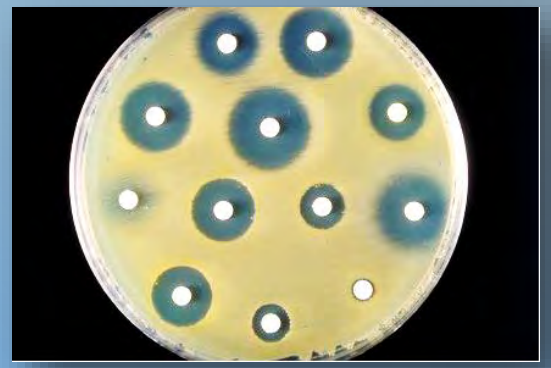
ANTIBIOTICS IN AQUACULTURE:
A (FISH) VETERINARIAN'S PERSPECTIVE



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Healthful move to cut antibiotics in livestock

On Nutrition

Carrie Dennett
Special to The Seattle Times

In June, the Food and Drug Administration (FDA) issued guidelines designed to reduce use of antibiotics in livestock animals, one critical part of ramped-up efforts to fight the growing threat of "superbugs," bacteria that no longer respond to treatment with common antibiotics. It's a potentially lifesaving move for both meat-eaters and vegetarians alike.

The FDA plan, which goes into effect in December 2016, will prevent farmers and ranchers from using medically important antibiotics, or those used for both animals and humans, for growth promotion and other production purposes.

About 2 million Americans get sick — and 23,000 die — each year because of bacterial infections that antibiotics don't cure, according to the Centers for Disease Control and Prevention (CDC). At a talk this month at the Academy of Nutrition and Dietetics' Food and Nutrition Conference and Expo in Nashville, Dr. Steve Solomon, former director of the CDC's Office of Antimicrobial Resistance, called antibiotic resistance "a critical problem that we've been trying to solve for decades."

Using antibiotics when they aren't medically necessary encourages the development and spread of antibiotic-resistant bacteria. Such bacteria from livestock can spread to humans via soil, air, water and food, generally from contamination with manure. For example, food crops may be fertilized with manure that contains antibiotic-resistant bacteria.

Studies have found high levels of contamination with antibiotic-resistant bacteria in meat sold in retail stores. In 2012, an outbreak of Salmonella that was resistant to multiple antibiotics was traced back to ground beef sold in a supermarket.

Think of recent deadly E.coli and Listeria outbreaks that have traced back to meat and cantaloupes — imagine how much more catastrophic it would be if these bacteria were immune to antibiotics. That's not so far-fetched. Another bacteria, carbapenem-resistant Enterobacteriaceae (CRE), is called 'the nightmare bacteria' because it's becoming resistant to all known antibiotics.

Antibiotics have saved millions of lives since the discovery of penicillin in 1928. By 1969, they were so successful at fighting bacterial infections that the U.S. Surgeon General declared, "It is time to close the book on infectious disease." Unfortunately, a problem with antibiotic resistance was already developing.

Solomon cited a 1955 article and editorial in The New England Journal of Medicine about the emerging problem of antibiotic resistance that said we're not doing enough to stop it. Fast-forward 60 years, and Solomon says we're in the middle of a crisis.

"Antibiotic resistance spreads very quickly," he said. "We may have a post-antibiotic era every bit as bad as the pre-antibiotic era before the discovery of penicillin."

