

Antibiotic Use in Animal Agriculture IS Linked to Rising Resistance: *What are the Policy Options?*



David Wallinga, MD, MPA
Keep Antibiotics Working
Institute for Agriculture & Trade Policy
dwallinga@iatp.org

What we know

Aarestrup FM, Wegener HC, Collignon P.

Resistance in bacteria of the food chain: epidemiology and control strategies. *Expert Rev. Anti Infect. Ther.* 2008, 6(5):733-750.

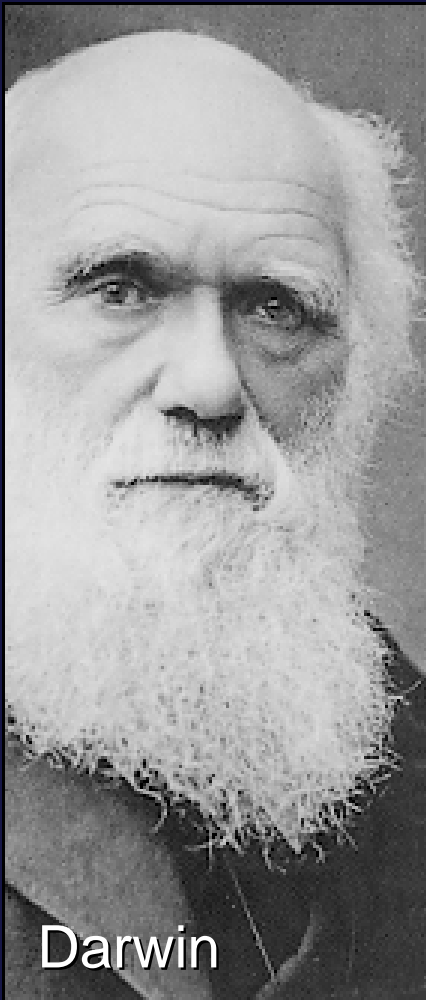
Very large quantities of antibiotics are used in industrialized livestock.



These antibiotics are often identical or belong to the same classes as human antibiotics.



These conditions favor selection, persistence and spread of antibiotic-resistant bacteria capable of causing infections in both animals and people.



Darwin

What we know

The Science Consensus

Aarestrup FM et al. Expert Rev. Anti Infect. Ther. 2008, 6(5):733-750

Antibiotic use in animal
agriculture DOES
contribute to rising
resistance transmitted
to humans



www.KeepAntibioticsWorking.com/new/indepth_keyevid.cfm

What we know

Resistance gets transmitted to people via contaminated food, other routes



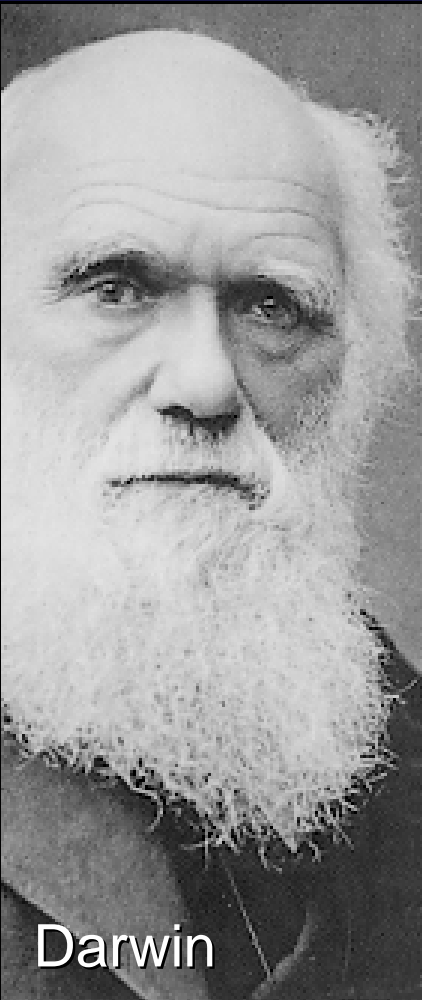
What we know – Microbiological fundamental **Resistance = Ecological**

- Extent of antibiotic use
- “Reservoirs” of resistance genes

Levy S. Scientific American. March 1998

“[B]ecause we share pathogenic and benign bacteria with other humans and animals and because bacteria readily transfer genes among themselves....once multi-resistant bacteria proliferate in a clinical or agricultural ecosystem, they can spread to other ecosystems.”

Nandi et al. 2004. PNAS



Darwin

What to do

Curb antibiotic overuse, 1976 → 2003

“The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage. The only means to curtail this trend is to control the indiscriminate use of these drugs. All areas of antibiotic usage deserve critical evaluation.”

Dr. Stuart Levy, NEJM **1976**; 295:583

“Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well.”

Smolinski MS, Hamburg MA, Lederberg J, editors. Microbial threats to health: emergence, detection, and response. Washington: Institute of Medicine. **2003**.

