An Overview of Veterinary Antimicrobial Use Policies, Legislation, and Regulations: Background, Scientific Data, and the Basis for Discussions in the USA

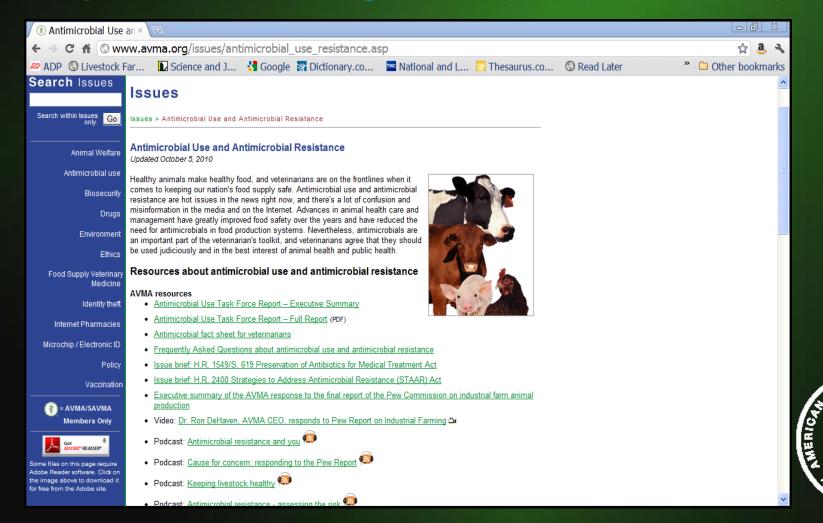
Dr. Christine Hoang, DVM, MPH, CPH
Assistant Director, Scientific Activities Division,

AVMA



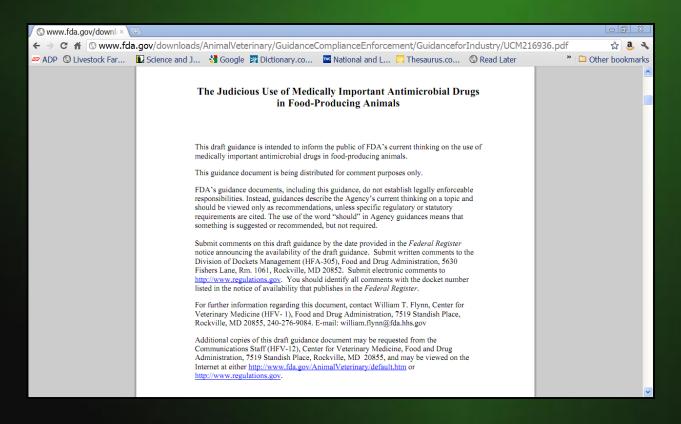
Policies

http://www.avma.org/issues/policy/default.asp



Policies

http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf





Policies

- FDA Guidance For Industry #209
 - limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health
 - 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation

Legislation

AMDUCA – for Extra Label Drug Use



(a) GENERAL RULE- Section 512(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(a)) is amended by adding the following new paragraphs at the end: '(4)(A) Except as provided in subparagraph (B), if an approval of an application filed under subsection (b) is in effect with respect to a particular use or intended use of a new animal drug, the drug shall not be deemed unsafe for the purposes of paragraph

SEC. 2. UNAPPROVED USES.



Regulations

ELDU – Extra-Label Drug Use

VFDs –
 Veterinary
 Feed Directive

Food and Drug Administration, HHS

(b) A veterinarian shall keep all required records for 2 years or as otherwise required by Federal or State law, whichever is greater.

(c) Any person who is in charge, control, or custody of such records shall, upon request of a person designated by FDA, permit such person designated by FDA to, at all reasonable times, have access to, permit copying, and verify such records.

Subpart B—Rules and Provisions for Extralabel Uses of Drugs in Animals

§ 530.10 Provision permitting extralabel use of animal drugs.

An approved new animal drug or human drug intended to be used for an extralabel purpose in an animal is not unsafe under section 512 of the act and is exempt from the labeling requirements of section 502(f) of the act if such use is:

(a) By or on the lawful written or oral order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship; and (b) In compliance with this part.

§ 530.11 Limitations.

In addition to uses which do not comply with the provision set forth in \$530.10, the following specific extralabel uses are not permitted and result in the drug being deemed unsafe within the meaning of section 512 of the act:

- (a) Extralabel use in an animal of an approved new animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian);
- (b) Extralabel use of an approved new animal drug or human drug in or on an animal feed;
- (c) Extralabel use resulting in any residue which may present a risk to the public health; and

§ 530.13

narian shall bear or be accompanied by labeling information adequate to assure the safe and proper use of the product. Such information shall include the following:

- (a) The name and address of the prescribing veterinarian. If the drug is dispensed by a pharmacy on the order of a veterinarian, the labeling shall include the name of the prescribing veterinarian and the name and address of the dispensing pharmacy, and may include the address of the prescribing veterinarian:
- (b) The established name of the drug or, if formulated from more than one active ingredient, the established name of each ingredient;
- (c) Any directions for use specified by the veterinarian, including the class/ species or identification of the animal or herd, flock, pen, lot, or other group of animals being treated, in which the drug is intended to be used; the dosage, frequency, and route of administration; and the duration of therapy;
- (d) Any cautionary statements: and
- (e) The veterinarian's specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food which might be derived from the treated animal or animals.

§ 530.13 Extralabel use from compounding of approved new animal and approved human drugs.

- (a) This part applies to compounding of a product from approved animal or human drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of veterinary medicine. Nothing in this part shall be construed as permitting compounding from bulk drugs.
- (b) Extralabel use from compounding of approved new animal or human drugs is permitted if:
- All relevant portions of this part have been complied with;



Proposed Legislation



- PAMTA The Preservation of Antibiotics for Medical Treatment Act
 - Only treatment ("therapeutic") administration
 - No growth promotion, no prevention use
 - Maybe no control use

What Else PAMTA Might Do...