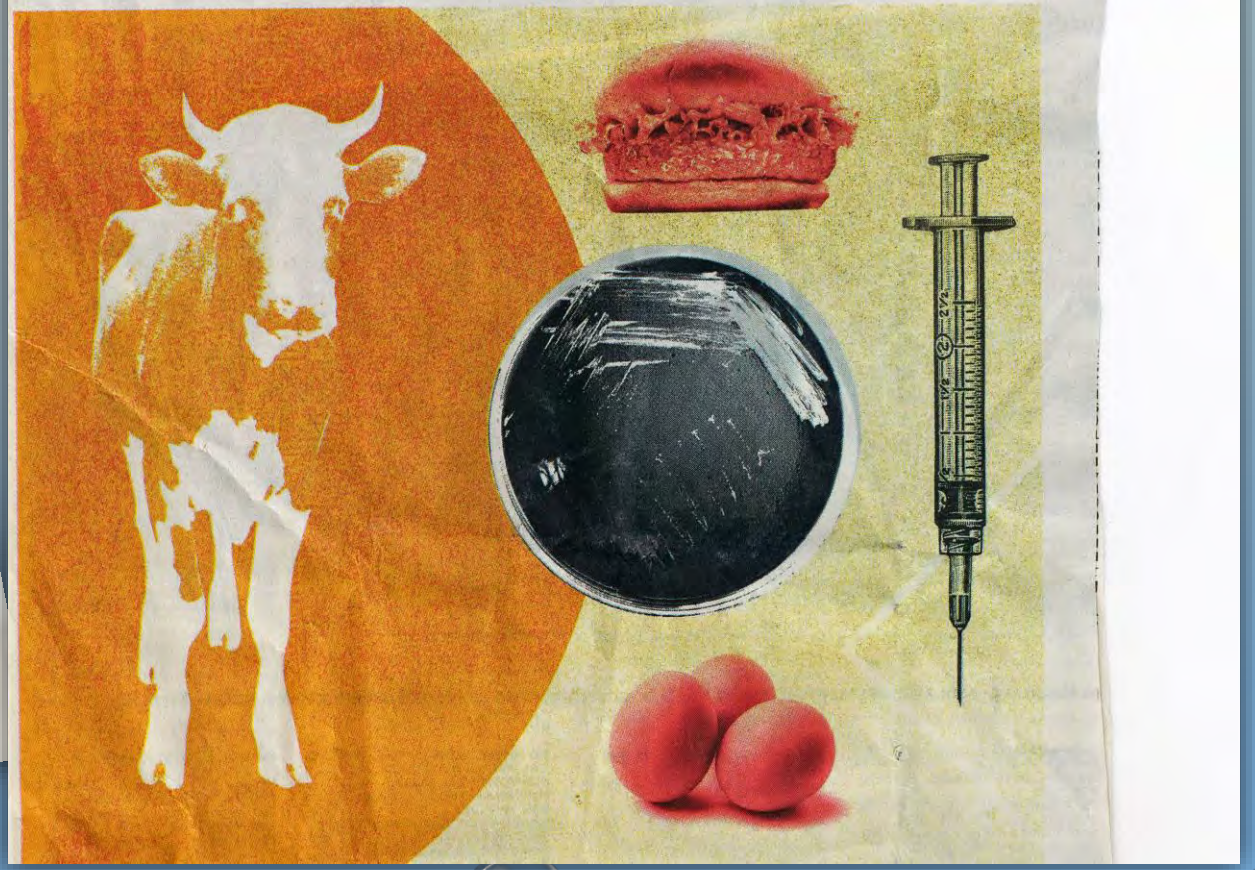
Almost half all antibiotics produced in the U.S. are used for the production of meat, milk and eggs. Ever since farmers realized that animals on antibiotics grew faster, they began using low, continuous doses to promote growth even in healthy animals. These "sub-therapeutic" doses of antibiotics bathe the animal's gut bacteria, killing off a lot of the normal bacteria and giving any antibiotic-resistant bacteria to multiply and thrive.

Some food producers, such as Chipotle, Whole Foods, Panera Bread and Applegate, have already taken steps to reduce antibiotic use, thanks to consumer demand. Now that the writing is on the wall, more companies — including McDonald's, Tyson and Perdue — are making moves to reduce antibiotic use in advance of the FDA deadline.

"There is no public-health problem more complex than antibiotic resistance," Solomon said. "It involves every living thing on the face of the earth, because every living thing on the face of the earth is part of an ecosystem with bacteria."

Carrie Dennett, MPH, RDN, CD is a registered dietitian nutritionist at Menu for Change and Nutrition By Carrie. Her blog and website is nutritionbycarrie.com. Reach her at nutritionbycarrie@gmail.com

HEALTH & FITNESS



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MISSION STATEMENT OF A FOODFISH VET PRACTICE:

"To assist our clients in obtaining the people, knowledge, skills, and products required to safely and consistently produce wholesome, palatable fish by the most cost-efficient methods that are available, humane, and in compliance with the regulatory agencies."

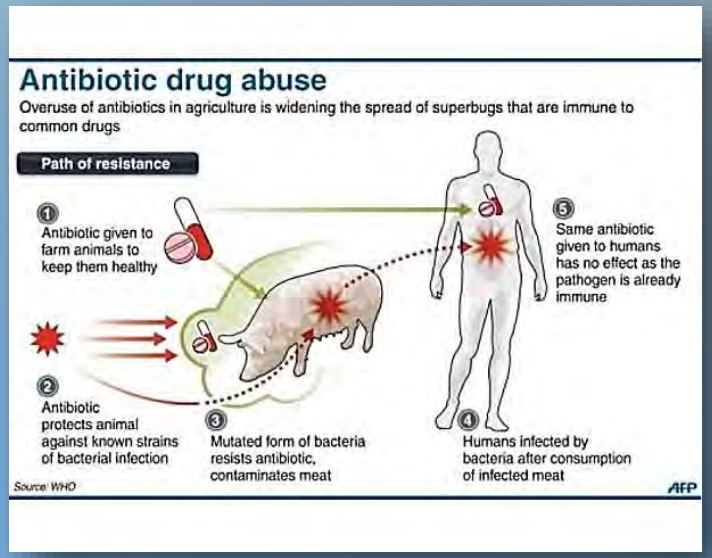
SIMILAR TO WHAT GAA-BMP IS ENDEAVORING TO DO.

