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PRESERVING EFFECTIVE ANTIBIOTICS:

Strong Public Health Action Needed to Avoid the 'Tragedy of the Commons'

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Abstract: In 1968, ecologist Garrett Hardin described "The Tragedy of the Commons"[1] , the notion that individuals will deplete a shared resource by acting short-term out of self-interest, despite everyone's understanding that to do so runs contrary to their long-term best interests. So it is with effective antibiotics.

The overall usage of antibiotics is perhaps the major factor in driving bacteria to become resistant to them. That is fundamental to microbiology. Yet in much of the world today, there is routine and enormous use of antibacterials in animal agriculture. This usageensures farm environmentsare replete with both the residues of antibiotics and the genetic determinants of antibiotic resistance. These conditions have helped to create what some call a "perfect storm", i.e. conditions ripe for the formation and spread of resistance that is then transmitted via various routes to the human population. In short, the overuse of animal antibiotics by some few parties, acting out of their own self-interest, is undercutting the effectiveness of antibiotics for the rest of us.

This talk employs the very active debate about the scale and impact of this antibiotic usage in U.S. animal agriculture to illuminate possible better policies and practices that can support public health as well as better animal health.In the United States, it was only when Congress passed the 2008 amendments to the Animal Drug User Fee Act that data on sales of antimicrobials were first collected and publicly reported by the U.S. Food and Drug Administration. Today, these data indicate over 80% of all U.S. antimicrobials are sold for use in animal agriculture – more than 29 million pounds each year (Tables 1&2) – most of them from medically important antibiotic classes, including penicillins, tetracyclines, macrolides, cephalosporins, etc. Ninety percent of animal antimicrobials are added to animal feed or drinking water, for what are often non-therapeutic, economic purposes such as growth promotion and feed efficiency.[2]

Aside from the recent collection of data on antibiotic sales, federal agencies regulating animal antibiotics in the United States have demonstrated little action to date to restrict or reduce such use. In

Table 1. Antimicrobial Drugs FDA-Approved for Use in Food-Producing Animals 2010 Sales and Distribution Data Reported by Drug Class

	Antimicrobial Class	Annual Totals[1]	
		Kilograms	pounds
Domestic	Aminoglycosides	200,794	441,747
	Cephalosporins[2]	24,588	54,094
	Ionophores	3,821,138	8,406,504
	Lincosamides[2]	154,653	340,237
	Macrolides[2]	553,229	1,217,104
	Penicillins[2]	870,948	1,916,086
	Sulfas[2]	506,218	1,113,680
	Tetracyclines[2]	5,592,123	12,302,671
	NIR[2,3]	1,517,447	3,338,383
Export[4]	Tetracyclines[2]	9,968	21,930
	NIRE[2,5]	206,566	454,445
	Total	**13,457,672**	**29,606,878**

Source: U.S. Food and Drug Administration, ADUFA Reports: 2010 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Accessed December 28, 2012 at www.fda.gov.

[1] kilograms or pounds of active ingredient.
[2] Includes products labeled for use in multiple species, including both food- and nonfood-producing animals.
[3] NIR = Not Independently Reported. Antimicrobial classes for which there were less than three distinct sponsors (companies) actively marketing products were not independently reported, including: Aminocoumarins, Amphenicols, Diaminopyrimidines, Fluoroquinolones, Glycolipids, Pleu romutilins, Polypeptides, Quinoxalines, Streptogramins.
[4] Only includes exports of FDA-approved, US-labeled antimicrobial drugs approved for use in food-producing animals. Export totals from 2009 summary report inadvertently included some non-FDA-approved antimicrobial drug products, which resulted in an incorrect, larger number.
[5] NIRE = Not Independently Reported Export. Antimicrobial Classes for which there were less than three distinct sponsors exporting products were not independently reported. These classes include: Aminocoumarins, Aminoglycosides, Amphenicols, Cephalosporins, Diaminopyrimidines, luoroquinolones, Glycolipids, Ionophores, Lincosamides, Macrolides, Penicillins, Pleuromutilins, olypeptides, Sulfas, Quinoxalines, Streptogramins.