"any use of the drug as a feed or water additive for an animal in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose"

- "any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide; or any other drug or derivative of a drug that is used in humans or intended for use in humans to treat or prevent disease or infection caused by microorganisms"
- Would likely include all prevention uses and potentially control uses
 [Note: This could be far more restrictive than other bans that have been implemented. Therefore, negative impacts could be far worse than any experienced in other countries.]
- Ionophores and arsenicals would likely be exempted

Impacts of Potential Legislation

Preservation of Antibiotics for Medical Treatment Act (PAMTA)

Approvals of any "nontherapeutic" drug will be withdrawn unless...

"there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance that is attributable in whole or in part to the nontherapeutic use of the drug"

 FDA Officials have indicated that they know of no process that can provide this information. Many assume GFI#152 can be used, but GFI#152 was designed as a pre-approval process and cannot be used as a post approval microbial safety assessment that would satisfy this requirement

PAMTA-like State Legislation



How are Antimicrobials Used?

- Treatment of disease
- Control of disease
- Prevention of disease
- "Production Uses" = Growth promotion = Feed efficiency / Improved rate of gain



Antimicrobials Regulation

- Over-the-counter (OTC)
 - Oral (feed/water)
 - Injectable
 - Intramammary
- Prescription
 - Oral
 - Injectable
 - Intramammary
- Veterinary Feed Directive (VFD)





The Debate...

Disease Experts: Antibiotics Are a Natural Resource that Needs Protection

- Public News Service

Livestock superbugs threaten humans: doctor

-CBC News

Doctors sound alarm over antibiotics in animal feed

- Vancouver Sun

Deadlier than AIDS: Why is this Travesty allowed to continue in the U.S.?

- Food Consumer

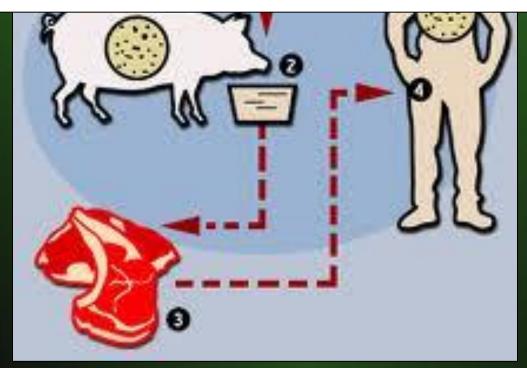


People Think...



Animal Farms are Pumping up Superbugs

- International Business Times















WE'VE GOT FIVE TO GIVE AWAY

Standards Agency



Pray for me says Liz Taylor as she has vital heart operation

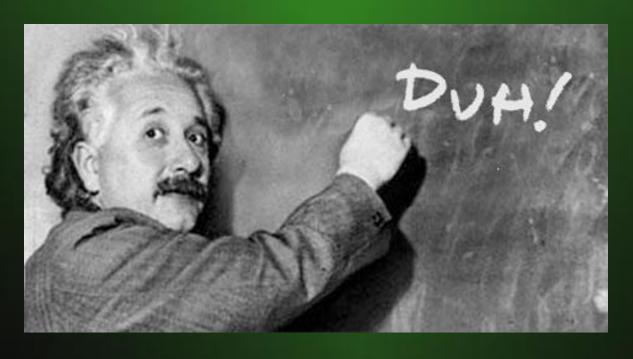


Perceptions

Antimicrobial use

Selection pressure

RESISTANCE





Surveillance Systems

- National Antimicrobial Resistance Monitoring System (NARMS)
- Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- The Danish program for surveillance of antimicrobial resistance (DANMAP)
- Monitoring of Antimicrobial Resistance and Antimicrobial usage in animals in the Netherlands (MARAN)
- Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) & Swedish Antimicrobial Utilisation and Resistance in Human Medicine (SWEDRES)

NARMS

- http://www.cdc.gov/narms/i ndex.htm
- The "arms" of NARMS
 - Human Arm enteric bacteria up to 2009
 - Animal Arm slaughter and diagnostic samples up to 2008
 - Retail Arm meats up to 2009
- 2008 Executive "summary" Report currently available

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References and Resources

FAQ: Antibiotic Resistance

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<u>Publications</u>

Enterococci Study

Reports

Quick Links

National Antimicrobial Resistance Monitoring System (NARMS): Enteric Bacteria

NARMS is a collaboration among Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (Center for Veterinary Medicine) and U.S. Department of Agriculture (Food Safety and Inspection Service and Agricultural Research Services).

The National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria was established in 1996, within the framework of the CDC's Emerging Infections Program's Epidemiology and Laboratory Capacity Program and the Foodborne Diseases Active Surveillance Network (FoodNet)

Get Smart on the Farm

- Centers for Disease Control Antimicrobial Resistance
- Food and Drug Administration - NARMS
- Foodborne and Diarrheal Diseases Branch
- Related CDC Activities
- United States Department of Agriculture - NARMS