PURPOSE OF TALK

- WHAT IS BEHIND THE ANTIBIOTIC PHOBIA IN FOOD ANIMALS AND IS IT VALID?
- WHAT EXACTLY ARE ANTIBIOTICS AGAIN?
- WHAT IS BEING DONE TO MONITOR THEIR USE AND EFFECT?
- HOW CAN BEST MANAGEMENT PRACTICES HELP?

3 areas of concern regarding animals:

1. Total amount used (relative to other uses)
2. Preventative use (instead of therapeutic)
3. Use for growth promotion



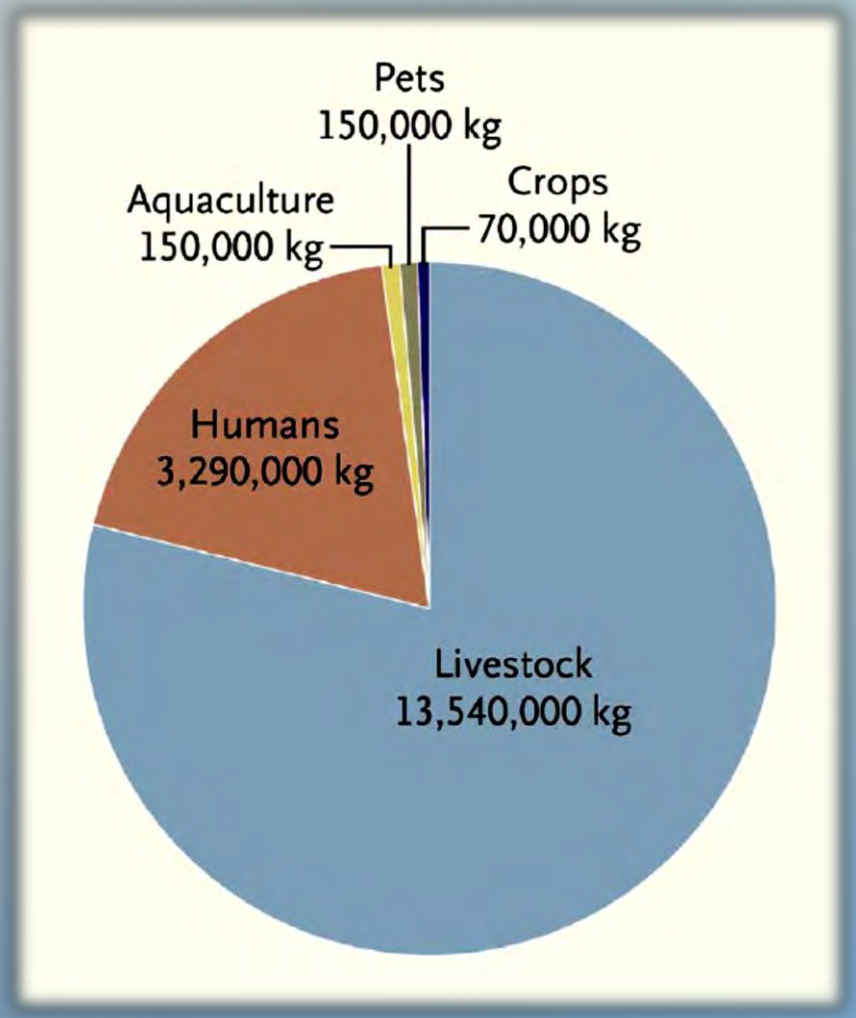
- Fear seems to stem from ***antibiotic resistance cases in human medicine*** and how animal use might contribute to this.

- Sentiment seems to be very **sensational and reactionary** with **a simplistic understanding** of antibiotics and their use (ulterior motives?).

Estimated annual
antibiotic use in US in animals is:

"TOO MUCH"

But: 45% are ionophores with no use in human medicine and 42% are tetracycline – only used 1%
In human medicine, so:
87% are never or rarely used in human medicine.



From:
Hollis and Ahmed, 2013,
Preserving Antibiotics, Rationally. N Eng J Med 369:2474-2476

This distinction is important, because ionophores have no use in human medicine and do not have any link or possible effect on antimicrobial resistance to therapeutic antibiotics in either people or food animals

PERSPECTIVE: SO, WHAT ARE ANTIBIOTICS, AGAIN?

- ***ANTIBIO*TICS**, ALSO KNOWN AS **ANTI*MICRO*BIAL DRUGS**, ARE DRUGS THAT FIGHT **INFECTIONS CAUSED BY BACTERIA**.
- **FIRST ANTIBIOTIC, PENICILLIN, IN 1928 BY ALEXANDER FLEMING**
- **TRANSFORMED MEDICAL CARE** AND DRAMATICALLY REDUCED ILLNESS AND DEATH FROM INFECTIOUS DISEASES.
- **ORIGINALLY REFERRED TO A NATURAL COMPOUND** PRODUCED BY A FUNGUS OR ANOTHER MICROORGANISM KILLS BACTERIA. **NOW, "ANTIBIOTICS" MAY BE SYNTHETIC COMPOUNDS.**

PERSPECTIVE: SO, WHAT ARE ANTIBIOTICS (Cont.)?

