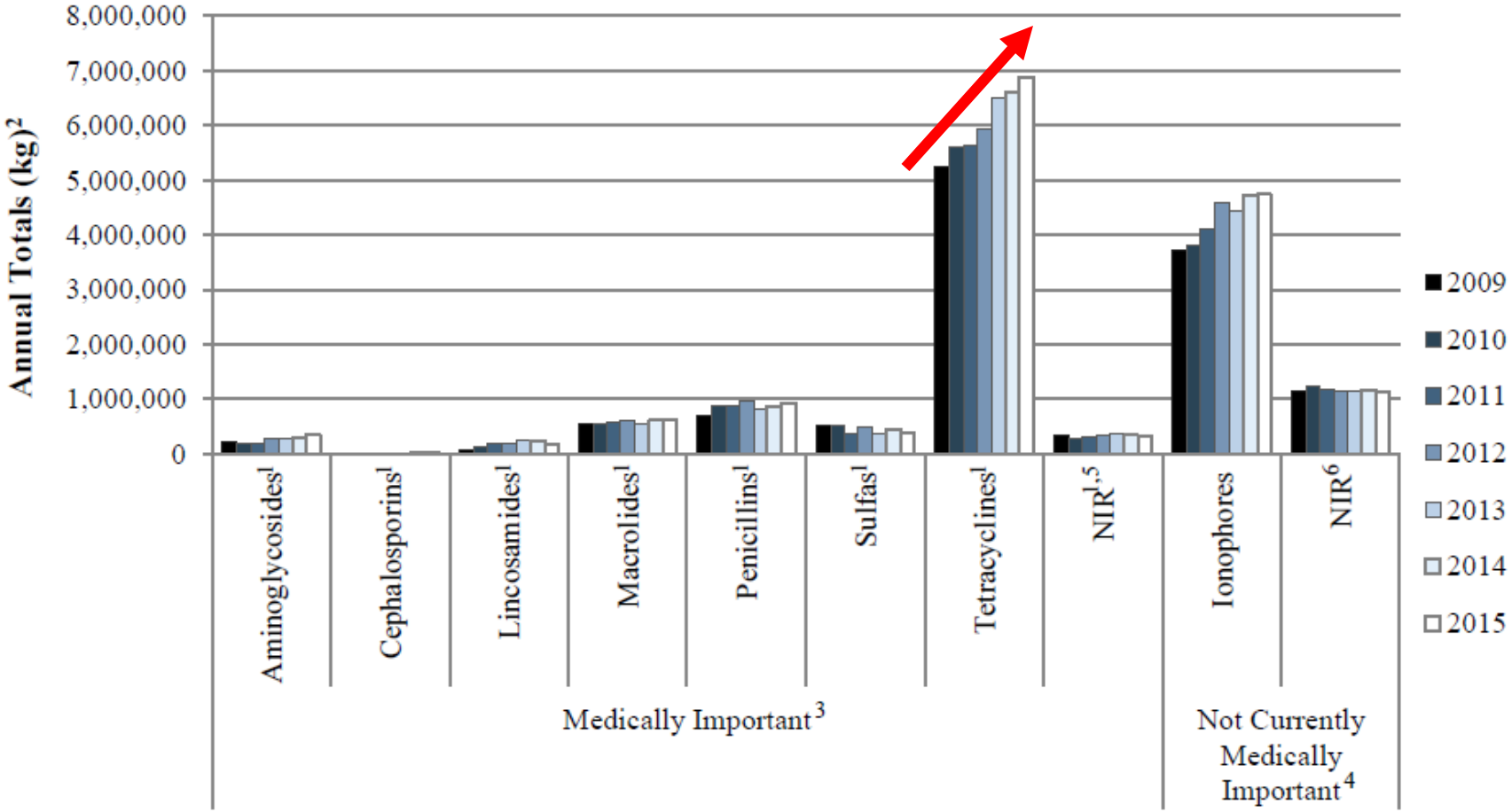
TABLE 4

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%***

FIGURE 10

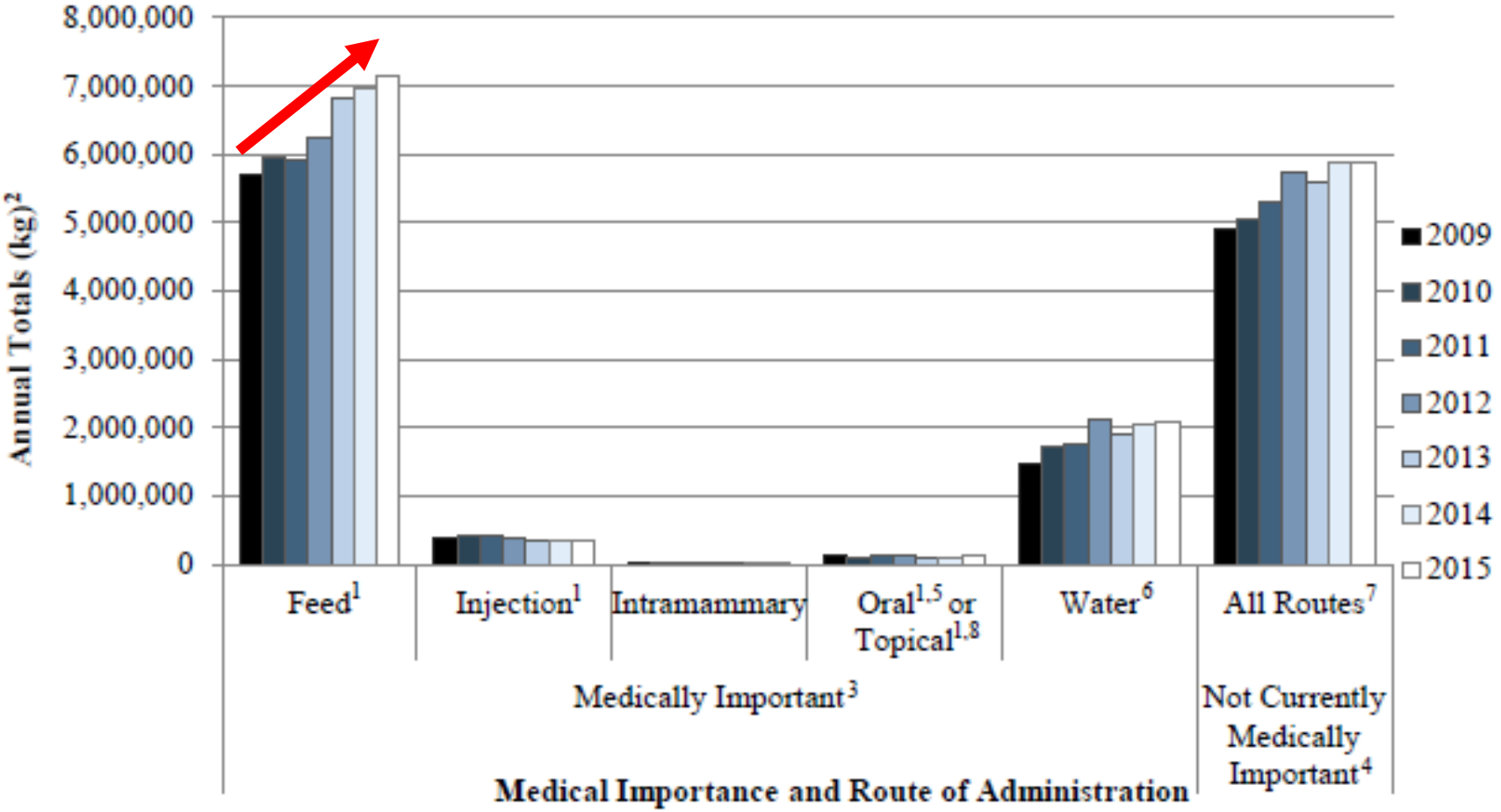
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS[1]
ACTIVELY MARKETED 2009-2015
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE AND DRUG CLASS



	Drug Class	2009 Annual Totals (kg)[2]	2015 Annual Totals (kg)[2]	% Change 2009 - 2015	% Change 2014 - 2015
Domestic	*Aminoglycosides*[1]	223,117	344,120	54%	13%
	Cephalosporins[1]	20,145	32,341	61%	2%
	Ionophores	3,739,352	4,740,615	27%	0%
	Lincosamides[1]	93,330	182,543	96%	-22%
	Macrolides[1]	562,062	627,770	12%	1%
	Penicillins[1]	691,644	936,669	35%	6%
	Sulfas[1]	505,880	380,186	-25%	-16%
	Tetracyclines[1]	5,260,995	6,880,465	31%	4%
	NIR[1,4]	1,490,932	1,452,267	-3%	-4%
	Subtotal	*12,587,457*	*15,576,975*	*24%*	*1%*
Export[3]	*NIRE*[1,5]	202,556	20,773	-90%	-32%
	Grand Total	*12,790,013*	*15,597,749*	*22%*	*1%*