Contact Info

1600 Clifton Road NE, MS-D63 Atlanta GA 30333 Phone: +1(404) 639-2206 Fax: +1(404) 639-3535

NARMS Member Site

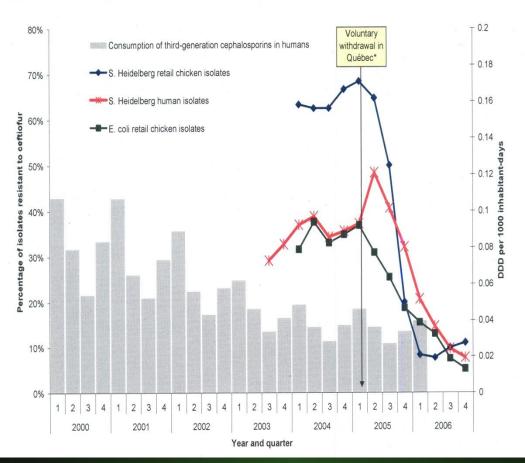
NARMS Highlights

- National Antimicrobial Resistance Monitoring System Enteric Bacteria (NARMS) 2008 Annual Report PDF 1.59MB
- National Antimicrobial Resistance Monitoring System Enteric Bacteria (NARMS) 2007 Annual Report PDF 3.7MB
- National Antimicrobial Resistance Monitoring System Enteric Bacteria (NARMS) 2006 Annual Report PDF 2.3MB
- National Antimicrobial Resistance Monitoring System Enteric Bacteria (NARMS) 2005 Annual Report PDF 1.2MB Errata PDF 103KB
- International Spread of Multidrug-resistant Salmonella Schwarzengrund in Food Products. Aarestrup FM, Hendriksen RS, Lockett J, Gay K, White DG, Hasman H, Sørensen G, Bangtrakulnonth A, Pornreongwong S, Pulsrikarn C, Angulo FJ, Gerner-Smidt P
- Fluoroquinolone-Resistant Campylobacter Species and the Withdrawal of Fluoroquinolones from Use in Poultry: A Public Health Success Story PDF 268KB Nelson, JM, Chiller TM, Powers JH, and Angulo FJ., CID April 2007; 44(7); 977-980
- Increase in quinolone resistance among non-Typhi Salmonella in the United States, 1996-2002 Stevenson J, Gay K, Barrett TJ, Medalla F, Chiller TM, Angulo FJ. AAC Jan 2007; 51 (1):
- Surveillance for antimicrobial resistance among foodborne bacteria: The U.S. Approach (chapter of book titled "Infectious Disease Surveillance"), Whichard JM, Gav K., White DG, Chiller TM
- Human Salmonella and concurrent decreased susceptibility to quinolones and extendedspectrum cephalosporins. Whichard JM, Gay K, Stevenson JE, Joyce K, Omondi M, Medalla F, Jacoby GA, Barrett TJ



CIPARS 2005-2006

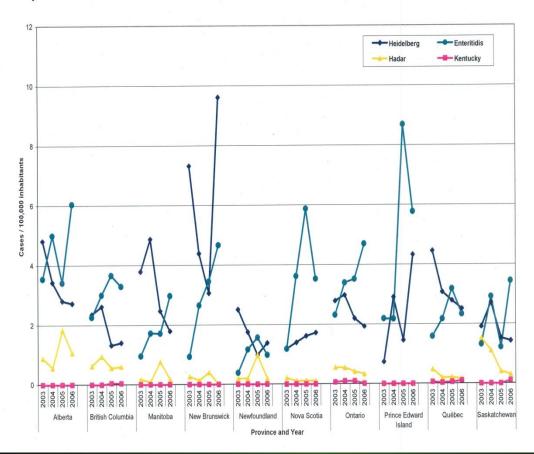
Figure 1. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S.* Heidelberg isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (*IMS*² Health) in Québec.





CIPARS

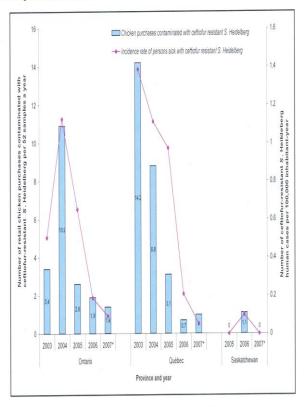
Figure 10. Estimated incidence of reported human cases per 1,000 inhabitants by province for the most frequent serovars identified in chicken; *CIPARS*, 2003-2006.





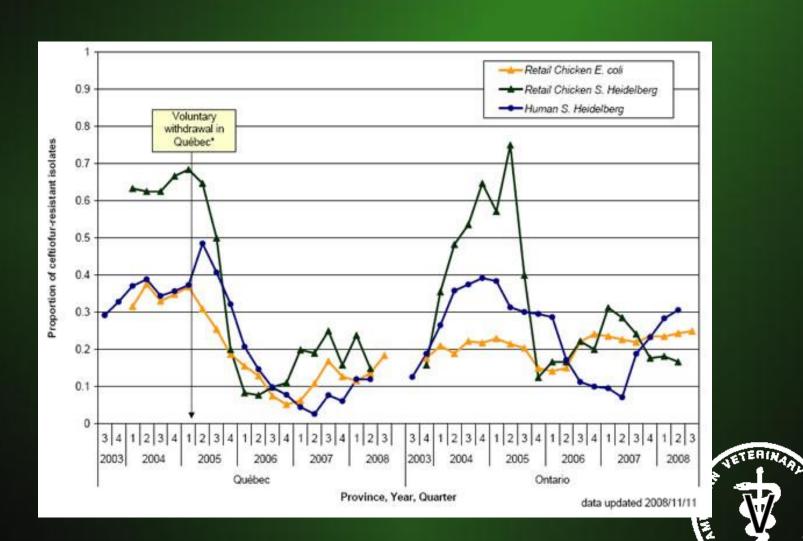
CIPARS 2003-2007

Figure 41. Estimated human annual exposure to retail chicken contaminated with ceftiofur-resistant S. Heidelberg strains compared to the incidence of human ceftiofur-resistant S. Heidelberg cases, based on purchasing chicken once a week.