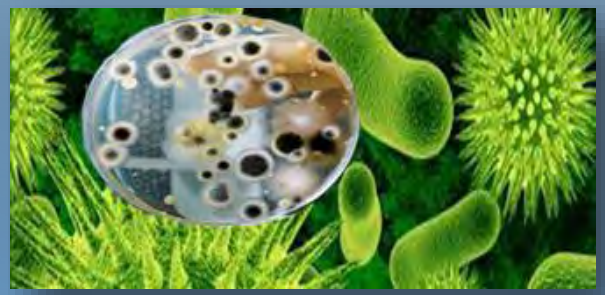
- **Natural antibiotics are everywhere (SOIL, AIR and WATER) for microbial competition.**

- **CLASSIFIED ACCORDING TO:**

  - **THE WAY THEY ACT** (**BACTERICIDAL** OR **BACTERIOSTATIC**),
  - THEIR CHEMICAL STRUCTURE,
  - THEIR MOLECULAR MECHANISMS OF ACTION,
  - WHETHER THEY ACT ON MANY BACTERIAL SPECIES (**BROAD SPECTRUM**) OR JUST A FEW (**NARROW SPECTRUM**).

TO BE CLEAR ON ANTIBIOTICS:

- DESIGNED TO **ACT ON BACTERIA, NOT HUMAN** OR ANIMAL CELLS.
- **NOT PERSISTENT IN THE BODY OR THE ENVIRONMENT**.
- **BACTERIAL RESISTANCE IS NOT PERMANENT**.
- A RESISTANT BACTERIA **DOES NOT MEAN A MORE VIRULENT** ONE.
- ***EVERY ANTIBIOTIC HAS BACTERIA THAT IS RESISTANT*** ***(****RIGHT FROM THE START).*



TO BE CLEAR ON USING ANTIBIOTICS (2):

- **ALL HAVE A SPECIFIC WITHDRAWAL TIME TO ENSURE NONE IN MEAT.**
- **RESISTANCE CAN HAPPEN WITHOUT MISUSE (OR USE!)**.
- **EARLY (PROPHYLACTIC USE?) MAY ACTUALLY BE MORE EFFICIENT** AND LEAD TO LESS RESISTANCE.
- GROWTH PROMOTING ANTIBIOTICS ARE NOT INTENDED FOR THERAPY AND IT IS A MEDICAL APPROACH TO **ALTER THE GUT FLORA TO ALLOW FOR MORE EFFICIENT NUTRIENT ABSORPTION AND ASSIMILATION** - WHICH MAY MEAN LESS OF A "CARBON FOOTPRINT".

FDA PACKAGE REQUIRED FOR FOOD ANTIBIOTIC APPROVAL

- EFFICACY TECHNICAL SECTION
- TARGET ANIMAL SAFETY TECHNICAL SECTION
- HUMAN FOOD SAFETY TECHNICAL SECTION – TOXICOLOGY AND RESIDUES
- CHEMISTRY, MANUFACTURING AND CONTROLS TECHNICAL SECTION (GMP COMPLIANCE)
- ENVIRONMENTAL SAFETY TECHNICAL SECTION
- LABELING TECHNICAL SECTION
- FREEDOM OF INFORMATION
- ALL OTHER INFORMATION
- ANALYTICAL METHOD VALIDATIONS MAY BE PART OF EACH OR ALL OF THE ABOVE

THE FDA and Aquaculture Antibiotics

- No new aquaculture antibiotics in the US since 2004.
- No new aquaculture antibiotics foreseeable in the next decade
- Continuous examination and response to concerns regarding antibiotic resistance.

- E.g.: FDA implemented "Guidance for Industry GFI#152" in 2003
  - Assigns a high ranking for intended administration to flocks or herds of animals, **it is virtually impossible for FDA to approve antibiotics for use in feed or water if those same antibiotics are also used in humans.**
  - A "no risk policy": antibiotics with a reasonable certainty of no harm to human health are rejected

This is actually troubling because antibiotics approved decades ago may be the only ones available in flocks, herds, and schools to combat infectious diseases and safeguard the food supply.

- There ARE **multiple monitoring and surveillance systems in place in the US** that recognize impactful events and trigger further investigation to determine the level of associated risks:

1. FDA Adverse Event reporting system – treatment failure
2. National Antimicrobial Resistance Monitoring System (NARMS)
    - Monitors resistance in:
        - A) foodborne human enteric pathogens
        - B) resistance in animals (overrepresentation of samples)

3. Post-harvest HACCP based pathogen reduction programs
4. Many specific antimicrobial risk assessments have been performed.

The question of what the nature and magnitude of the risk to humans can only be answered by performing systematic risk assessments.