I. What we know

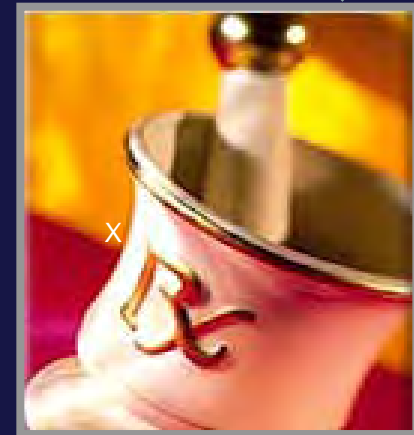
II. Reducing overuse: *Options*

- Self-regulation
- Market-led change
- State policies
- Federal policy options
 - Stricter regulation
 - Legislation

Tragedy of the Commons



Def. "Individuals acting independently in their own self-interest can ultimately destroy a shared resource even where it is clear that it is not in anyone's long-term interest for this to happen."



The issue

Industrialized livestock → **Huge antimicrobial use**
...but no tracking of that use

- 1) Institute of Medicine (1998),
Antimicrobial Resistance: Issues and
Options, Forum on Emerging Infections.
www.nap.edu
- 2) Animal Health Institute (2002), Press
Release dated September 30, 2002,
accessed at <http://www.ahi.org>.
- 3) Union of Concerned Scientists. (2001).
Hogging It! Estimates of Antimicrobial
Abuse in Livestock. www.UCSUSA.org

*Industry, IOM, NGO
estimates^{1,2,3} agree:*

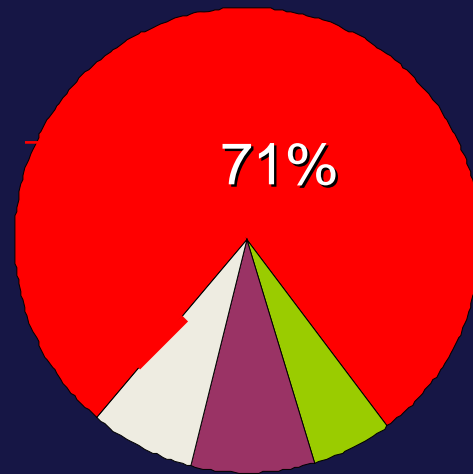


≈ 20 to 30 million lbs
in 2001

The issue

Industrialized livestock → **Huge antimicrobial use**
...but no tracking of that use

Nontherapeutic agricultural antimicrobials³ as a percentage of U.S. totals



Soaps, other, 8% 6%, Animal Tx
15%, Human Tx.

- 1) Institute of Medicine (1998), Antimicrobial Resistance: Issues and Options, Forum on Emerging Infections. www.nap.edu
- 2) Animal Health Institute (2002), Press Release dated September 30, 2002, accessed at <http://www.ahi.org>.
- 3) Union of Concerned Scientists. (2001). Hogging It! Estimates of Antimicrobial Abuse in Livestock. www.UCSUSA.org



Policy option #1

Collecting antibiotic use data

2008 Animal Drug User Fee Act (ADUFA)

“Section 5. Antimicrobial animal drug distribution reports

Section 5 amends section 512(l) of the FDCA. This section requires that for each new animal drug containing an antimicrobial active ingredient... the sponsor of the drug shall submit an annual report to the Secretary on the amount of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals.... Each report shall specify the amount of each antimicrobial active ingredient by container size, strength, and dosage form; by quantities distributed domestically and quantities exported; and by dosage form, including, for each such dosage form, a listing of the target animals, indications, and production classes that are specified on the approved label of the product.”

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_reports&docid=f:hr804.110.pdf