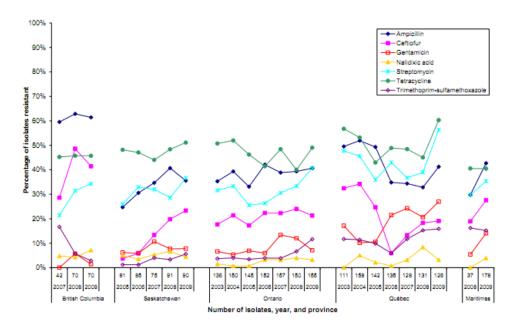
CIPARS 2003-2007



CIPARS 2009

Antimicrobial Resistance - Chickens

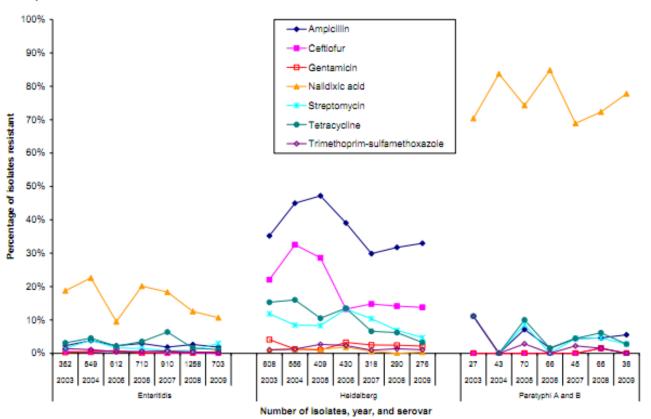
Figure 18. Temporal variation in resistance to selected antimicrobials in *Escherichia coli* isolates from chicken; *Retail Meat Surveillance*, 2003–2009.





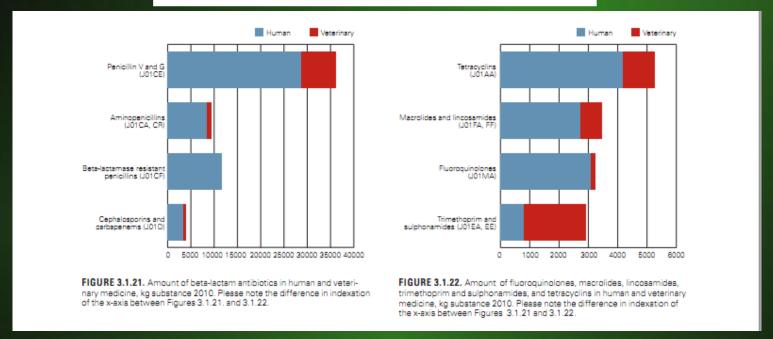
CIPARS 2009

Figure 1. Temporal variation in resistance to selected antimicrobials in human isolates of *Salmonella* serovars Enteritidis, Heidelberg, and Paratyphi A and B; *Surveillance of Human Clinical Isolates*, 2003–2009.



ETERINA

SWEDRES 2010



- Figure 3.1.21 displays the sales of beta-lactam antibiotics. These substances are by far the most used antibiotics in both human and veterinary medicine and also represent the largest amounts measured as kilograms.
 From an environmental and resistance most of them are relatively harmless
- The substances in Figure 3.1.22 are sold in much smaller quantities, but their impact on the emergence of antibiotic resistance and the environment is more pronounced due to their chemical and pharmacological properties.

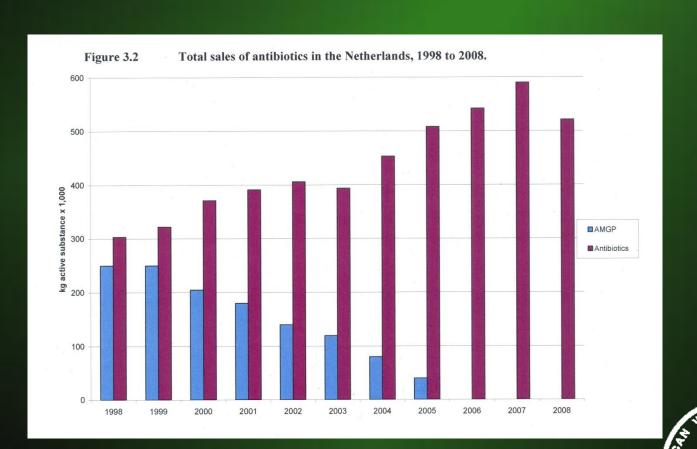
SVARM 2010

- Prevalence of E. Coli resistant to 3rd generation cephalosporins has increased in recent years in some countries and some suggest that the increase is linked to use of cephalosporins in broilers.
- In Sweden, cephalosporins are not used in broilers. Therefore, the occurrence of *E. coli* of *CTX-M-1* and *CMY-2* genotypes is NOT associated with selection pressures associated with use in poultry.

SWEDRES 2010

- Majority of E. coli resistance to 3rd
 generation cephalosporins is caused by
 plasmid mediated ESBLs of CTX-M type.
- From AVMA's response to the original order of prohibition on ELDU of cephalosporins:
 - "Substantial amounts of data exist suggesting mechanisms of cephalosporin resistance may be entirely unrelated to use of cephalosporins"

Maran 2008



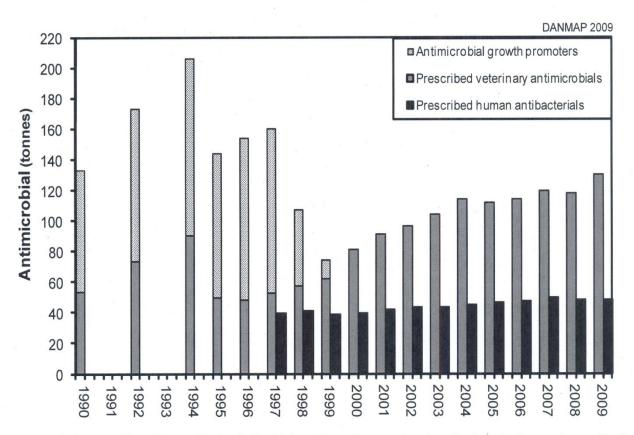


Figure 46. Consumption of prescribed antimicrobials and growth promoters in animal production and prescribed antibacterials in humans, Denmark