FIGURE 11a

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS[1]
ACTIVELY MARKETED 2009-2015
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE AND ROUTE OF ADMINISTRATION



	Route	2009 Annual Totals (kg)[2]	2015 Annual Totals (kg)[2]	% Change 2009 - 2015	% Change 2014 - 2015
Medically Important[3]	*Feed*[1]	5,687,084	7,139,853	26%	2%
	Injection[1]	388,518	353,297	-9%	3%
	Intramammary	23,409	16,049	-31%	40%
	Oral[1,5] *or Topical*[1,8]	120,506	121,288	1%	17%
	Water[6]	1,467,048	2,071,492	41%	1%
	Subtotal	***7,686,564***	***9,701,978***	***26%***	***2%***
Not Currently Medically Important[4]	*All Routes*[7]	4,900,893	5,874,997	20%	<1%
	Grand Total	***12,587,457***	***15,576,975***	***24%***	***1%***

Changes

- How the use of antibiotics in food animals are authorized
- Social media and marketing campaigns as drivers of public perception of antibiotic use in food animals

Drivers of Change in Food Animal Antimicrobial Use

California SB27

PARA – S621

DART – HR2459

Legislation

PAMTA – HR1552

ADUFA

Fluoroquinolones

VFD

Cephalosporins

Regulation

AMDUCA

GFI 209

McDonald's

GFI 213

Chipotle

Tyson

Retailation

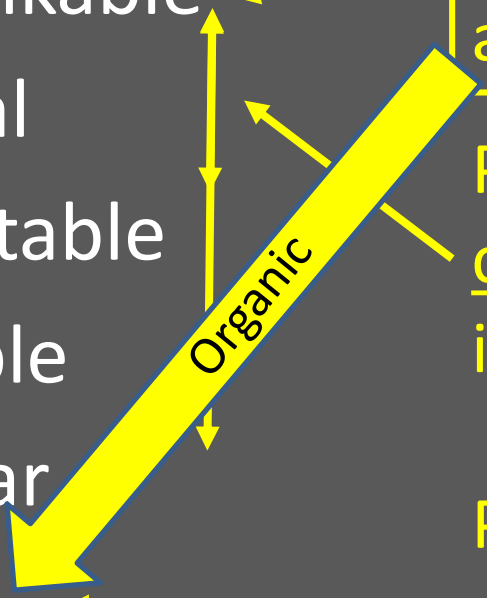
Panera

Walmart

Chic –Fil - A

The Overton Window

- Unthinkable
- Radical
- Acceptable
- Sensible
- Popular
- Policy



Prohibition of therapeutic uses of medically important antimicrobials

Prohibition of prevention and control uses of medically important antimicrobials

Prohibition of growth promotion uses of medically important antimicrobials

How to tell how long someone has been involved in the antibiotic resistance issue…

“If we just understood all of the data the way forward would be clear”