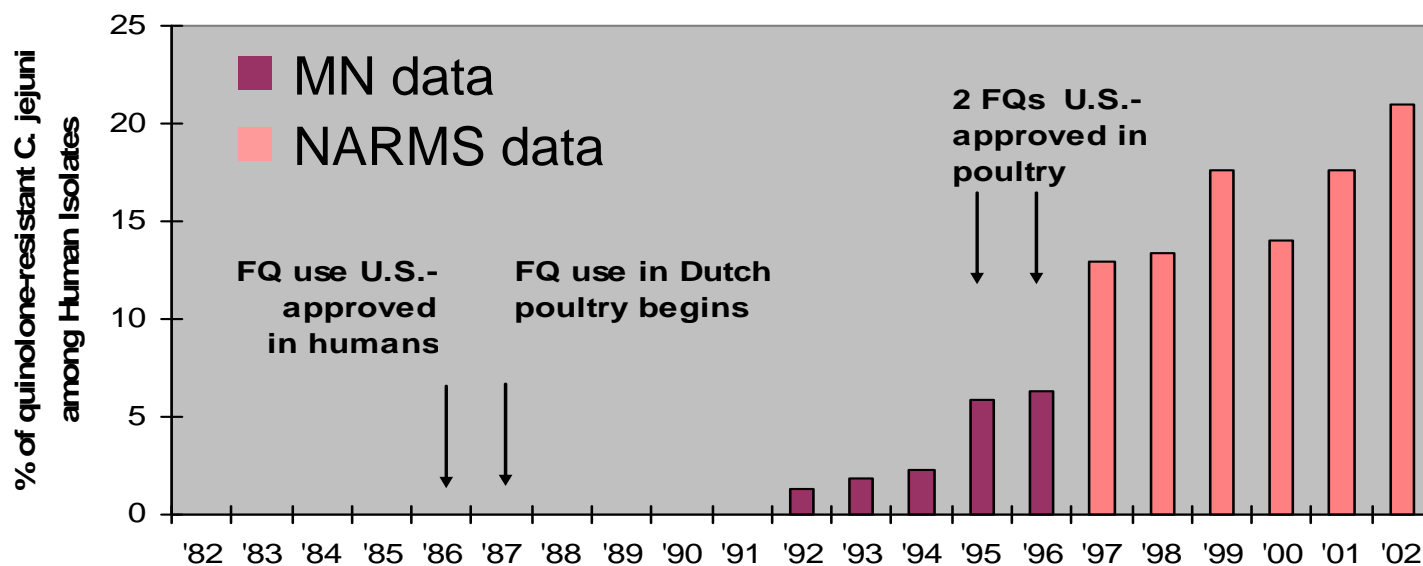


Issue

Agricultural overuse of fluoroquinolones

Considered one of the most valuable antibiotic classes for human infections. Commonly prescribed for severe foodborne disease. Beginning in 1995, added to water for treating flocks. www.FDA.gov/cvm

Fluoroquinolone resistance in human *Campylobacter*



Sources: Data on MN quinolone resistant *C. jejuni* from Smith KE et al. 1999. Other data on FQ-resistant *C. jejuni* from NARMS. See Gupta A et al. 2004. Estimates of FQ rx. use in humans from Linder J, et al. 2005.



Policy option #2a

Withdraw FDA approval for old therapeutic antibiotics “not shown to be safe”

Poultry FQ ban, 2000 - 2005

- “[U]se of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant Campylobacter, a human pathogen, in poultry; this resistant Campylobacter is transferred to humans and is a significant cause of the development of resistant Campylobacter infections in humans.”
- Eating contaminated chicken left an estimated **153,580** Americans with fluoroquinolone (Cipro)-resistant Campylobacter, according to FDA. 66 FR 6623-6624 (01/22/01), using 1999 data.
- Still took 5 years to get Baytril off the market

Source:

Food and Drug Administration.
Enrofloxacin for Poultry;
Opportunity For Hearing.
Department of Health and Human Services.
Federal Register Notice dated 10/26/00.



Question:

Can the FDA act in a timely way?

“The Agency’s experience with contested, formal withdrawal proceedings is that the process can consume extensive periods of time and Agency resources.”

– then CVM Director, Stephen Sundlof, DVM

Fluoroquinolones – 5 years

DES (carcinogen) - 6 years

Nitrofurans (carcinogen) - 20 years

Letter from Dr. Stephen Sundlof, Director, Center for Vet Medicine, FDA,
February 28, 2001 in response to CSPI Citizen Petition



Policy option #2b

Withdraw FDA approval for old **non-therapeutic** antibiotics “not shown to be safe” (also under FFDCA)

- 1977: FDA proposes ban on non-therapeutic penicillin, tetracyclines in animal feeds.^{1,2}
- 1978: Congress directs FDA to hold actions in abeyance pending further study.

1. U.S. Food and Drug Administration. Notice of opportunity for hearing. Penicillin-containing premixes; Opportunity for hearing. *Federal Register* 1977; 42: 43772-43793.
2. U.S. Food and Drug Administration. Notice of opportunity for hearing. Tetracycline (chlortetracycline and oxytetracycline)-containing premixes; Opportunity for hearing. *Federal Register* 1977; 42: 56264-56289.

FDA has never removed an approved antibiotic feed additive from market

Supported by:

- **World Health Organization**

WHO. *The Medical Impact of the Use of Antimicrobials in Food Animals*, Report of a WHO Meeting; 1997 October 13-17; Berlin, Germany.


- **World Veterinary Association.**

WVA. *Antibiotics Should Not Be Used As Growth Promotants*. Press release, Sept. 9, 1998 at www.worldvet.org/press27.htm.



Supported by:

- **Institute of Medicine.** Smolinski MS, **Hamburg MA**, Lederberg J, editors. 2003.

 DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Testimony of

Joshua M. Sharfstein, M.D.