Risk assessments actions:

1. Allow continued availability of product with no changes
2. Withdraw drug
3. Review by Veterinary Medicine Committee
4. Limitations of use / under only certain conditions

Risk assessments actions EXAMPLES:

1. 1998 Fluroquinolone resistant *Campylobacter* in poultry
   - Outcome: withdrawal Result: human cases continue to rise

2. 2004 - Virginiamycin as a growth promoter in food animals contributes to resistant strains of E. fecium in humans
   - Outcome: found inconsistent resistant genes; 14 in 100 million risk IF it were to occur
   - Result: None (banned in Denmark since 1998, but resistance still greater than in U.S.)

- One risk assessment actually concluded that withdrawal of macrolide and fluroquinolone use would cause more illness days than it would prevent.

Efforts on the Part of the American Veterinary Medical Association

TESTIMONY OF

Christine Hoang, DVM, MPH, CPH
Assistant Director
American Veterinary Medical Association

Concerning

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

Before the U.S. House of Representatives,
Committee on Energy and Commerce,
Subcommittee on Health

July 14, 2010

Veterinary Foresight and Expertise in Antimicrobial Discussions

The AVMA should be at the forefront of discussions that may impact drug availability, such as regulatory changes in veterinary oversight especially pertaining to antimicrobial use. The AVMA must:

- Proactively engage stakeholders and aggressively pursue opportunities to participate in and, where appropriate, lead those discussions.
- Make certain that decisions are informed by science.
- Ensure that risks and benefits to both humans and animals are given due consideration.
- Strive to minimize the potential for unintended negative consequences and maximize potential benefits.
- Incorporate members' expertise to effectively advocate for the veterinary profession, the animals in its care, and the public whose health veterinarians safeguard.

National Antimicrobial Resistance Monitoring System (NARMS)

The AVMA recognizes the importance of NARMS as a valuable resource for information on resistance monitoring of bacterial isolates from animals, animal products, and humans. Therefore, the AVMA recommends that the USDA, FDA, and CDC budget for adequate and equitable funding of the resistance monitoring system and for the timely reporting of results in order to be able to provide a current and relevant resource regarding information for bacterial re

Approval and Availability of Antimicrobials for Use in Food-Producing Animals

The AVMA recognizes that it is essential to maintain the safety of the US food supply. Central to this process is the Food and Drug Administration's use of scientific methods supported by substantial data to evaluate product safety and efficacy when approving antimicrobials for use in food-producing animals.

The AVMA supports a national, coordinated, and appropriate response to the issue of antimicrobial resistance. This includes a rigorous, transparent FDA approval process with assessment of impact on public health, animal health and animal welfare, and food safety. The AVMA supports the science-based processes of the FDA in the regulation of antimicrobials for their intended use in food animals in accordance with the Food, Drug, and Cosmetic Act and the Animal Medicinal Drug Use Clarification Act.

AVMA says Pew Commission report is flawed unscientific

An AVMA report says recommendations by a prominent critic of industrial animal agriculture are unscientific and can actually threaten human health.

- AVMA Antimicrobial Use Task Force
- AVMA Task Force for Antimicrobial Use Data Collection in Animal Agriculture

AVMA Strategy Regarding Antimicrobial-Resistant Bacteria

The AVMA's comprehensive science-based strategy of legislative, regulatory, and public education activities regarding antimicrobial resistant bacteria in animals and drug availability is as follows:

1. Interaction of the Councils on Public Health and Regulatory Veterinary Medicine, Veterinary Service, Biologic and Therapeutic Agents, and Public Relations, Food Safety Advisory Committee, and the Legislative Advisory Committee to define and pursue coordinated efforts towards additional research regarding the ecology of antimicrobial resistance.
2. Risk/benefit assessments of the effects of antimicrobial use on animal health and welfare and public health to support translation of knowledge into sound management practices.
3. A science-based education program to include:
   a. General consumer education about the value of antimicrobials in improving animal welfare and public health;
   b. Education of federal legislators and their staffs regarding the public and animal health aspects of antimicrobial drug availability; and
   c. Education of veterinarians, and through them their clients, practices to sustain drug efficacy, mechanisms of antimicrobial resistance, and the potential implications for trade.

Extralabel Use of Cephalosporin in Food-Producing Animals

Formal title: Docket Number [FDA-2008-N-0326] New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition

In the July 3, 2008 Federal Register the Food and Drug Administration (FDA) issued an order prohibiting the extralabel use of cephalosporin antimicrobial drugs in food-producing animals. The FDA stated that it was issuing the order based on evidence that extralabel use of these drugs in food-producing animals will likely cause an adverse event in humans and, as such, presents a risk to the public health.

On August 18th the FDA extended the deadline of the comment period from September 2, 2008 to November 3, 2008 and delayed the effective date of the Order of Prohibition to November 30, 2008.