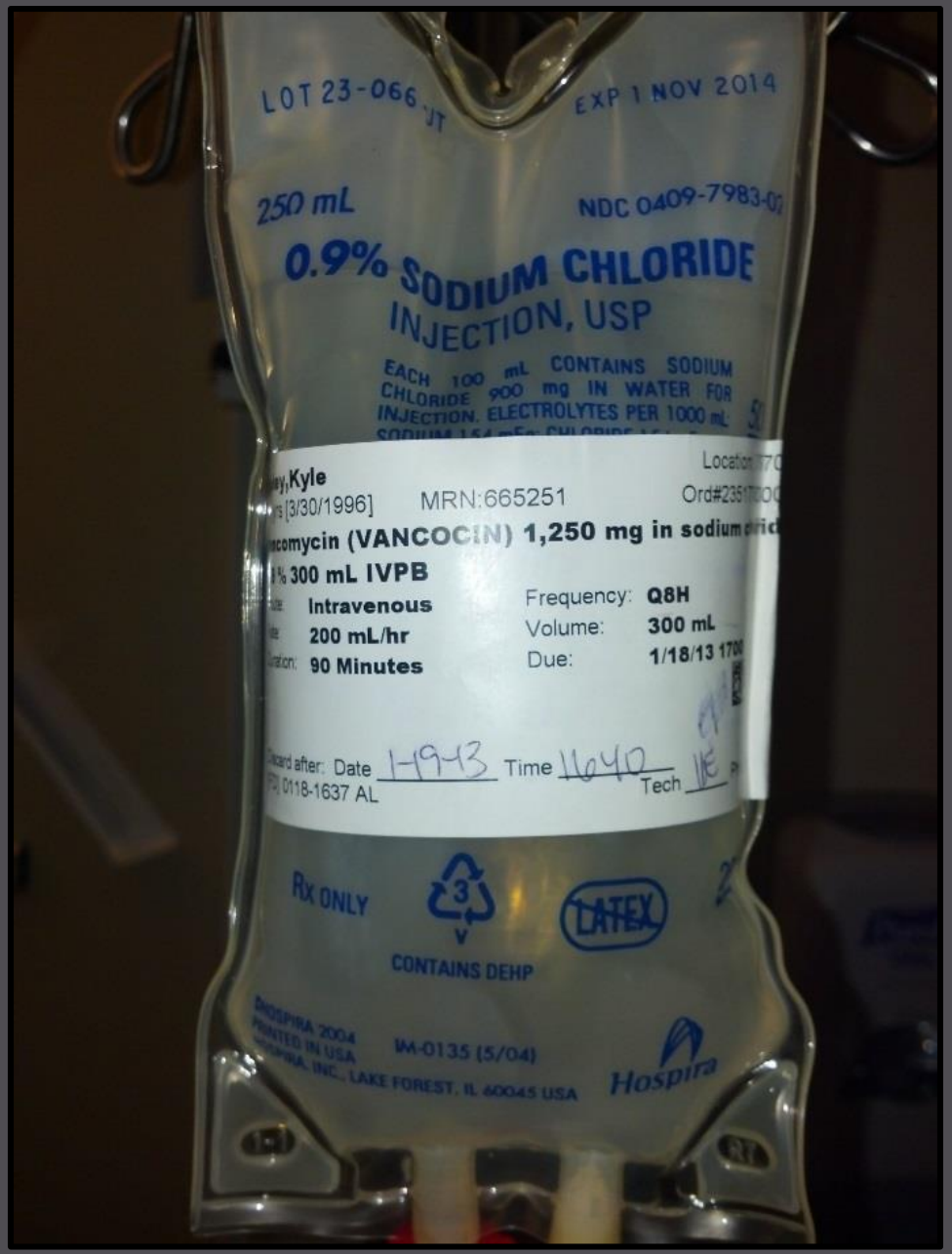
It is obvious that there are differing perceptions on how antibiotics fit in the grand scheme of treating infectious disease


ions
pH
diffusion
biofilms
Location
proteins
virulence
case definit
susceptibility
Progression
inocu
Anti-inflammatory?
Antimicrobials
regimen
pharmacokinetics
pharmacodynamics
Don’t you have to deal with this…..
biosecurity
stress
environment
because of what you do to the animal over here?
body temperature
total vs. free?

Changes

- How the use of antibiotics in food animals are authorized
- Social media and marketing campaigns as drivers of public perception of antibiotic use in food animals
- New tools to evaluate the relationship between food animal antibiotic use and antibiotic resistance in human medicine

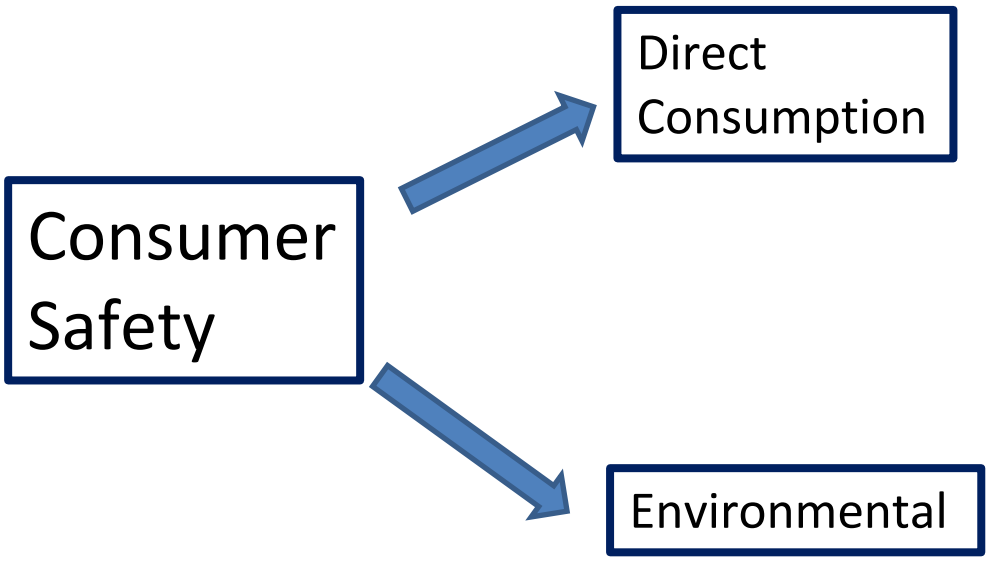
Is food animal use of antibiotics a contributor to resistance in human medicine?