Principal Deputy Commissioner of Food and Drugs

Food and Drug Administration

Hearing on

**H.R. 1549, "PRESERVATION OF ANTIBIOTICS FOR MEDICAL TREATMENT
ACT OF 2009"**

Committee on Rules

U.S. House of Representatives



Public health issue

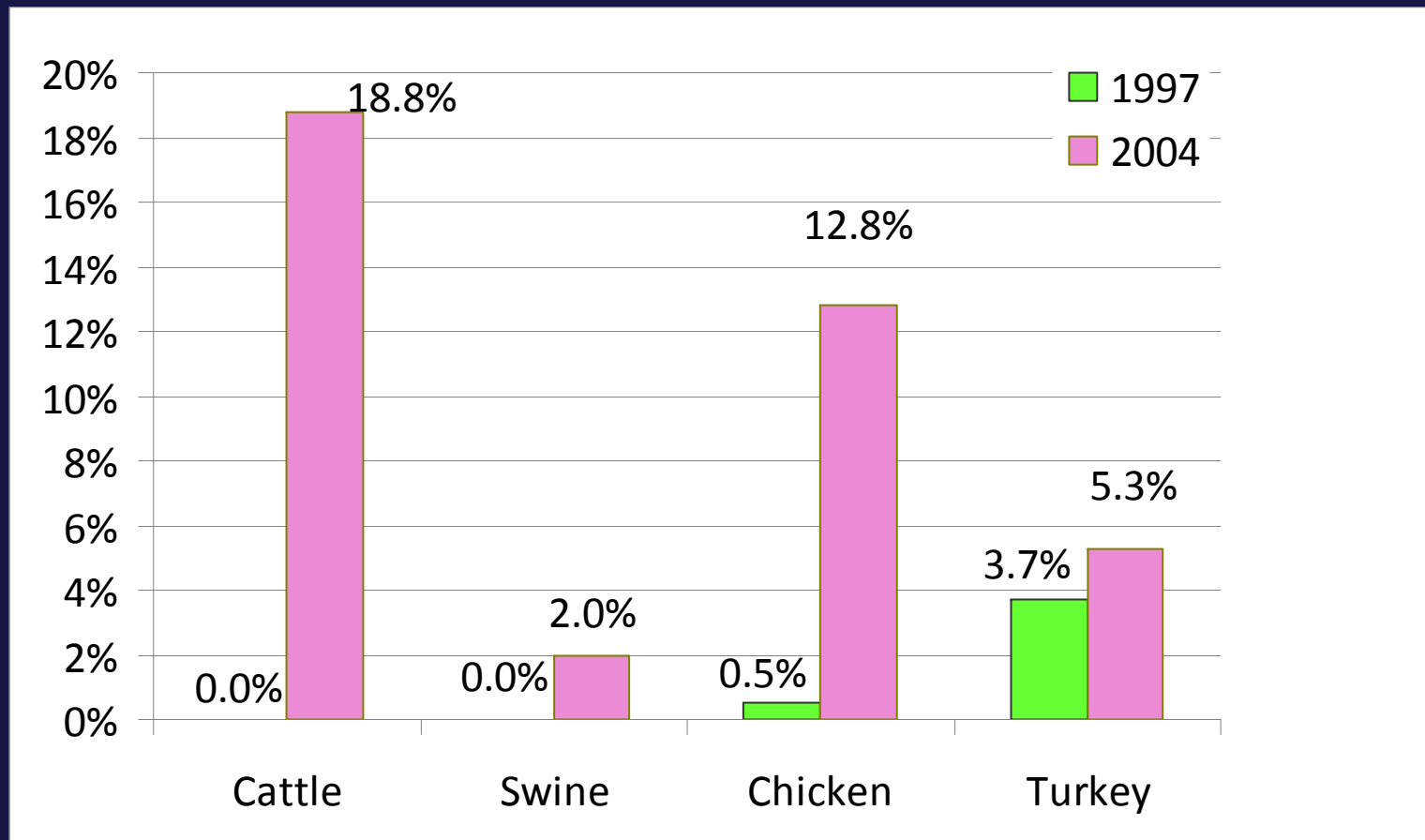
Cephalosporin use in food animals

- Extended spectrum antibiotics
- 3rd & 4th generation cephalosporins (*ceftriaxone, cefepime*) are important “last lines of defense” against severe, systemic *Salmonella* or *E coli* infections, other resistant infections.
- Widely used in food animals
 - *Ceftiofur* = 3rd gen ceph widely used in cattle, poultry worldwide
 - *Cefquinome* = 4th gen ceph, used in Europe



Ceftiofur-resistant Salmonella in animals

Linked to ceph-resistance found in meat, humans



Source: U.S. Department of Health and Human Services, National Antimicrobial Resistance Monitoring System/Enteric Bacteria (NARMS/EB) Salmonella Annual Veterinary Isolates Data, U.S. Department of Agriculture, <http://www.ars.usda.gov/Main/docs.htm?docid=6750&page=4>, 2006.



Public health issue

Rising cephalosporin resistance

Use of 3rd & 4th generation cephalosporins in food animals results in development of pathogenic bacteria – including *Salmonella* and *E coli* – carrying multi-drug resistance, such as ESBL-type. Collignon & Aarestrup, 2007.

ESBL-carrying bacteria often are resistant to cephalosporins, as well as to fluoroquinolones, aminoglycosides, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim.



30,000 British annually are infected with deadly, ESBL-producing *E coli*. ESBL strains increasingly are community-acquired. Helfand et al. 2006; Rodriguez-Bano 2006.



This strain found in 1 in 4 foreign retail chickens tested from UK supermarkets. Collignon P, Aaerstrup. 2007



Policy issue

“Extra-label” cephalosporin use

AMDUCA, the Animal Medicinal Drug Use Clarification Act of 1994 (Public Law 103-396), permits veterinarians to prescribe extra-label uses of approved animal and human drugs in animals.

