Scientific Analysis of The Preservation of Antibiotics for Medical Treatment Act of 2011

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The Preservation of Antibiotics for Medical Treatment Act of 2011

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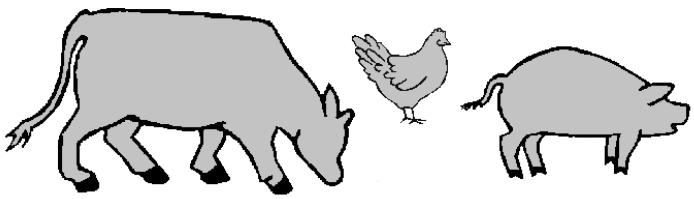

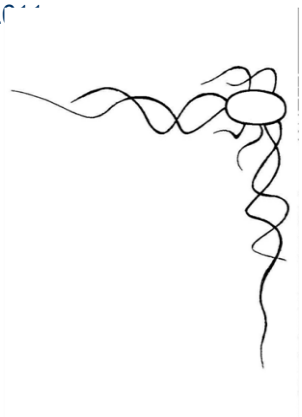

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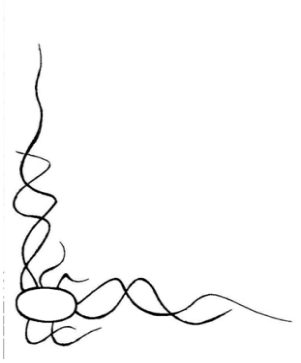


Executive Summary

Resistance to antibiotics is a public health issue of rising urgency. Drugs that we rely on to treat infections, such as strep throat, pneumonia, and gastroenteritis, are losing effectiveness as bacteria develop resistance and proliferate. New antibiotic approvals are in decline – only two have been approved since 2008 – so our resources for fighting life-threatening diseases are dwindling. This increasing resistance to antibiotics creates the potential for a future where the medical system is unable to provide effective treatment against bacterial infections.

The emergence and spread of resistant bacteria is an inherent consequence of using antibiotics. These drugs eliminate susceptible bacteria, but a small percentage of resistant bacteria remain, reproduce and thrive despite continued application of antibiotics. Increased use leads to increased resistance. To combat this problem, the solution seems clear – reduce the use of antibiotics.

Antibiotic use is appropriate to treat sick humans or animals; these drugs are critical tools in managing health. 80% of the total antibiotics produced in the United States are used in animal agriculture, so managing use in this sector is critical to limiting resistance. Within animal agriculture, 80% of the antibiotics are given to healthy animals to prevent them from getting sick or to increase their growth rates. This nontherapeutic use has allowed meat production to achieve a cost-efficient model – more animals raised in less space, without increasing the spread of disease. However, this heavy reliance on antibiotics contributes to the spread of resistance. Such overuse is exacerbated by the fact that this low-dose nontherapeutic application of antibiotics over long periods of time drastically increases the rate at which resistance develops. Once resistant populations of bacteria are established, they can reach humans through various pathways – direct contact with animals or farm workers, consumption of contaminated animal products, contact with the packaging used on animal products, or environmental routes.

The Preservation of Antibiotics for Medical Treatment Act aims to address the resistance problem by regulating the amount and types of antibiotics used non-therapeutically in animal agriculture and thereby decreasing the likelihood of antibiotic-resistant infections in humans. The Act creates a new safety standard for the nontherapeutic use of antibiotics on animals. To be approved for nontherapeutic use, new antibiotics must pass a safety review requiring evidence that this use in animals will not lead to the development of resistance. Antibiotics critical to human health, that are already in use are also subject to this new standard. Drug companies will be given two years to demonstrate compliance with the same safety standard for products. Unless the companies can provide evidence of their safety, approval for the nontherapeutic use of these drugs will be withdrawn. As it is well established that the use of antibiotics leads to resistance, and many of these antibiotics are used in human treatment, the likely outcome of the Act would be sharp reduction in the nontherapeutic use of antibiotics in animals.

Restricting antibiotic use in agriculture, however, may not necessarily reduce the populations of resistant bacteria in food producing animals. In 1998, Denmark banned the use of antimicrobial growth promoters in livestock. As of 2009 an increase in the therapeutic use of antibiotics had counteracted the reductions in nontherapeutic use. Furthermore, no discernable decrease in resistance has been detected. Denmark's restrictions were limited to the use of antibiotics for growth promotion so healthy animals were still being given antibiotics to prevent disease which may account for the lack of reduced resistance. The Preservation for Medical Treatment Act provides a more comprehensive ban as compared to Denmark by banning antibiotic use for both disease prevention and growth promotion, but the results remain unpredictable.

Although growing antimicrobial resistance is a clear threat, the outcome of various policy solutions is uncertain. The outcomes that can be expected from a partial or complete ban on nontherapeutic use of antibiotics are difficult to predict. Consequently, limitations on antibiotics might not be sufficient to reduce resistance. A broader solution requires alternatives to antibiotic use in meat production. Improved husbandry practices, such as cleaner quarters, more space and the use of probiotics and vaccines, are some measures that can be used to reduce overall antibiotic use. In the goal to protect medically important antibiotics from becoming ineffective neither these practices nor legislation will change the fact that contemporary industrial models of farming are not viable without significant antibiotic use. Systemic changes in meat production might be the only means to significantly reduce resistance.