RESISTANCE CHALLENGES IN HUMAN MEDICINE

Antibiotic-Resistant Microorganism	Infections Included	Infections not Included	Estimated Annual Number of Cases	Estimated Annual Number of Deaths
Carbapenem Resistant Enterobacteriaceae (CRE)	HAIs caused by *Klebsiella* and *E. coli* with onset in hospitalized patients	1, 2, 3	9,300	610
Drug-resistant *Neisseria gonorrhoeae* (any drug)	All infections		246,000	<5
Multidrug-resistant *Acinetobacter* (three or more drug classes)	HAIs with onset in hospitalized patients	1,2	7,300	500
Drug-resistant *Campylobacter* (azithromycin or ciprofloxacin)	All infections		310,000	28
Drug-resistant *Candida* (fluconazole)	HAIs with onset in hospitalized patients	1,2	3,400	220
Extended-spectrum β-Lactamase producing Enterobacteriaceae (ESBLs)	HAIs caused by *Klebsiella* and *E. coli* with onset in hospitalized patients	1,2,3	26,000	1700
Vancomycin-resistant *Enterococcus* (VRE)	HAIs with onset in hospitalized patients	1,2	20,000	1300
Multidrug-resistant *Pseudomonas aeruginosa* (three or more drug classes)	HAIs with onset in hospitalized patients	1,2	6,700	440
Drug-resistant non-typhoidal *Salmonella* (ceftriaxone, ciprofloxacin[7], or 5 or more drug classes)	All infections		100,000	40

Antibiotic-Resistant Microorganism	Infections Included	Infections not Included	Estimated Annual Number of Cases	Estimated Annual Number of Deaths
Drug-resistant *Salmonella* Typhi (Ciprofloxacin[7])	All infections		3,800	<5
Drug-resistant *Shigella* (Azithromycin or ciprofloxacin)	All infections		27,000	<5
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Invasive infections	4	80,000	11000
Streptococcus pneumoniae (full resistance to clinically relevant drugs)	All infections		1,200,000	7000
Drug-resistant tuberculosis (any clinically relevant drug)	All infections		1,042	50
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	All infections		<5	<5
Erythromycin-resistant Group A *Streptococcus*	Invasive infections	5	1,300	160
Erythromycin-resistant Group B *Streptococcus*	Invasive infections	6	7,600	440
Summary Totals for Antibiotic-Resistant Infections			2,049,442	23,488
Clostridium difficile Infections	Healthcare-associated infections in acute care hospitals or in patients requiring hospitalization		250,000	14,000



Metrics?

Foodborne bacterial outbreaks

Resistance in these outbreaks

Illness, hospitalizations, deaths

Capable of quantitative risk assessment

Metrics?

"Reservoir of Resistance"

Non-foodborne exposure

Residue effect on gut microbiota

Maintenance and spread of resistance in the community

Not as well suited for risk assessment

Changes

- How the use of antibiotics in food animals are authorized
- Social media and marketing campaigns as drivers of public perception of antibiotic use in food animals
- New tools to evaluate the relationship between food animal antibiotic use and antibiotic resistance in human medicine
- An expectation of stewardship in the use of antibiotics in any species (including humans)

What is "Stewardship"?