Brief Description and AVMA Response:

The AVMA responded to the FDA's call for public input with an exhaustively researched and thoughtfully drafted letter. In that letter the AVMA states that it is committed to judicious use of antimicrobials, ensuring efficacy of antimicrobials and upholding animal and public health.

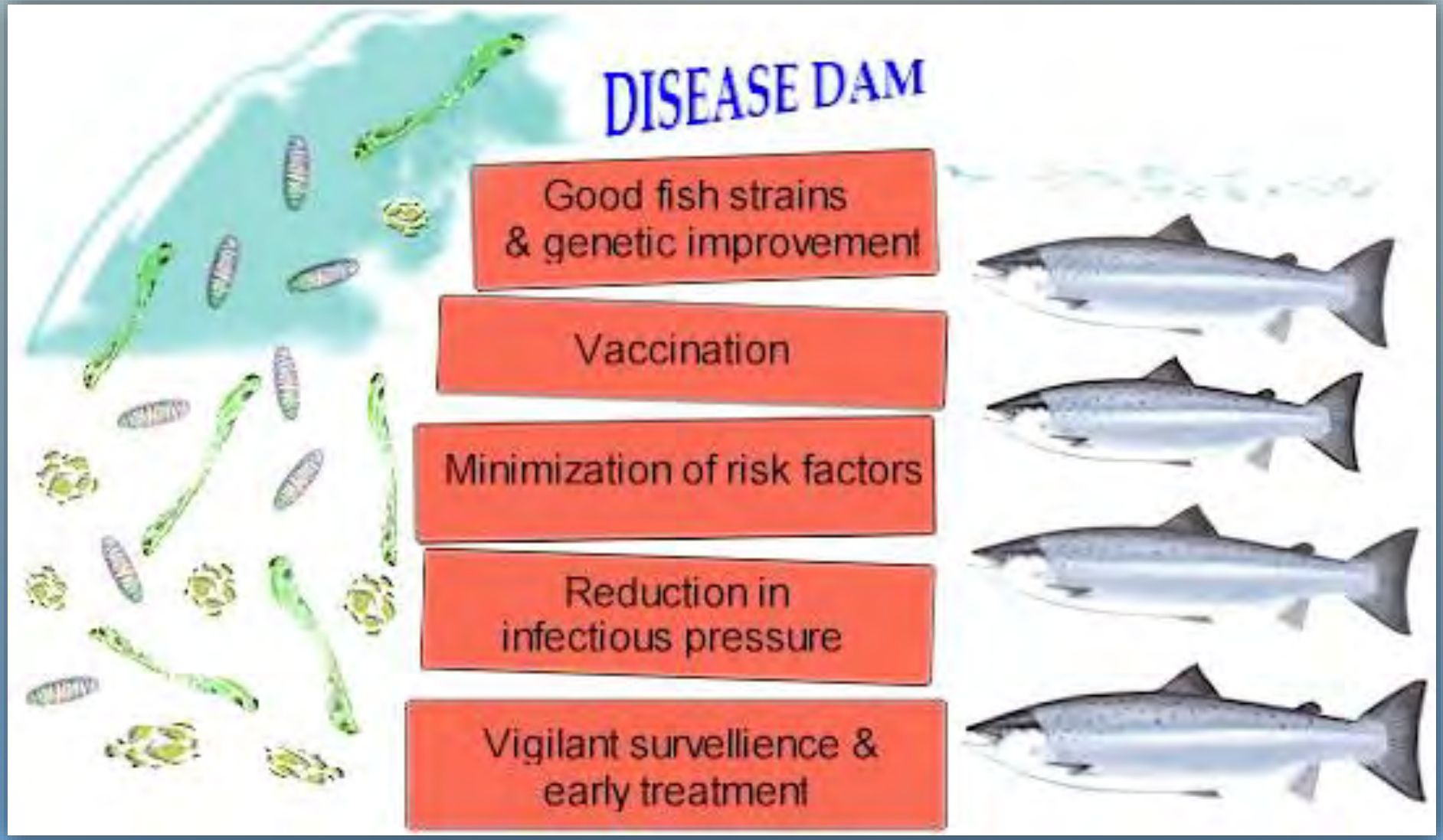
While the AVMA admires the FDA's intent, the organization has reached scientific conclusions that differ greatly from those offered by the FDA. The AVMA strongly recommends that the FDA postpone its final rule prohibiting all extralabel use of cephalosporin antimicrobials in food-producing animals, in order to perform a risk assessment characterizing the hazard, evaluating the risk, and ascertaining the impact of any risk management recommendations

The AVMA bases its recommendations on the following:

- The lack of scientific evidence showing any significant risk to human health by extralabel use of cephalosporins in food producing animals
- The lack of any demonstrated benefit of the rule to human health

The Role of the Veterinarian in Animal Antimicrobial Use

Veterinarians should be involved in the decision-making process for the use of antimicrobials in animals regardless of the distribution channels through which the antimicrobials were obtained.