Source: UK Guardian

Introduction

> *"Without continuing to improve on our response to the public health problem of antibiotic resistance, we are potentially headed for a post-antibiotic world in which we will have few or no clinical interventions for some infections."*
>
> ~Thomas R. Frieden, M.D., M.P.H.
> Director Centers for Disease Control and Prevention U.S. Department of Health and Human Services (HHS) in 2011

Antibiotic resistance is a growing concern in the United States (McEwen and Fedorka-Cray, 2002). The development of bacteria that cannot be treated by medically important drugs such as penicillin and amoxicillin poses a serious threat to public health by rendering these antimicrobials ineffective (UCS, 2001). Infectious diseases once easily cured are becoming more difficult to treat as the effectiveness of our antibiotic arsenal is being reduced due to resistance (UCS, 2001). The practice that led to this resistance is well established – the overuse of antibiotics (Jansen et al, 2006). When these drugs are applied to a population of bacteria, susceptible bacteria are eliminated, but resistant individuals are able to survive and pass on their resistance genes, which are then pervasive within the next generation.

The medical treatment of humans currently accounts for 20% of antibiotics used in the United States, with the remaining 80% of antibiotics used on livestock in industrial farming (US FDA, 2009). Some of this 80% is used therapeutically to treat sick animals, but the vast majority is used non-therapeutically, meaning these drugs are given to healthy animals to prevent the spread of disease and to accelerate growth (US FDA, 2009). Using antibiotics daily in this manner reduces the cost of producing meat by allowing large populations of animals to be grown in confined conditions, however, this widespread overuse of antibiotics has led to the proliferation of resistant bacteria (Scott, 2005). These resistant bacteria, once released into the environment, can come into contact with and infect humans through our consumption of contaminated food or through direct contact with animals or farm workers (McEwen and Fedorka-Cray, 2002).

This report provides an analysis of one proposed solution to the threat of increasing antibiotic resistance – the Preservation of Medically Important Antibiotics for Medical Treatment Act (hereafter 'the Act'). By restricting the approval for the nontherapeutic application of antibiotics – those drugs that are administered to healthy animals - the Act intends to limit the spread and persistence of drug-resistant bacteria that pose a critical threat to human health. In this report we will examine the extent of the bacterial resistance problem as well as the scientific basis for the Act's proposed solution. Particular attention is devoted to the substantial uncertainty surrounding previous attempts to curb the proliferation of resistant bacteria– focusing on the outcomes of international legislation and the complexity of bacterial genetics. We will also consider alternatives to nontherapeutic antibiotic use, addressing the success of these options within the context of industrial farming's contribution to antibiotic resistance.

A Legislative Solution to Antimicrobial Resistance

The Preservation of Antibiotics for Medical Treatment Act of 2011, introduced by Congresswoman Louise Slaughter on March 9, 2011, seeks to maintain the effectiveness of medically important antibiotics by addressing the growing problem of antibiotic resistance. The Act aims to amend the Federal Food, Drug, and Cosmetic Act (FD&C Act) to address the approval process of antibiotic drugs used for nontherapeutic purposes in animal food production. Particular focus is placed on critical antibiotics, which are intended for use in food-producing animals and are composed of any kind of drug or derivative that is used in humans to treat or prevent disease or infection caused by microorganisms. While the FD&C Act requires manufacturers to account for the clinical effectiveness and safety of critical antimicrobial drugs on humans and animals, the legislation does not specifically address the development of antibiotic resistance resulting from overuse in animal husbandry. Although the Food and Drug Administration now considers antibiotic resistance as a safety requirement in their agency regulations, most antibiotics currently used in animal production systems were approved prior to this change. This precluded any review of these drugs and practices, with the effect of continued high use of antibiotics and increasing antimicrobial resistance. The Act would address this issue by making two important changes to the approval process of medically important antibiotics that are used routinely as an additive in feed or water for healthy animals:

1. Applications for new drugs: The Secretary of Health and Human Services would be required to deny an application for any critical antimicrobial animal drugs unless the applicant demonstrates that there is reasonable certainty of no harm to human health due to the development of antimicrobial resistance attributable to the nontherapeutic use of the drug.

2. Retroactive Review: The Secretary will withdraw nontherapeutic antibiotics approved prior to enactment unless the holder proves within a two-year period that nontherapeutic use does not lead to microbial resistance detrimental to humans, as explained above.

These two changes could effectively phase out the use of many critical nontherapeutic antibiotics for growth promotion and disease prevention in animal agriculture.