2012, there was limited action to end the off-label injection of cephalosporins into hatchery eggs, for example[3] ; and, in 2005 the FDA successfully removed fluoroquinolones from therapeutic use in poultry flocks (albeit not from swine production). However, despite the bulk of antibiotics being used in animal feed, no FDA-approved feed antibiotics has ever been removed from the market. In mid-2012, the FDA announced a framework for pharmaceutical companies to voluntarily withdraw their non-therapeutic feed antibiotic products from the market, reducing sales and profits, while putting remaining products solely under veterinary control; it remains unclear what motivation the pharmaceutical industry has for doing so. Even the changes to antibiotics

Table 2. Marketed Antimicrobial Drugs and Drug Classes FDA-Approved for Use in Food-Producing Animals in the United States

Aminocoumarins	**Fluoroquinolones**	**Macrolides**	**Quinoxalines**
Novobiocin	Danofloxacin	Carbomycin	Carbadox
	Enrofloxacin	Erythromycin	
Aminoglycosides		Oleandomycin	**Streptogramins**
Apramycin	**Glycolipids**	Tilmicosin	Virginiamycin
Gentamicin	Bambermycins	Tulathromycin	
Neomycin		Tylosin	**Sulfas**
Spectinomycin	**Ionophores**		Sulfachlorpyridazine
	Laidlomycin	**Penicillins**	Sulfadiazine
Amphenicols	Lasalocid	Amoxicillin	Sulfadimethoxine
Florfenicol	Monensin	Ampicillin	Sulfamerazine
	Narasin	Cloxacillin	Sulfamethazine
Cephalosporins	Salinomycin	Penicillin	Sulfaquinoxaline
Ceftiofur	Semduramicin		
Cephapirin		**Pleuromutilins**	**Tetracyclines**
	Lincosamides	Tiamulin	Chlortetracycline
Diaminopyrimidines	Lincomycin		Oxytetracycline
Ormetoprim	Pirlimycin	**Polypeptides**	Tetracycline
		Bacitracin	
		Polymixin B	

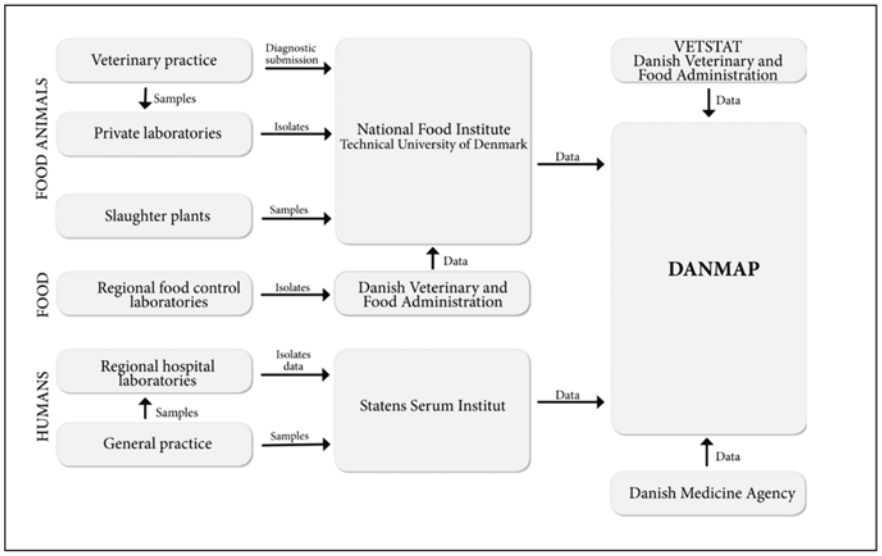
Source: U.S. Food and Drug Administration, ADUFA Reports: 2010 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Accessed December 28, 2012 at www.fda.gov.

sales and usage optimistically envisioned by the FDA would only take place several years in the future.