1. Responsibility for appropriate diagnostics and establishment of an accurate and functional case definition

Enter…

2. Is there a non-antibiotic alternative which will appropriately prevent, control, or treat this disease challenge?

If not…

3. Selection of an antibiotic which has been demonstrated to be safe and effective for this purpose

While…

4. Assuring use of the antibiotic as shown to be safe and effective

While asking…

5. Is this antibiotic intervention still necessary?

Yes…

No: Stop

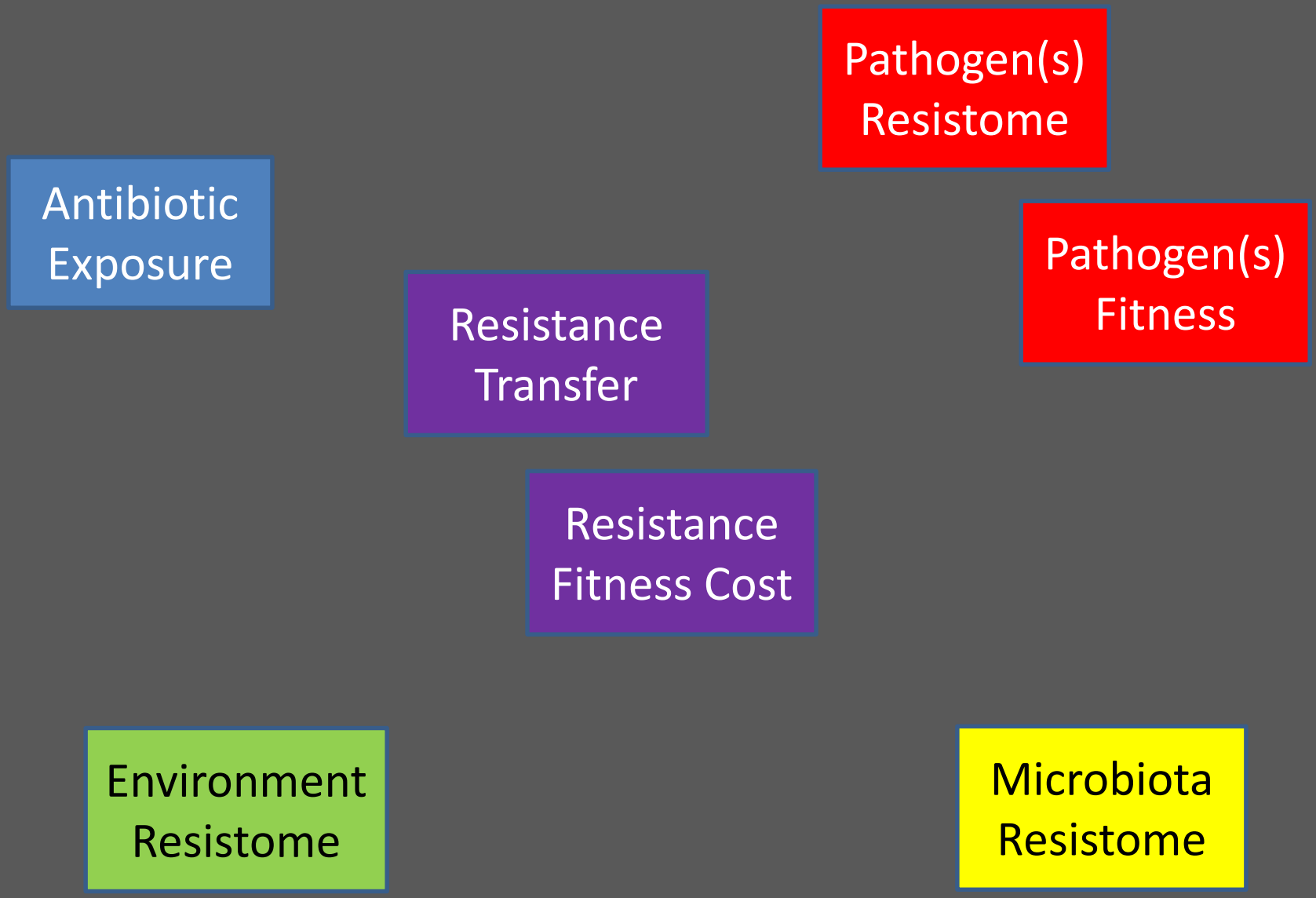
If we want to keep antibiotics

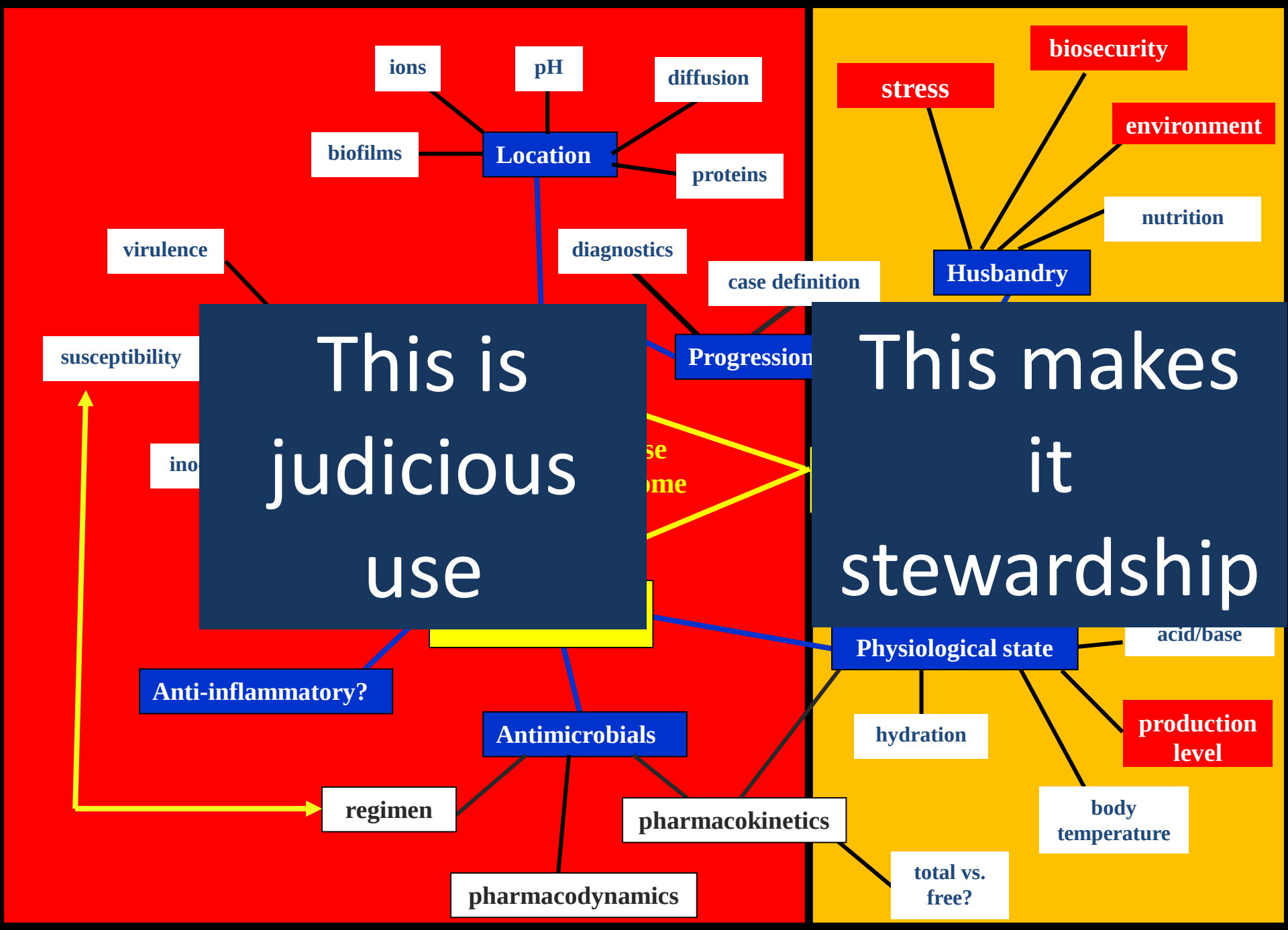
- Veterinarians should have control of all uses of antimicrobials in animals.
- Veterinarians and producers must practice true stewardship.
- Duration of therapy research is an absolute requirement.
- Continue the emphasis on prevention of infectious disease.
- Protocols and records!

Things that just aren't true

- "All pork-beef-chicken-turkey is antibiotic free because we observe slaughter withdrawal times."
- "Antibiotic resistance isn't an issue because they don't use oxytetracycline or chlortetracycline in human medicine."

The Building Blocks of Antibiotic Resistance




ions
pH
diffusion
biofilms
Location
proteins
virulence
diagnostics
case definition
susceptibility
Progression
This is judicious use
Anti-inflammatory?
Antimicrobials
regimen
pharmacokinetics
pharmacodynamics
biosecurity
stress
environment
nutrition
Husbandry
This makes it stewardship
Physiological state
acid/base
hydration
production level
body temperature
total vs. free?