> *"Antibiotic resistance is driven by antibiotic use. When antibiotics are superseded and therefore used less, strains resistant to these tend to disappear."*
>
> ~ Geoff Scott, Consultant in Clinical Microbiology at University College London Hospitals

Antibiotic Resistance from Overuse

Development of Resistance

The problems of antibiotic resistance that the Act is designed to address are as old as antibiotics themselves. In the mid twentieth century, soon after antibiotic use became widespread, scientists began to see the development of resistance to certain antibiotics, sometimes within a year of their introduction (Scott, 2005). When humans and animals consume antibiotics – for any purpose – the antibiotics kill or weaken select microorganisms by interfering with the structures or processes essential to their survival (Walsh, 2000). However, as soon as antibiotics alter the environment, microbes begin to evolve in response to those changes. In other words, antibiotic effectiveness inevitably diminishes over time—selective pressure in the microbial community favors resistant bacteria in the presence of antibiotics (Walsh, 2000; Hogberg et al., 2010). Countries with the highest sales of antibiotics have the highest levels of resistant bacteria (Figure 1, Brownzawer et al., 2002). It is clear that the emergence of resistance is intrinsically linked to the use of antibiotics; **increased use leads to increased resistance** (Jansen et al, 2006).

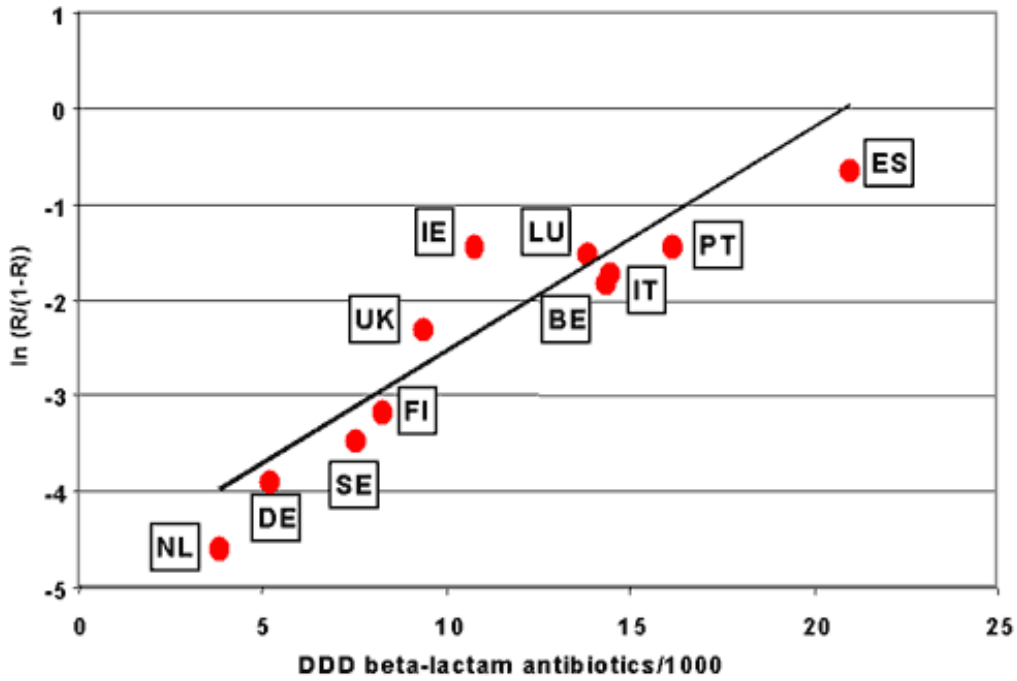


Figure 1. The log-odds ratio of resistance to penicillin among invasive isolates of *Streptoccus pneumoniae* (PNSP; ln(R/[1-R])) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries; antimicrobial resistance data are from 1998 to 1999 and antibiotic sales data are from 1997. DDD = defined daily dose; BE = Belgium; DE = Germany; FI = Finland; IE = Ireland; IT = Italy; LU = Luxembourg; NL = the Netherlands; PT = Portugal; ES = Spain; Se = Sweden; UK = United Kingdom (adapted from Brownzawer et al., 2002).

Spontaneous Mutations

The basis of antibiotic resistance is spontaneous mutations in microbes that occur at a rate ranging from one in a million to one in a billion (10^{-6} to 10^{-9}; Scott, 2005). While this number seems miniscule, putting it into the context of microbial population dynamics reveals how frequently mutations arise. A cow's rumen, for example, contains nearly 10 quadrillion (10^{17}) microbes per liter of fluid (Brooker et al. 2008), which means that there are generally over 10 billion (10^{7}) bacteria with new spontaneous mutations within this population at any given time. Whether exposed to antibiotics or not, a small percentage of these mutations confer resistance to antimicrobial drugs. Resistant genes can affect the physiology of bacteria such that under antibiotic-free conditions there is often a fitness cost associated with resistance. For example, bacteria with the resistance mutation may grow more slowly, which would put them at a disadvantage relative to other bacteria. In the presence of antibiotics, however, the benefit of resistance exceeds the fitness cost so that resistant bacteria are favored (Levin et al. 2000; Andersson, 2003; Jansen et al. 2006; Summers, 2006; Hogberg et al., 2010). Once an environment advantageous to resistance is established, resistant genes can spread through direct inheritance. Since bacteria can divide every 15 minutes to an hour, one resistant bacterium could potentially produce 2.81×10^{14} genetically identical bacteria within 24 hours (Todar, 2008). Despite the rarity of mutations and the even lower probability that a mutation confers antibiotic resistance, a few resistant bacteria can quickly create a population that is unaffected by antimicrobial drugs.