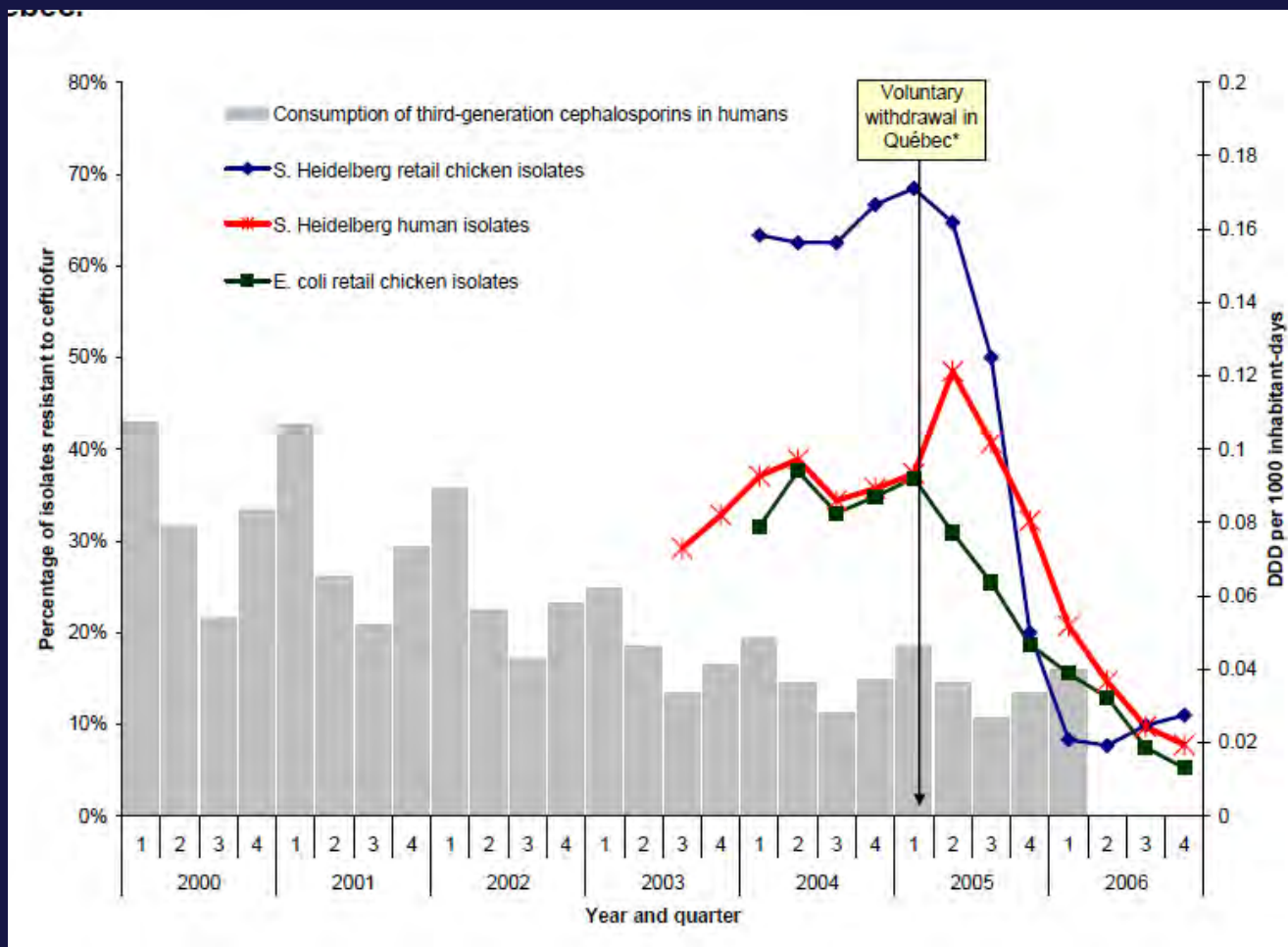
No extra label veterinary use was allowed prior to 1994.

Example: Antibiotic injections in 27 hatcheries
(producing > 500 million birds per year)

| | Ceftiofur | Gentamicin |
|---------------------------------------|-------------------------------|-------------------------------|
| Egg injections (Off-label) | 4 chicken hatcheries | 6 chicken |
| Bird injections | 3 chicken 1 turkey | 4 chicken 3 turkey |
| Total | 8 hatcheries (30%) | 13 hatcheries (48%) |

Quebec's success reducing extra-label use, and resistance

Declining ceftiofur resistance in retail chicken and human *E. coli* and *Salmonella* following withdrawal of extra-label use in Quebec hatcheries





Policy option #3

Prohibit “extra-label” cephalosporins*

Under AMDUCA, FDA may issue a prohibition order if it finds extralabel use of a drug in animals presents a risk to public health.

Order of Prohibition: July 3, 2008

“[I]t is likely that the extralabel use of cephalosporins in food-producing animals is contributing to the emergence of cephalosporin-resistant foodborne bacteria.”

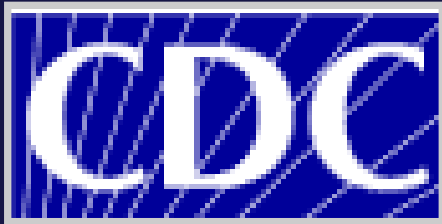
Food and Drug Administration. Extralabel Animal Drug Use; Order of Prohibition – Final Rule. [Federal Register: July 3, 2008 (Volume 73, Number 129)] Accessed <http://edocket.access.gpo.gov/2008/E8-15052.htm>

What happened?