Denmark offers a contrasting example – one where public policy has better reflected effective antibiotics as a part of the public commons. In Denmark, a major meat producer and the world's largest exporter of pork, there has been nearly 15 years of deliberate public policy focused on reducing the overall usage of antibiotics, in both human and animal settings. An announced phase-out of antibiotic growth promoters, first in poultry and then in swine was accompanied by government monitoring, research and assistance to farmers to help accomplish the phase-out.

In 1995, the Danish Ministry of Food, Agriculture and Fisheries and the Danish Ministry of Health jointly began DANMAP, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. The timing, three years before the poultry phase out had even begun, was so that a programme would be in place to follow the eventual impact of the growth promotion phase out. As its name suggests, DANMAP integrates information about the consumption of antimicrobials in human, veterinary and food production settings, as well as the occurrence of antimicrobial resistance in humans, in animals and on food.

Dr. Frank Aarestrup, head of the EU Reference Laboratory for Antimicrobial Resistance and the WHO Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens at the National Food Institute, Technical University of Denmark, states that Denmark's subsequent use of antimicrobials dropped by 60 percent, measured by the amount of antimicrobials used per unit of meat produced[4]. According to a 2002 expert panel convened by the World Health Organization, the Danish antimicrobial growth promoter phase-out accomplished a reduction in public health risk due to resistance but no or minimal consequence to animal health, to farm



Source: DANMAP Organization and workflow www DANMAP.org

productivity or earnings, or to consumer prices. Today, the United States uses what is estimated as about five times more antimicrobials per pound of meat produced than does Denmark, and ten times more than Norway or Sweden[5].

Another key early change in Denmark was the restriction on veterinary profits from the sales of antibiotics beginning in 1995; it was a change supported by the Danish Veterinary Association, possibly in part because larger hog and cattle producers were then required to receive monthly veterinary visits. In effect, the veterinary profession adopted a changed role as advisors rather than as drug providers. To our knowledge, the FDA is not considering any restrictions on veterinarian sales or profits from drug sales at this time.

More broadly, the global epidemic of antibiotic resistance is an ecological problem. And the microbial ecosystem respects neither the borders of the United States nor of Denmark. Because trade in pharmaceuticals, in animal feeds, in meat products and, to a lesser extent, in food animals, has become increasingly global, the risk is the Tragedy of the Commons with respect to effective antibiotics will increasingly be a supranational rather than a national problem. Much of this trade is conducted by global corporations with a fiduciary duty to their shareholders to maximize profit without regard for the public health consequences. In addition, the impact of bilateral and multilateral trade agreements over the last three decades has been to decrease the ability of national entities to impose public health-based restrictions on corporate activities. The lack of any supranational public health authority with any regulatory powers lends further pessimism to the prospect of preserving a global commons of available antibiotics effective for sick animals and people who need them.

1. Hardin G, Hardin, G. (1968). The Tragedy of the Commons.Science 1968.162 (3859): 1243–1248.

2. Office of Congresswoman Louise Slaughter, US House of Representatives, Press release dated May 11, 2011. Accessed December 28, 2012 at http://bit.ly/TnU5SY.

3. Food and Drug Administration.Cephalosporin Order of Prohibition Goes Into Effect. April 4, 2012. Accessed December 28, 2012 at www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm299054.htm.

4. Aarestrup FM. Sustainable farming: Get pigs off antibiotics. Nature 2012.486: 465–466.

5. Testimony of Dr. Frank MøllerAarestrup and Dr. Henrik Wegener, U.S. House of Representatives Committee on Rules,Hearing on H.R. 1549, the Preservation of Antibiotics for Medical Treatment Act of 2009, JULY 13, 2009. Page 72. Available at http://democrats.rules.house.gov/111/ojhearings/111_hr1549_oj.pdf.