Mechanisms of Bacterial Genetic Transfer

Aside from inheritance, genes can spread between bacteria through a variety of mechanisms that complicate the transmission and management of resistance. These include horizontal gene transfer, gene linkage, and transformation (Andersson, 2003; Scott, 2005). Horizontal gene transfer is a physical process where genetic information is transferred by self-replicating DNA molecules called plasmids or bacterial viruses called bacteriophages (Summers, 2006). Because bacterial genes are often physically linked on plasmids, horizontal gene transfer may involve the transference of multiple genes—a process known as gene linkage (Summers, 2006). Moreover, through a process known as transformation, bacteria can develop resistance when they consume and express resistant genes absorbed from the environment. These unbound genes come from the decomposition of dead bacteria or the shedding of genes by living bacteria (Summers, 2006). Collectively, these mechanisms allow resistance to spread to closely and distantly related species of bacteria. As a result that resistance can establish within communities that do not have the associated fitness cost conferred by the original mutation (Summers, 2006). Gene transfer in microbes is clearly a complicated and versatile process, emphasizing the potentially pervasive capacity of antibiotic resistance.

[Case Study:

Antimicrobial Resistance Development in *Salmonella*]

The management of *Salmonella* provides a useful example for the discussion of how antimicrobial resistance develops in animals and is transferred to humans. *Salmonella* is a zoonotic food-borne pathogen, which means that resistant *Salmonella* bacteria that develop in animals are the same bacteria that can causes resistant infections in humans. The transmission line of resistance for zoonotic food borne illnesses like *Salmonella* (including *E. coli* and *Campylobacter*) is easier to follow relative to the more complicated mechanisms by which other resistant bacteria residing in the gut are able to transfer resistance to the pathogenic bacteria that cause human infections (Gustafson, 1991). Further, select *Salmonella* types like Typhimurium DT104 and Heidelberg have developed antimicrobial resistance mechanisms that continuously challenge public health infrastructure (Foley and Lynne, 2007).

Salmonella bacteria. Image courtesy of the Centers for Disease Control and Prevention.

Salmonella outbreaks have inspired scientific investigation into overuse of antibiotics in agriculture for decades. From 1971 to 1983, Dr. Scott Holmberg of the Center of Disease Control (CDC) examined 52 *Salmonella* outbreaks, some of which were caused by antimicrobial-resistant strains, to determine their source and impact on human mortality (Holmberg, et al.1984). The human fatality rate was significantly higher for patients infected with the antimicrobial-resistant *Salmonella* strains (4.2%) relative to the fatality rate of those with antimicrobial-sensitive infections (0.2%) (Holmberg, et al. 1984). Moreover, animals were the source of 11 of 16 (69%) of resistant outbreaks (Holmberg, et al. 1984). Many cases were linked to beef herds that had received Tetracycline in their feed (Gustafson, 1991). The Tetracycline class of antibiotics has been widely used for many purposes and is a model case for the dissemination of resistance genes (Davies, 1996). The shift towards more consolidated, intensive food animal production leads to increased demand for antibiotics (Campagnolo et al., 2002), leading to the development and transmission of antimicrobial resistance to humans.

Widespread Antibiotic Use in Meat Production Exacerbates the Problem

The risk of developing resistance is inherent in any application of antibiotics, but the magnitude of risk is correlated with the level of use. Although reliable data on antimicrobial use for animals is not publicly available, it is estimated that more than 64% of all antibiotics in the United States are used to treat healthy animals (Figure 2; US FDA, 2009). Current estimates are that 4.5 million pounds of antibiotics are used by humans annually, 2 million pounds are used therapeutically to treat sick animals, and 27.5 millions pounds are used non-therapeutically for growth promotion and prophylaxis (McEwen and Fedorka-Cray, 2002). Since resistance increases with use, the administration of large quantities of antibiotics as growth promoters is a major contributor to the emergence of antibiotic resistant bacteria and consequent reduction in antibiotic potency (Alexander et al., 2008). The present situation, however, is a relatively recent development. When antibiotic use first began in the 1940s, only 5% was administered to animals. Once nontherapeutic use was approved in 1949 and the cost-effectiveness realized, treatment of livestock began to dominate the antibiotic market. This practice was so widely adopted that in 1951 the demand for antibiotics for use in farming exceeded the supply (Jukes, 1972). By 1959, 54% of all antibiotics produced in the United States were used in animal agriculture (Smart and Marstrand, 1972). By 1999, nearly 100% of poultry, 90% of swine, and 60% of beef cattle were fed antimicrobial-dosed feed (National Academy, 1999).