Table 2. Production of food animals and the production of meat and milk, Denmark

DANMAP 2009

Year -	Broilers		Turkeys		Cattle (slaughtered)		Dairy cows		Pigs			Farmed fish	
												Fresh	Salt water
	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg milk	a) 1,000 heads	Export b) 1,000 heads	mill. kg	mill. kg	mill. kg
1990	94,560	116	571	2.5	789	219	753	4,542	16,425	4 3 3	1,260	-	-
1992	107,188	137	761	5.4	862	236	712	4,405	18,442	-	1,442	35	7
1994	116,036	152	1,091	8.6	813	210	700	4,442	20,651	11 to -	1,604	35	7
1996	107,895	149	961	9.3	789	198	701	4,494	20,424	-	1,592	32	8
1998	126,063	168	1,124	11.6	732	179	669	4,468	22,738		1,770	32	7
2000	133,987	181	1,042	10.3	691	171	636	4,520	22,414	-	1,748	32	7
2001	136,603	192	1,086	13.2	653	169	623	4,418	23,199	Hill Finds	1,836	31	8
2002	136,350	190	1,073	12.8	668	169	611	4,455	24,203	-	1,892	32	8
2003	129,861	181	777	11.2	625	161	596	4,540	24,434	400 - HO	1,898	34	8
2004	130,674	181	1,086	19.6	632	165	569	4,434	25,141	1,712	1,967	34	9
2005	122,179	180	1,237	17.4	549	145	559	4,449	25,758	2,720	1,988	31	8
2006	106,182	163	785	11.3	509	140	556	4,492	25,763	3,204	1,957	29	8
2007	107,952	178	1,009	14.4	512	141	545	4,515	26,311	3,522	2,046	31	10
2008	107,595	186	1,068	12.3	509	138	559	4,575	27,078	4,943	1,985	30	10
2009	108,851	181	1,175	11.1	507	137	569	4,733	27,603	6,642	1,898	-	-
Increase ^{c)} (%)	1	-3	10	-10	0	-1	2	3	2	34	-4	-	-

Source: Statistics Denmark (www.dst.dk) and The Danish Directorate for Fisheries. All data include export of live animals for slaughter a) Including export of all age groups (not only for slaughter)

b) Export of 15-50 kg pigs. These are included in total number of heads, but antimicrobial use after export until slaughter is not registered as it takes place outside Denmark

c) Increase from 2008 to 2009

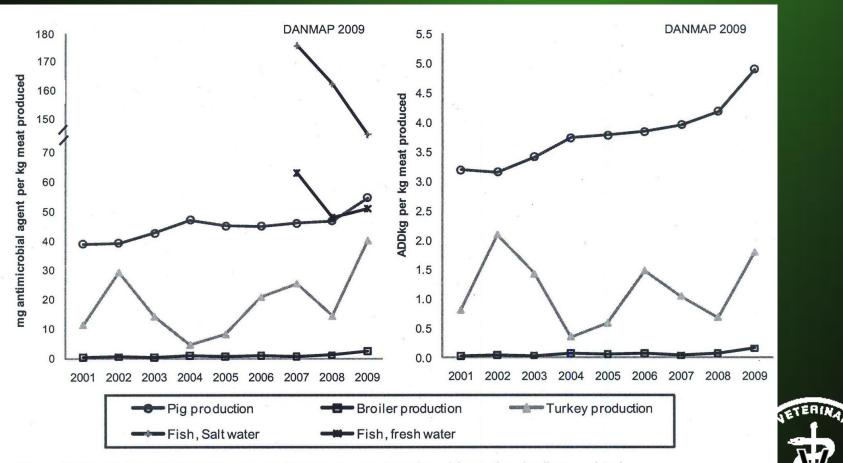


Figure 5. Trends in antimicrobial consumption per kg meat produced from pigs, broilers and turkey

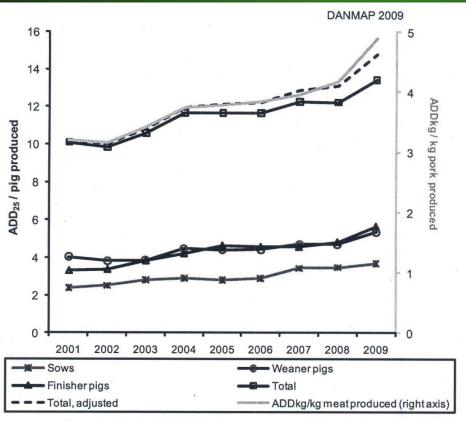


Figure 6. Trends in consumption of antimicrobials in the pigs, given as Animal Daily Doses (ADDs) relative to different measures of production, Denmark

Consumption in sows and weaners are given as ADD25 divided by number of weaning pigs produced Consumption in finishers is given as ADD25 divided by number of finisher pigs produced

The adjusted total is given with same units as the total, but adjusted for the increasing export of pigs at 30 pigs.