DISEASE DAM
Good fish strains & genetic improvement
Vaccination
Minimization of risk factors
Reduction in infectious pressure
Vigilant surveillience & early treatment

ONLY THREE IN U.S. AQUACULTURE!

(one more in Canada)

First approved in 1970's

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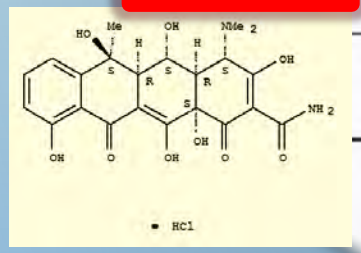

• HCl

OXYTETRACYCLINE DIHYDRATE

Species	Indication	Dosing	
Pacific salmon	Mark skeletal tissue	• 250 mg per kg fish per day for 4 days	• Salmon • In feed as s • 7-day withdra
Salmonids	Control of **ulcer disease** (*Hemophilus piscium*), **furunculosis** (*Aeromonas salmonicida*), **bacterial hemorrhagic septicemia** (*A. liquefaciens*), and **pseudomonas disease** (*Pseudomonas* spp.)	• 2.5 - 3.75 g per 100 lbs fish per day for 10 days	• In mixed ration • 21-day withdrawal time • No temperature restrictio on use
Freshwater-reared salmonids	Control of mortality due to **cold-water disease** caused by *Flavobacterium psychrophilum*	• 3.75 g per 100 lbs fish per day for 10 days	• In mixed ration • 21-day withdrawal time • No temperature restriction on use
All freshwater-reared *Oncorhynchus mykiss*	Control of mortality due to **columnaris disease** (*F. columnare*)	• 3.75 g per 100 lbs fish per day for 10 days	• In mixed ration • 21-day withdrawal tim • No temperature restri on use
Catfish	Control of **bacterial hemorrhagic septicemia** (*A. liquefaciens*) and **pseudomonas disease** (*Pseudomonas* spp.)	• 2.5 - 3.75 g per 100 lbs fish per day for 10 days	• In mixed rati • Water tem below • 21
	Control of **gaffkemia** (*Aerococcus viridians*)	• 1 g per	

First approved in 2004?

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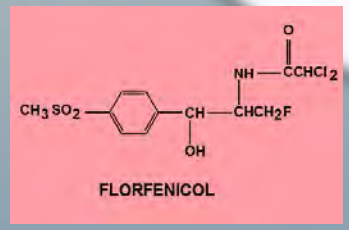


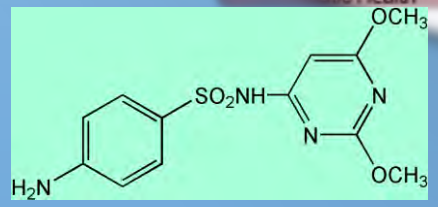
FLORFENICOL

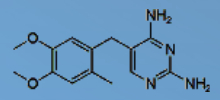
FLORFENICOL

Species	Indication	Dosing	
Catfish	Control of mortality due to **enteric septicemia** associated with *Edwardsiella ictaluri*	• 10 mg florfenicol per kg fish per day for 10 days	• Veter Directive drug • 12-day withdra time
	Control of mortality due to **columnaris disease** associated with *Flavobacterium columnare* (Conditional Approval)		• VFD drug • 12-day withdrawal time • Must use AQUAFLOR®-CA1 product
Freshwater-reared salmonids	Control of mortality due to **furunculosis** associated with *Aeromonas salmonicida*	• 10 mg florfenicol per kg fish per day for 10 days	• VFD dr • 15
	Control of mortality due to **coldwater disease** associated with *F. psychrophilum*		