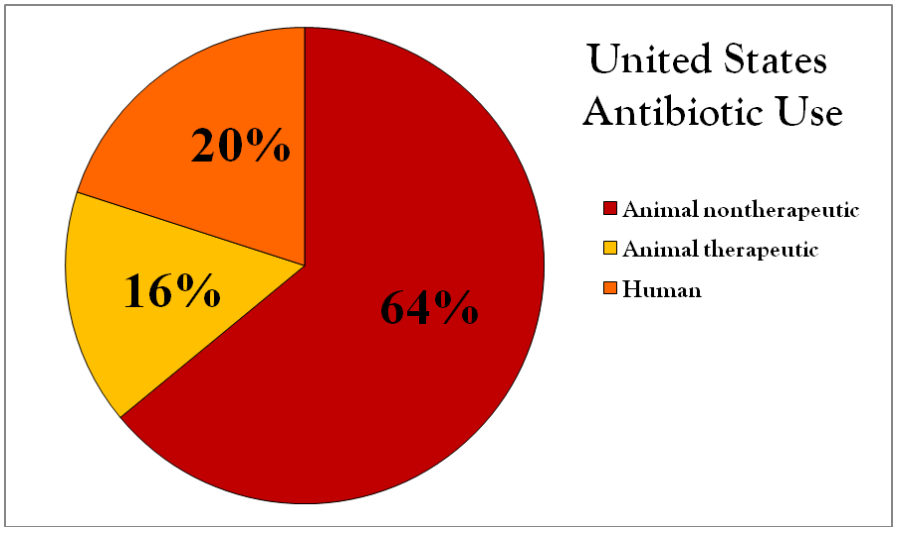


Figure 2: The breakdown of antibiotic use in the United States between those used for medical purposes on humans and those used for therapeutic and nontherapeutic treatment in animal agriculture (US FDA, 2009)

Intensity and Scale of Animal Agriculture

The increase in nontherapeutic use of antibiotics has contributed to the intensification of animal production in the United States – fewer, larger farms raising huge numbers of animals (McEwen and Fedorka-Cray, 2002). Animal crowding, poor sanitation, and insufficient temperature and ventilation control, all contribute to stress which lowers the ability of animals to resist disease (Gustafson and Bowen, 1997; Gilchrist et al., 2007). Low dose antibiotic treatment allowed farmers to intensify their operations and increase profits without severe health impacts on their animals.

The prevalence of confined animal feeding operations has led to increases in herd sizes of cattle, poultry, and swine at farms. In 2000, approximately 35% of cattle were fed on facilities of 32,000 heads or more (McEwen and Fedorka-Cray, 2002). More than 83% of feedlots administer at least one antibiotic through feed or water for prophylaxis or growth promotion (McEwen and Fedorka-Cray, 2002). Between 1945 and 1999, broiler chicken production increased from an estimated 5 billion to nearly 40 billion pounds per year (McEwen and Fedorka-Cray, 2002). Most farms raise these chickens in pens containing 10,000 to 20,000 birds, making constant treatment with antimicrobials necessary (McEwen and Fedorka-Cray, 2002).

Source: stay-healthy-enjoy-life.blogspot.com

Nontherapeutic Use Facilitates Resistance

The problem posed by the sheer amount of antibiotics used is compounded by the fact that using antibiotics non-therapeutically over long periods of time, drastically increases the rate at which resistance develops (Andersson, 2003; Harbottle et al. 2006; Summers, 2006; Hogberg et al. 2010). A growing body of evidence indicates that the nontherapeutic use of antibiotics in animal agriculture fosters the proliferation of antimicrobial resistance (Andersson, 2003; Harbottle et al. 2006; Summers, 2006; Hogberg et al. 2010). As early as 1969, the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine in the United Kingdom, found that "there has been a dramatic increase… in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics" and that "[t]his resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock" (Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, 1969). This finding has been supported by subsequent research and remains the position of scientific, governmental and non-governmental organizations around the globe, including the United States Food and Drug Administration (FDA), The World Health Organization (WHO), United Nations Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE) (US FDA, 2009). Not only have farms drastically increased the amount of antibiotics used, leading to heightened resistance, but the method in which these drugs are used amplifies the dangers posed.

Source: Pew Environment

Consequences of Increasing Resistance

Humans and Animals Share Antibiotics

Overuse of antibiotics applied non-therapeutically, has increased the resistance to those treatments in agriculture, however, the main concern for human health is that these microbes are also resistant to antibiotics used in human medicine (UCS, 2001). Drugs used to treat meat-producing animals, such as penicillin, erythromycin, and amoxicillin are also used therapeutically in humans to treat a variety of illnesses, including strep throat, pneumonia, sexually transmitted diseases, and gastroenteritis (Table 1). According to the Union of Concerned Scientists, 55% of drugs used for growth promotion and disease prevention in animals are the same drugs used to treat humans (UCS, 2001). As a result, the nontherapeutic use of antibiotics in food animal production has severe impacts on human health (Aarestrup, 2005). This was the conclusion of a report published by the United States Department of Agriculture (USDA) that reviewed a collection of 63 studies researching the development of antimicrobial resistance within food animal production and the mechanisms by which resistance can be transferred to humans (MacDonald and McBride, 2009; Tomson, 2011). This review led the USDA to suggest that we may enter the 'post antibiotic era' where effective antibiotics for treating several life-threatening infections would not be available (MacDonald and McBride, 2009; Tomson, 2011).