July 3 **FDA Issues Final Order**, effective October 1, 2008

Aug 15 **FDA Extends Comment Period, Delays Final Rule until November**

Nov 7 **“CDC fully supports the FDA’s proposed order of prohibition.”**



“Human disease surveillance has shown an increase in multi-drug resistant (MDR) *Salmonella* and the emergence of resistance to antimicrobial agents important in human medicine, such as third generation cephalosporins in *Salmonella* and *E coli*, and fluoroquinolones in *Campylobacter*, *Shigella*, and *Salmonella* including *S. typhi*.” *Lonnie King, DVM, Director, CDC’s National Center for zoonotic, Vector-Borne and Enteric Diseases, Letter to Bernadette M. Dunham, DVM, Director, FDA’s Center for Veterinary Medicine, dated 7 November 2008.*

Nov 25 **FDA Revokes Order** Prohibiting Extralabel Cephalosporin Use



Policy option #4

FDA could raise the bar for approving new animal uses of human antibiotics

Following its Baytril experience, the FDA released its **Final Guidance to Industry #152, in October 2003**. Goals were:

- A more formalized risk-assessment process
- Criteria to minimize the risk of a regulatory “bad call”, i.e. approving a new animal antibiotic that would prove not “safe” in terms of resistance.

FDA (2003) Guidance for Industry #152: Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern. Available at www.fda.gov/cvm.



Cefquinome – a 4th gen cephalosporin

Europe

- Cefquinome has been widely used in cattle (since 1994), swine (1999), and horses (2005).
 - Lots of cephalosporin-resistant E. coli and Salmonella in animals, including ESBL-type resistance, and in humans.
 - In U.S.: Cephalosporin resistance in Salmonella & E coli still rare. [CDC just reported 2nd case of domestically-acquired human Salmonella with CTX-M resistance. Sjölund M et al 2008]

U.S.

- Approval sought for cefquinome use in treating respiratory disease in cattle
 - Many alternatives already available



Cefquinome & Guidance #152

The Washington Post

DISTRICT EDITION

\$1.50

SUNDAY, MARCH 4, 2007

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Weather

Today: Partly sunny.
High 46. Low 29.
Monday: Mostly sunny.
High 53. Low 29.

Details, C12

150TH YEAR No. 89 MI DC

INSIDE

THE NATION

The Reverser

In recent weeks, President Bush has changed his stance on a series of issues on which he once refused to budge. A5

Changes at Walter Reed: The Army revises its command structure to improve its operations. A4

THE WORLD

The Newspaper Tree

A woman in Darfur posts war news and more on a tree. A14

Protest in Russia: Pro-democracy demonstrators beaten. A14

OUTLOOK

Green Begets Green

Businesses are coming to believe that they can save the world, and make a profit along the way. B1

METRO

Suspicious Shooting

The FBI is investigating the death of a Russian intelligence expert. C1

Lunar eclipse: Feeling blue? C11

STYLE

Drive-in Art

The doors almost came off their

Timeline

Sept '06 For the first time ever, the FDA's Veterinary Medical Advisory Committee recommends against approving a new antibiotic due to resistance concerns.

Mar '07 Letters from **AMA, APA, IDSA** and to **APHA** all urge FDA not to approve

Apr '07 cefquinome's use in cattle.

Today Cefquinome still under consideration. **Why?** Because FDA considers cefepime, the human analog, not "critically important" because it's not used for treating foodborne illness.

FDA Rules Override Warnings About Drug

Cattle Antibiotic Moves Forward Despite Fears of Human Risk

By RICK WEISS
Washington Post Staff Writer

The government is on track to approve a new antibiotic to treat a pneumonia-like disease in cattle, despite warnings from health groups and a majority of the agency's own expert advisers that the decision will be dangerous for people.

The drug, called cefquinome, belongs to a class of highly potent antibiotics that are among medicine's last defenses against several serious human infections. No drug from that class has been approved in the United States for use in animals.

The American Medical Association and about a dozen other health groups warned the Food and Drug Administration that giving cefquinome to animals would probably speed the emergence of microbes resistant to that important class of antibiotics, which has been used, like other drugs,



Guidance #152 & Re-review of existing animal antibiotics?

- **Guidance #152** never applied to already-approved antibiotics, subsequent to 2003, nor is there a timeline to do.
- Pursuant to #152 criteria, Academy of Pediatrics, APHA, & 3 other groups have petitioned FDA to withdraw certain medically important drugs from feed/water use.

Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152. April 7, 2005. FDA docket no. 2005P-0139/CP1

I. What we know

II. Options for reducing antibiotic overuse

- Self-regulation
- Market-led change
- Policy options
 - Stricter regulation
 - Federal legislation





Policy option #5

Legislation directing FDA re-review of the safety of nontherapeutic abx in feed

“Preservation of Antibiotics for Medical Treatment Act”

S. 619: Senators Feinstein, Reed, Sanders, Snow [R-ME]

HR 1549 Rep. Slaughter and 50 co-sponsors, incl. McCollum [D-MN]

- Reviews safety of certain critical antibiotics for nontherapeutic purposes in food-producing animals
- Penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide

KEEP ANTIBIOTICS WORKING.com *The Campaign to End Antibiotic Overuse*

Take Action News

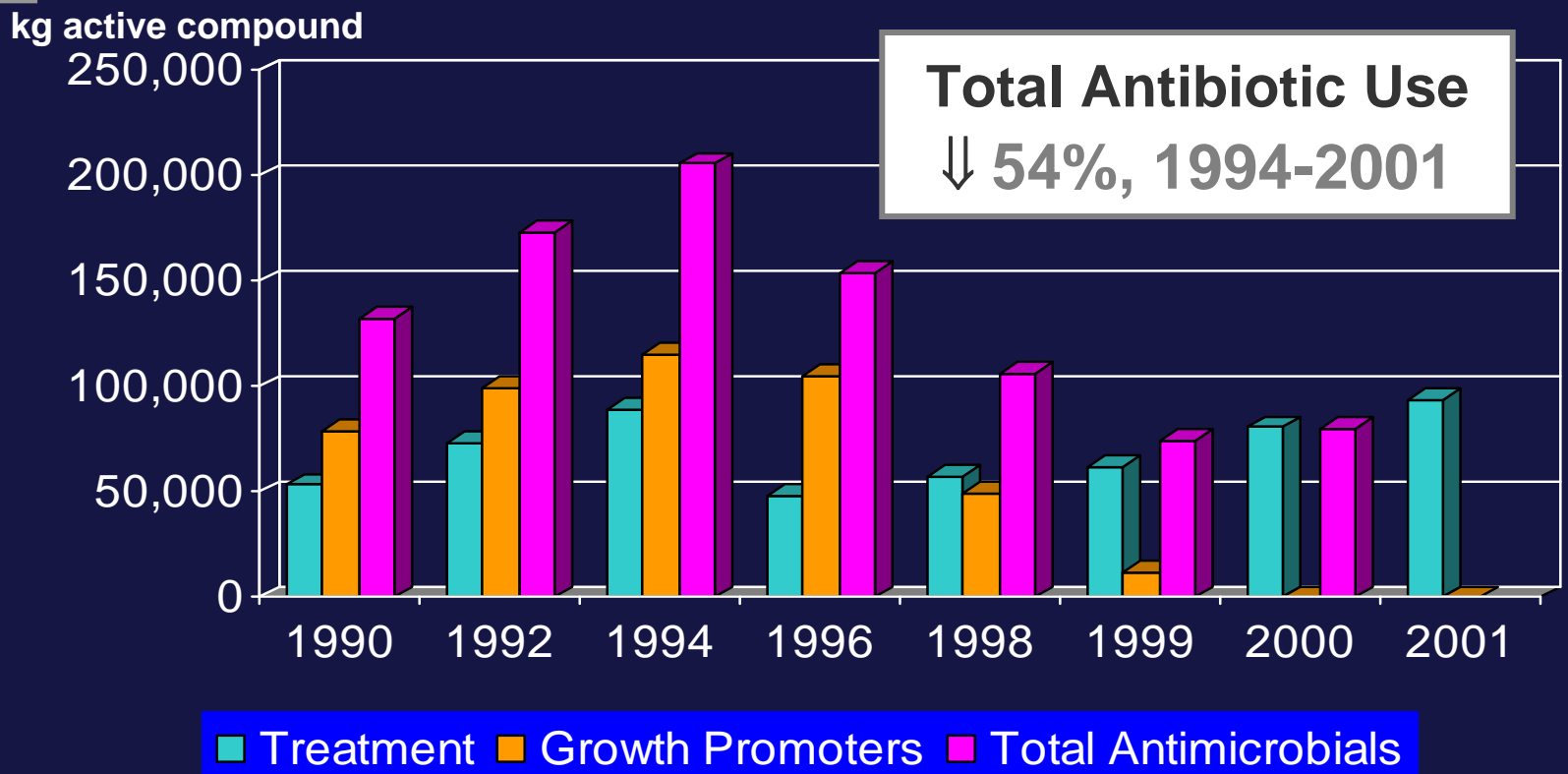
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| The Basics | In Depth: U.S. Government Involvement |
| Vulnerable Populations | <ul style="list-style-type: none">• Legislation• Federal Agencies<ul style="list-style-type: none">OverviewFood and Drug AdministrationEnvironmental Protection AgencyUnited States Department of Agriculture |
| In Depth | |
| For Consumers | |
| The Campaign Resources | 1. LEGISLATION |
| Contact Us | 1a. Phase-out of nontherapeutics KAW strongly supports federal bills to phase out "nontherapeutic" use (i.e., routine use in livestock and poultry that are not sick) of medically important antibiotics as feed additives. (See the bill summary .) S. 549 was introduced by Senators Ted Kennedy (D-MA), Olympia Snowe (R-ME), Sherrod Brown (D-OH), and Jack Reed (D-RI). Representative Louise Slaughter (D-NY) sponsored H.R. 962 . Also see the list of antibiotics covered by the legislation as well as a summary of their important clinical uses . |
| Sitemap | |
| Home | |

More than 350 organizations have [endorsed](#) this measure, including the American Nurses Association, American Academy of Pediatrics, American Public Health Association, and numerous other medical, public health, environmental, sustainable agriculture, and other groups.