The adjusted total is given with same units as the total, but adjusted forthe in creasing export of pigs at 30 kg (see text) Consumption per kg meat produced is given as ADDkg divided by meat production including live export



DANMAP 2009

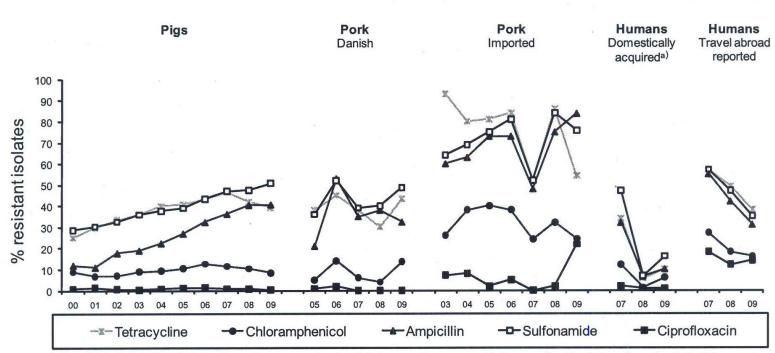


Figure 28. Trends in resistance to selected antimicrobial agents among Salmonella Typhimurium isolated from pigs, pork and from human cases, Denmark

The number of isolates varies between years and between source. For pigs, the annual number of isolates were between 216 and 736. For Danish pork, number of isolates was between 64 and 99, 2005-2009; data before 2005 not shown due to low number of isolates. For imported pork, the number of isolates varied between 21 and 56, except in 2007 when only 21 isolates were available a) Until 2007, includes cases where origin of infection is not documented; therefore only data from and after 2007 are included

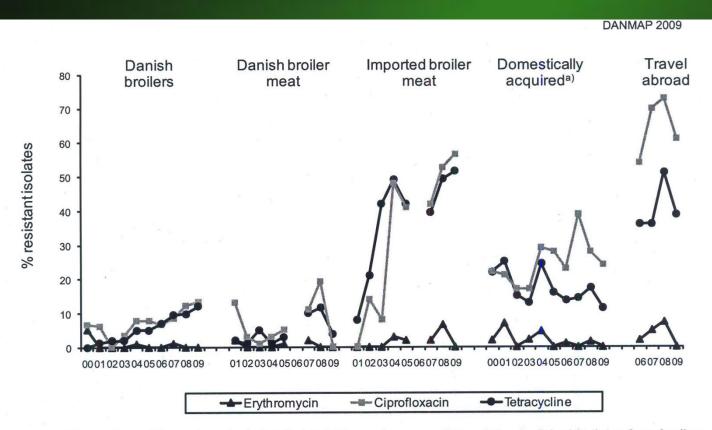


Figure 29. Trends in resistance to selected antimicrobial agents among Campylobacter jejuni isolates from broilers, broiler meat and human cases, Denmark

a) Until 2007, including cases where origin of infection was not documented and may therefore include isolates acquired abroad but not documented as such

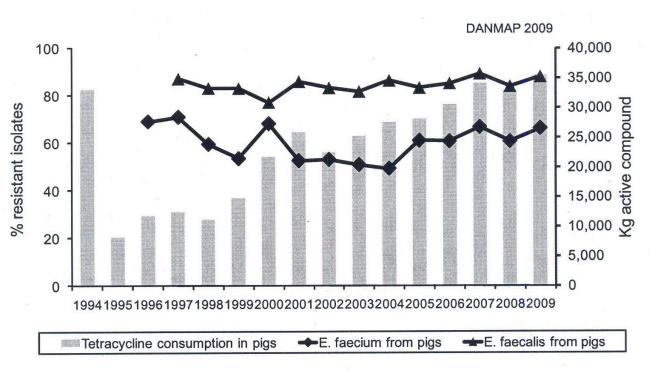


Figure 32 Trends in tetracycline resistance among Enterococcus faecium and Enteroccus faecalis from pigs and the consumption of tetracycline in pigs, Denmark, 1994-2009

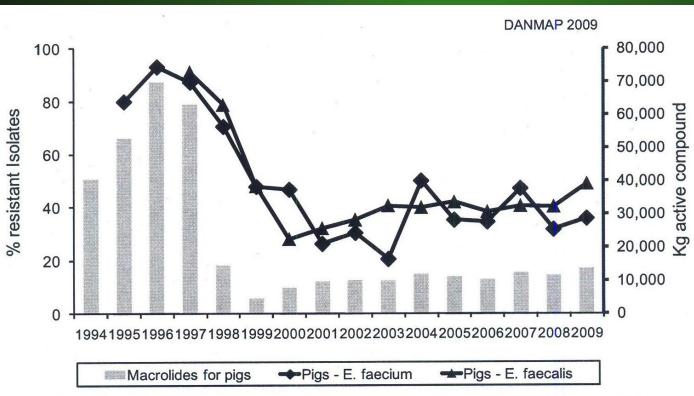


Figure 33. Trend in occurrence of resistance to erythromycin among Enterococcus faecium and Enterococcus faecalis from pigs and the consumption of macrolides for pigs, Denmark, 1994-2009

DANMAP 2009 – Human data

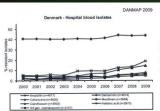


Figure 37a. Resistance (%) to ampicillin, gentamicin, cefuroxime, mecillinam, ciprofloxacin, nalidixic acid and 3rd generation cephalosporins in Escherichia coli blood isolates from humans, Denmark The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009



Figure 37b. Resistance (%) to gentamicin, cefuroxime, mecillinam, ciprofloxacin, nalidixic acid and 3rd generation cephalosporins in Escherichia coli blood isolates from humans, Denmark,

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009

Denmark - Hospital urine isolater

DANMAP 2009

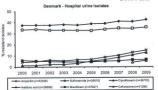


Figure 38a. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid, mecillinam and cefuroxime in Escherichia coli urine isolates from humans in hospitals, Denmark. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009. ses represents the number of isolates tested for susceptibility in 2009

DANMAP 2009

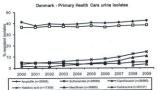


Figure 39a. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid, mecillinam and cefuroxime in Escherichia coli urine isolates from humans in primary health care. Denmark, The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009.