Table 1: Infections in humans, the antibiotic used to treat them, and the animal(s) that use the same antibiotic (UCS, 2001; Webmd.com)

Antibiotic	Animals receiving the antibiotic	Infections treated in Humans
Amoxicillin	Cattle, Swine	Strep throat
Penicillin	Cattle, Poultry	STIs
Erythromycin	Cattle, Poultry	Penicillin Alternative
Ampicillin	Swine	Pneumonia
Ciprofloxacin	Cattle, Poultry, Swine	Gastroenteritis

The development of resistance to antibiotics used by humans is effectively decreasing our ability to combat infection. The loss of effectiveness of existing antibiotics could be countered by the development of new antibiotics, but the approval of new antibiotics is rare. Over the past 30 years the number of approvals for antibiotics by the US FDA

(Food and Drug Administration) has steadily decreased, with only two drugs being approved since 2008 (Infectious Disease Society of America, 2011, Figure 3). New antibiotics are not being developed quickly enough to replace the antibiotics that are losing effectiveness.

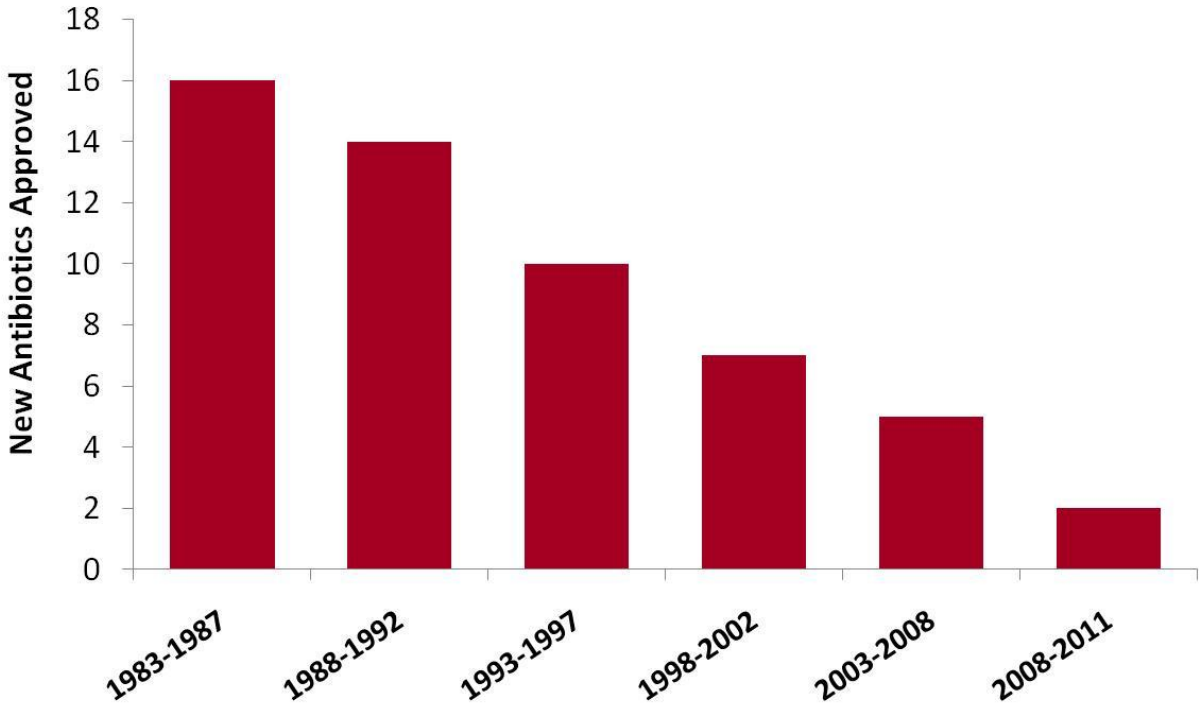


Figure 3: The number of New Molecular Entity Systemic Antibiotics approved by the United States Food and Drug Administration from 1983 through 2011, in five year increments (Infectious Disease Society of America, 2011)

Pathways to Human Exposure

Primary and Secondary Contact

The impact of resistant bacteria on public health is manifested through a variety of pathways leading to human contamination (Figure 4). Humans can be directly exposed to low levels of antibiotics and to resistant bacteria by working on or living in close proximity to farms (McEwen and Fedorka-Cray, 2002). Farm workers are at risk of direct exposure to resistant pathogens, which can spread through the health care system if infected workers seek treatment. Within six months of the introduction of a Tetracycline-supplemented feed in a poultry facility, 31% of fecal samples from farm workers contained Tetracycline-resistant bacteria (Levy et al., 1976). Similarly, two years after the introduction of Nourseothricin into swine feed, resistant bacteria were found in 33% of fecal samples from pigs, in 18% of samples from workers and their families living on the farms, and in 16% of samples from outpatients from medical facilities in nearby communities (Hummel et al., 1986). Prior to this application of Nourseothricin, resistant strains of bacteria were extremely rare in humans and animals (Hummel et al., 1986). These studies demonstrate the extent of pathogen transfer that could potentially occur at local and regional levels.