Evidence this approach works:

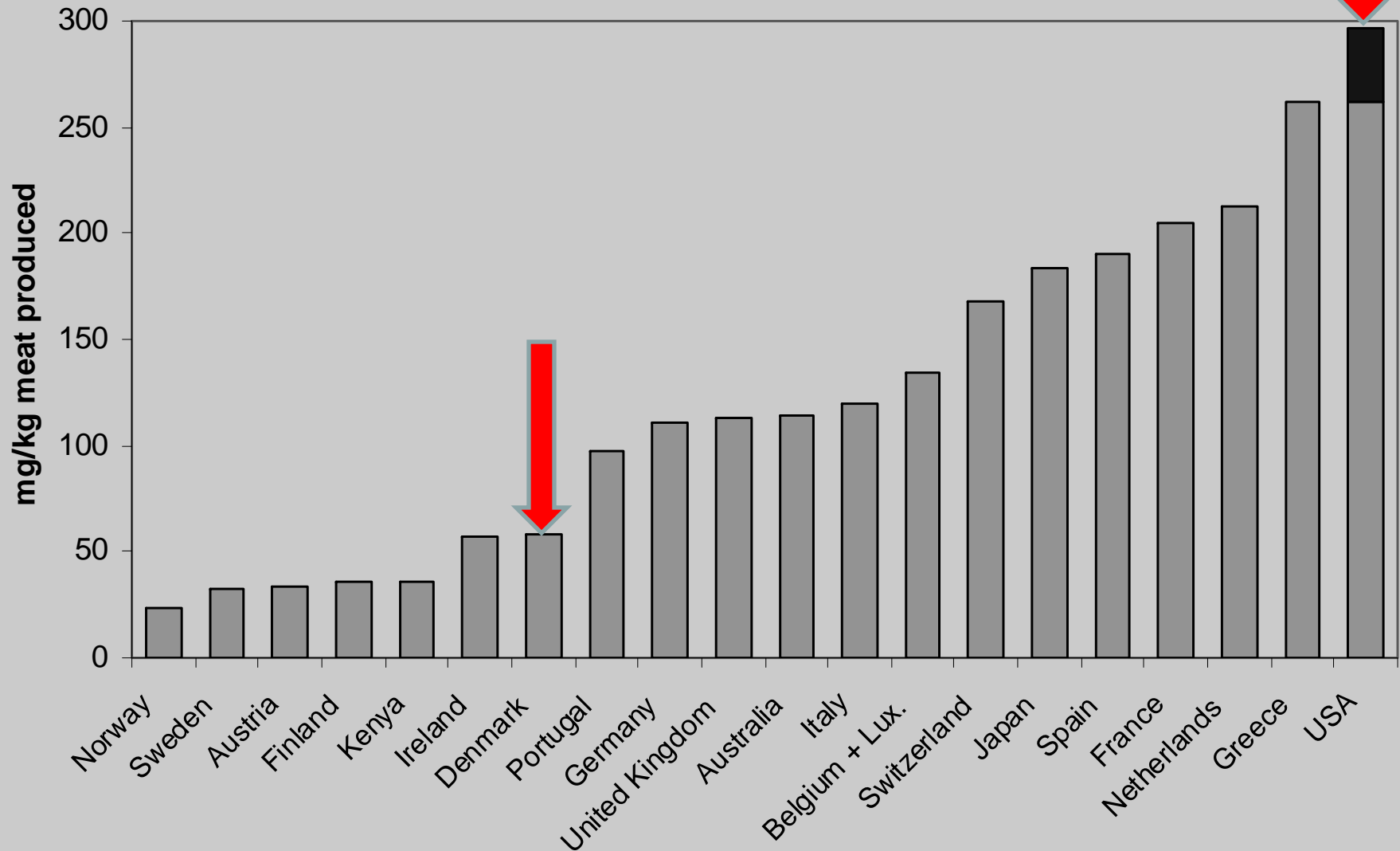
Denmark ('98-'99); Sweden (1986)



Eliminating the routine use of antibiotics in livestock reduces human health risks without significantly harming animal health or farmers' incomes.

WHO 2003. Wegener HC. Curr Opin Micro 2003.

U.S. antimicrobial use in meat production vs. other countries



Tobacco Use and Antibiotic Use

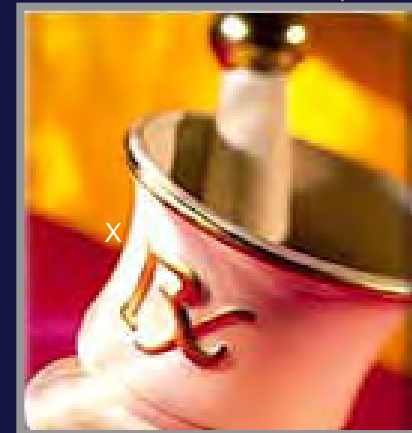
What's the physician's role?

- Who spoke up for the right to clean, healthy air?
- Who began environmental change by limiting smoking in hospitals?
- Who will speak up for the common good of effective antibiotics?

Tragedy of the Commons



Def. "Individuals acting independently in their own self-interest can ultimately destroy a shared resource even where it is clear that it is not in anyone's long-term interest for this to happen."





David Wallinga, MD, MPA
www.HealthObservatory.org
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dwallinga@iatp.org