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009



DANMAP 2009

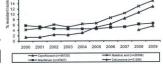


Figure 38b. Resistance (%) to ciprofloxacin, nalidixic acid, mecillinam and cefuroxime in Escherichia coli urine isolates from humans in hospitals, Denmark. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009.

The number (n) in parentheses represents the number of isolates ted for susceptibility in 2009

DANMAP 2009

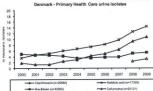
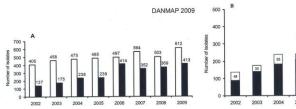
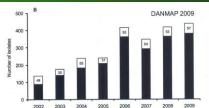


Figure 39b. Resistance (%) to ciprofloxacin, nalidixic acid, mecillinam and cefuroxime in Escherichia coli urine isolates from humans in primary health care, Denmark. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009.

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2009





ERINA

Figure 42a and 42b. Data on enterococcal blood culture isolates from 11 Danish Departments of Clinical Microbiology. (A) The number of enterococcal bacteraemias from 2002 through 2009. The white bars represent E. faecalis and the black bars represent E. faecium. (B) The number of ampicillin resistant and sensitive E. faecium blood culture isolates. The black bars represent the ampicillin resistant isolates and the white bars represent the ampicillin sensitive isolates.

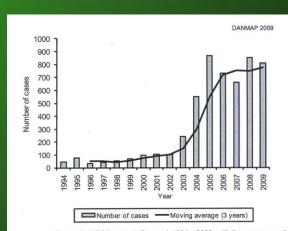


Figure 43. MRSA cases in Denmark 1994 - 2009, with three years moving average

DANMAP 2009 – Human data

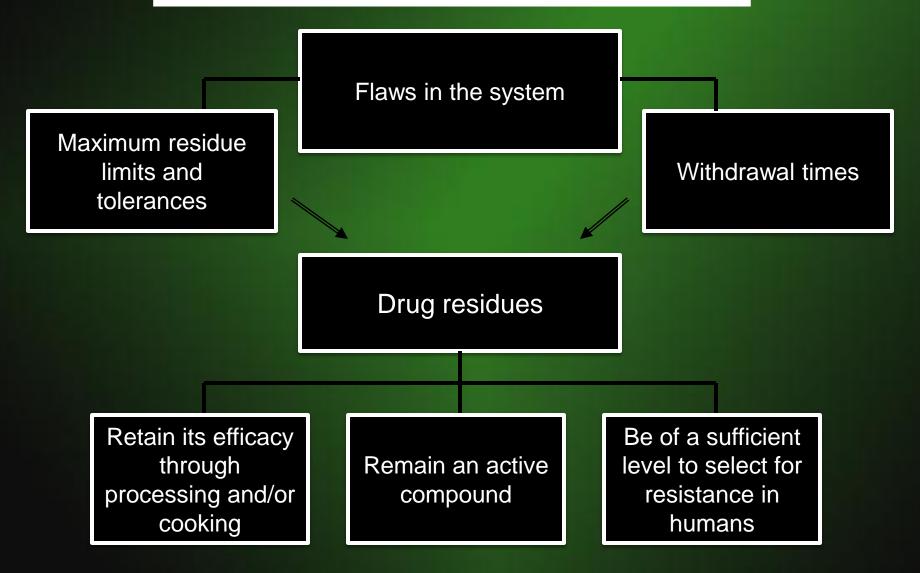
- Trends appear to be unclear
- Stable or increasing?
- A decline is not obvious



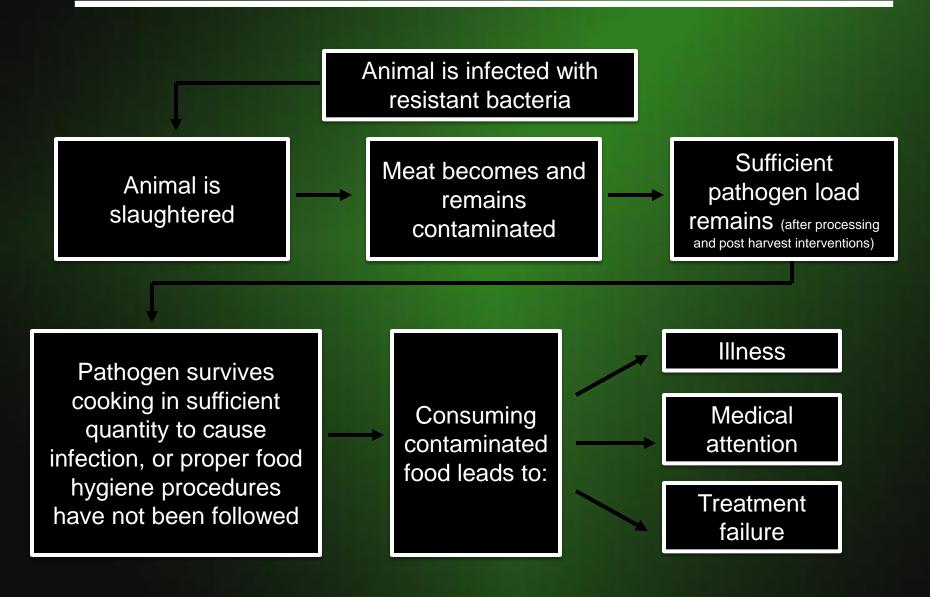
Denmark's Successes

- Elimination of the use of the following antimicrobials
 - virginiamycin
 - avoparcin
 - Avilamycin
- Significant decline in resistance in the following
 - Streptogramins in E. faecium in broilers and pigs
 - Avoparcin in E. faecium and E. faecalis in broilers and pigs
 - Avilamycin in E. faecium and E. faecalis in broilers