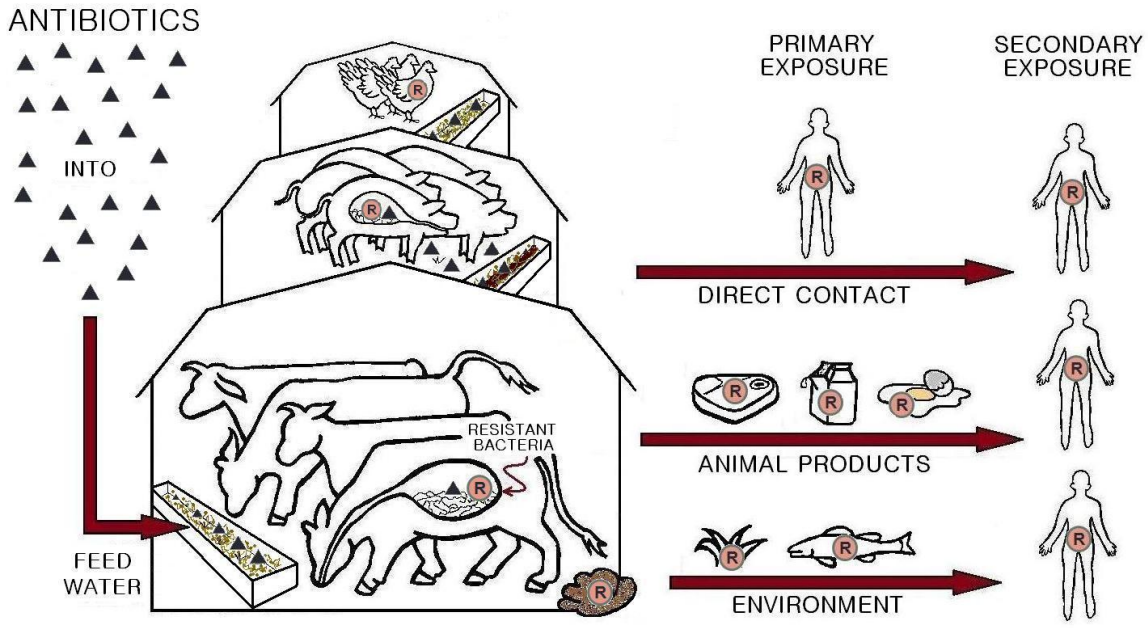


Figure 4: The main pathways of exposure of antibiotic resistant bacteria from nontherapeutic use in animal agriculture to humans. (Image: Rose Andreatta).

Antibiotic Residues and Resistant Bacteria in Meat

The administration of antibiotics to food animals creates some risk of antibiotic residues in animal products (Gustafson and Bowen, 1997). Normally, such residues are reduced via withdrawal periods, which specify a period between the final antibiotic treatment and slaughter (FDA, 2004). For instance, after cows are given antibiotics, there is a standard time interval when all milk is discarded (Gustafson and Bowen, 1997). Withdrawal times vary depending on the antibiotic, and range from 36 hours for Enthromycin to 96 hours for Tylosin (Merck Veterinary Manual, 2011). In 2003, the Food and Drug Administration reported over 1,800 antibiotic residue violations in different cattle products (FDA, 2004). The health impact to consumers of this continual low-dose exposure to antibiotics is unknown, and therefore should be regarded with caution.

Humans can also be exposed to antibiotic resistant bacteria through contaminated animal products. *Escherichia coli* (*E. coli*) and *Salmonella* infections kill hundreds of people in the US each year and sicken over one million, with the primary sources of exposure being meat, eggs, and dairy products (Thorne, 2007). 20% of ground meats sampled in Washington were contaminated with *Salmonella*, with 84% of those bacteria being resistant to antibiotics used in human and animal agricultural treatments (White et al., 2001). In order to better protect the public, it is critical to understand the pathways by which antibiotic resistant bacteria reach humans and how antibiotic residues in food products could impact human health.