First approved in 1984

ROMET® 30 and ROMET® TC



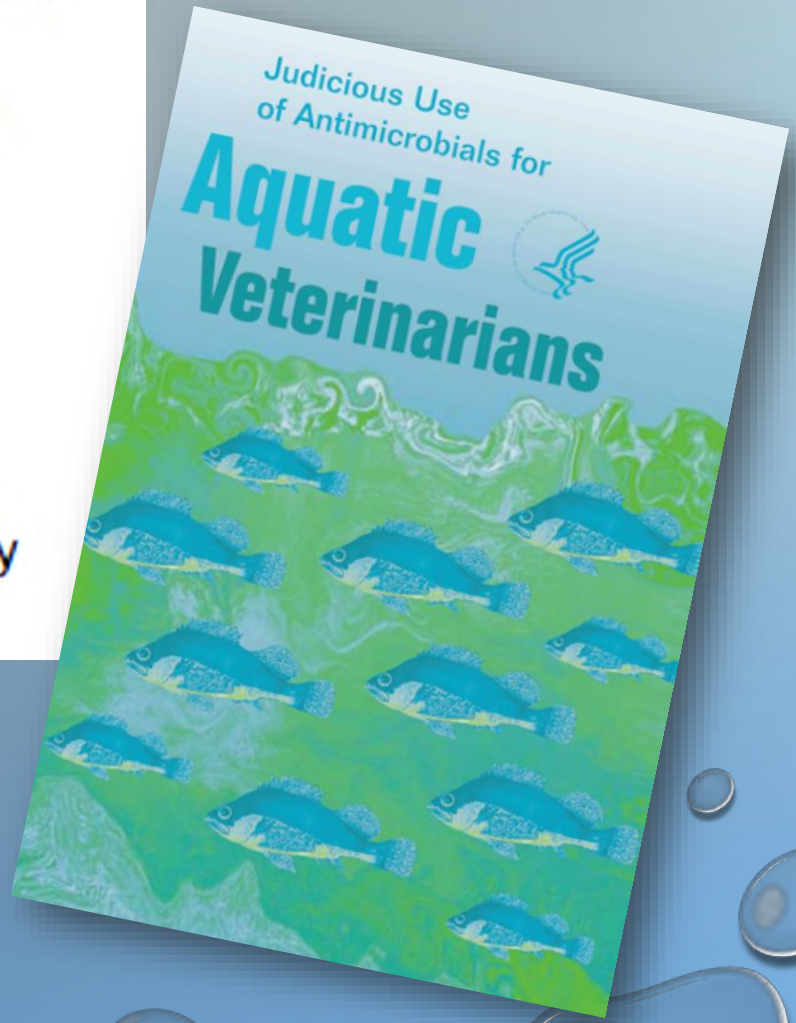


SULFADIMETHOXINE & ORMETOPRIM

...upplier	Species	Indication	Dosing	Limi... comme...
	Salmonids	Control of **furunculosis** due to *Aeromonas salmonicida*	• 50 mg per kg fish per day for 5 days	• In feed • 42-day withdrawal time
	Catfish	Control of **enteric septicemia** due to *Edwardsiella ictaluri*	• 50 mg per kg fish per day for 5 days	• In feed

Veterinarians treating food fish with antimicrobial drugs have four primary responsibilities:

- To optimize stock production for those who own and care for food fish through effective disease prevention;
- To diagnose and then treat or control disease in their patients through the safe and effective use of therapeutants;
- To ensure that fish harvested for food meet established safety standards; and,
- To ensure that antimicrobial drug administration does not adversely impact the environment receiving production facility effluent



Judicious Therapeutic Use of Antimicrobials

Position Statement

When the decision is reached to use antimicrobials for treatment, control, or prevention of disease, veterinarians should strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health and well-being.

Objectives

- Support development of a scientific knowledge base that provides the basis for judicious therapeutic antimicrobial use.
- Support educational efforts that promote science-based judicious antimicrobial use.
- Maintain efficacy of antimicrobials by minimizing potential for development and transmission of resistance.
- Foster an atmosphere within industry research and development programs and government regulatory bodies that facilitate current and future availability of veterinary antimicrobials.

NATIONAL Aquaculture ASSOCIATION

Judicious Antimicrobial Use in US Aquaculture:
Principles and Practices
(Approved by NAA Board of Directors March 2003)

It is the policy of the NAA that the use of antibiotics in aquatic animals is done only in accordance with the following Judicious Use Principles and Practices

1. **Emphasize disease prevention strategies, such as appropriate husbandry and hygiene, routine health monitoring and immunization.**
2. **Obtain accurate disease diagnosis prior to initiating disease treatment.**
3. **Ensure bacteria causing the aquatic animal disease are sensitive to the antimicrobial considered for use.**
4. **If medicated feed is used, ensure aquatic animals are feeding before treatment is applied.**
5. **Limit therapeutic exposure according to label instructions.**
6. **Observe all required withdrawal times.**
7. **Maintain accurate records of treatment.**
8. **Use good waste management practices.**

IN CONCLUSION, THERE IS A DILEMMA:

SHOULD BMP PROGRAMS INCORPORATE ANTIBIOTIC USE?

- BMP'S ARE MAKING AQUACULTURE PRODUCE MORE ACCEPTABLE – GOOD!
- THERE IS A SIMPLISTIC AND IRRATIONAL FEAR OF ANTIBIOTIC USE IN FOOD ANIMALS BY THE CONSUMER – BAD!
- SUPPLIERS CAN PANDER TO THIS FEAR TO SELL PRODUCT (EG: PEPSI & ASPARTAME; CHINESE RESTAURANTS AND MSG; GLUTEN-FREE, ETC.) – BAD!
- BY DOING THE ABOVE, THE INDUSTRY WILL BE HURT IN THE LONG RUN AND POTENTIALLY PUBLIC HEALTH – BAD!
- AT THE VERY LEAST ADOPT AND PROMOTE JUDICIOUS USE PRACTICES – GOOD!
- *BUT HOW DO WE EDUCATE THE PUBLIC? WHO SHOULD DO IT? AND IS THIS A POINTLESS TASK?*

THE GOOD IS IN THE DETAILS BUT WHO CARES ABOUT DETAILS?

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