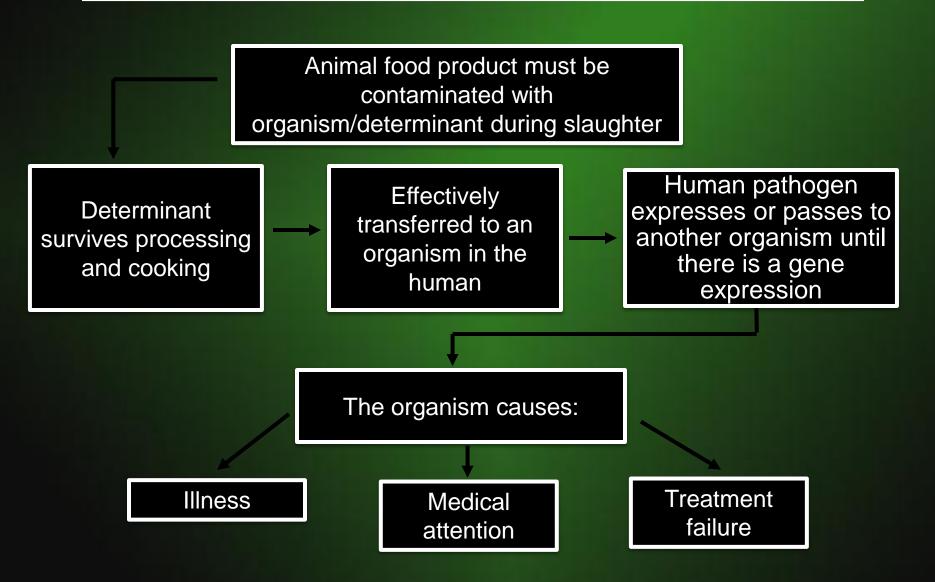
Antibiotic Residues



Direct Route of Transmission



Indirect Route of Transmission



Education Campaigns

- Judicious use
- Residue prevention
- Good management practices
- Follow instructions on labels
 - Anything else is ILLEGAL!



Follow your vet's instructions!!



More Education

- Federal regulation of use
- Withdrawal times
- Inspections and testing
- Accurate recordkeeping



Follow your vet's instructions!!



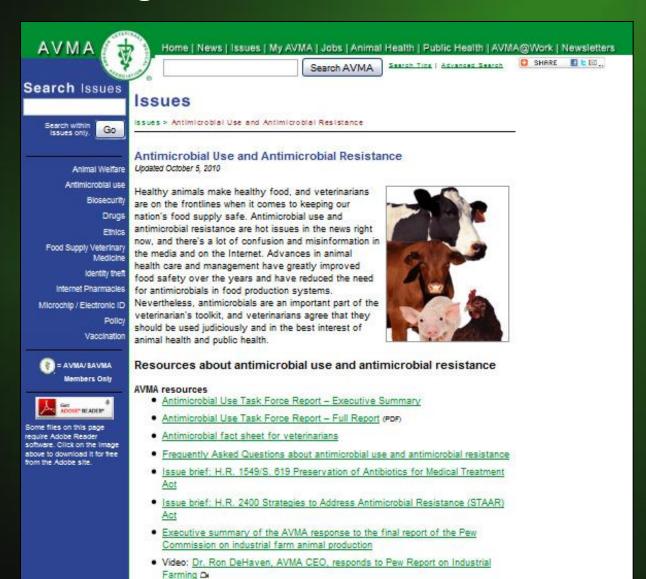
avmacan.avma.org/avma/home/





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www.avma.org/issues/antimicrobial_use_resistance.asp

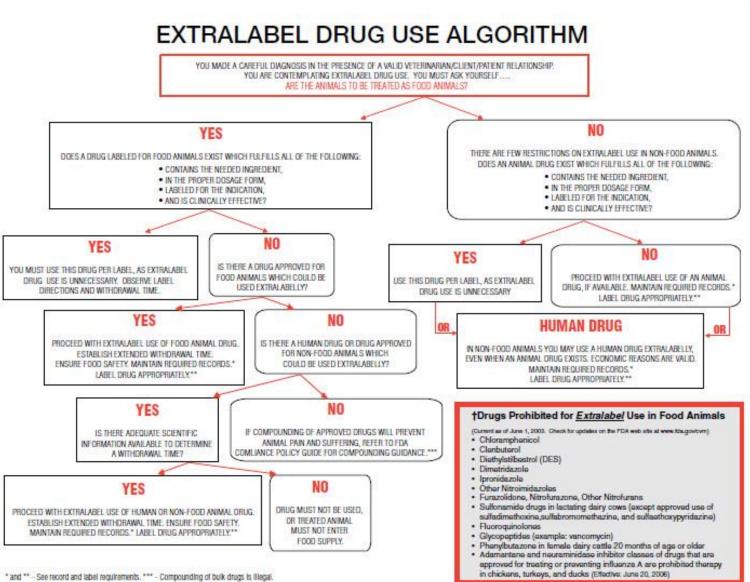


· Podcast: Antimicrobial resistance an

Podcast: Cause for concern: responding to the Pew Report



www.avma.org/reference/amduca/extralabel_brochure.pdf





Keepourfoodsafe.org



September 15, 2010

New Podcast: Antimicrobial Resistance and You

The FDA recently released new draft guidance on the appropriate uses for antimicrobial drugs in animal agriculture. The guidance calls for the judicious use of antimicrobial drugs in livestock to protect the effectiveness of these drugs as human therapies. In this new Chew on This podcast. Dr. Scott Hurd,



associate professor of veterinary diagnostic and production animal medicine at lowa State University, discusses the issues surrounding antibiotic resistance and what it means for you.

Chew on This is a podcast series that focuses on food safety and protecting our nation's food supply, featuring insights from America's leading food experts. You can find more podcasts on food safety here.



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