Ecological Concerns

Although the environmental impacts of nontherapeutic antibiotic use are not the main concern of the Act, there are some serious ecological concerns associated with the release of drugs into the environment. Due to their continual discharge and persistence, antibiotics are categorized as organic wastewater contaminants, which are a new class of environmental pollutant (Fraker & Smith, 2004; Harada et al., 2008). Since antibiotics are designed to have biological effects, there are concerns about their fate and impact on the wider environment (Alcock et al., 1999; Harada et al., 2008). Low-level exposure to antibiotics over time may have slow effects on biochemical, physiological, reproductive, and ecological processes (Brooks et al., 2008). In areas with high concentrations of antibiotics, there are concerns that micro-flora will be inhibited and also that antibiotic-resistant microorganisms will develop (Pouliquen et al., 2009). A number

Case Study: Bacterial Resistant Infections

In early June 2011, after persistent diarrhea requiring 20 diaper changes a day, the parents of 10-month-old Ruby Lee of Oregon took a second trip to the doctor. The doctor originally suspected a virus, but ordered blood tests on the second visit (Lynne, 2011). The next day Ruby's parents were instructed to take her to a Children's Hospital for immediate long-term care. Ruby spent seven days in the hospital, having been diagnosed with *Salmonella Heidelberg*, one of four strains of *Salmonella* that is resistant to many leading antibiotics (Lynne, 2011).

How the 10 month old had contracted this resistant strain of bacteria was unclear until mid July. After weeks of work, doctors and researchers finally connected Ruby's case to a growing number of cases across the country originating from contaminated ground turkey.

Continued...
As of August 9 2011, the Center for Disease Control (CDC) reported 107 confirmed cases of *Salmonella* poisoning across 31 states that can all be linked to ground turkey emanating from a single poultry processing plant in Arkansas. This link was made using a DNA fingerprint of the bacterial strain. Of the cases with available information, 39% patients have been hospitalized and one person has died (CDC, 2011).

On August 3 2011, Cargill Meat Solutions Corporation instituted a voluntary recall of roughly 36 million pounds of ground and frozen turkey because of potential *Salmonella* contamination, the third largest meat recall in US history.

of subtle impacts due to long-term, low-level exposure to pharmaceuticals have been found, including growth inhibition of cyanobacteria and aquatic plants as well as reduced rates of decomposition (Boxall, 2004). Antibiotics may have the potential to significantly alter or destroy micro-ecosystems due to their effect on microorganisms, which provide critical functions either as primary producers or as decomposers (Wei et al., 2011).

Antibiotics have been detected in surface water, groundwater, sediments and sludge (Fatta et al., 2005). Intensive animal production operations are some of the most important sources of antibiotics into the environment (Fatta et al., 2007; Richards & Cole, 2006). Of particular concern is the presence of medications in drinking water (Pouliquen et al., 2009). Antibiotics are often detected in surface waters in the nano-grams per Liter range, though levels of 15 micro-grams per Liter for a sulfonamide have been measured (Brooks et al., 2008). These concentrations are sufficient to induce biological and ecological effects. For example, sulfonamides reduce substrate-induced respiration in soil bioassays, indicating a reduction in microbial biomass in soils and residues (Thiele-Bruhn and Beck, 2005). The dose to reduce microbial biomass by 50% relative to the control was 6.2 $\mu g\ L^{-1}$, below the maximum levels detected in the environment (Thiele-Bruhn and Beck, 2005). This suggests that wild microbial communities and their ecosystem functions could be affected by pervasive antibiotic residues.

Transport

The dispersal and migration of microorganisms with antibiotic resistant traits is a major concern for public health and safety (Baquero and Garau, 2010). Antibiotic resistant microorganisms have been found in 31% of environmental water samples near swine farms and in 67% of samples taken near poultry farms (Campagnolo et al., 2002).

Antibiotics are dispersed into the environment after they are applied to livestock. Between 30 to 90% of antibiotics fed to animals are excreted via urine and in feces (Alcock et al., 1999; Kay et al., 2004; Boxall et al., 2009). From these wastes, antibiotics can enter the environment indirectly through the spreading of manure and slurry on farmland or directly through deposition by grazing livestock (Kay et al., 2004; McEwen and Fedorka-Cray, 2002). Because many farm animals are raised indoors for long periods, large quantities of manure are concentrated and subsequently disposed of in large quantities (Thorne, 2007; Boxall et al., 2009). This can result in the contamination of soil and water (Boxall et al., 2009). Contaminated bodies of water may then spread antibiotics further as the water leaches through the soil and surrounding

area, perhaps impacting the microorganisms in the soil. (McEwen and Fedorka-Cray, 2002).

Impacts on Wildlife

Wild animals are impacted by antibiotic residues (Pouliquen et al., 2009), and can acquire antibiotic-resistant bacterial infections through contact with domestic animals and humans and through exposure in the environment (Gilchrist et al., 2006; Kozak et al., 2009). These interactions are believed to be responsible for the spread of resistant bacteria and antibiotic-resistant genes into wild animal populations, such as mice, voles, and shrews (Kozak et al., 2009). Antibiotic resistance rates were higher for *E. coli* samples taken from small wild mammals living in close proximity to humans and animal farms than from those living in more isolated areas (Kozak et al., 2009). These *E. coli* isolates displayed resistance to antibiotics used on the farms, including Tetracycline and sulfonamides (Kozak et al., 2009).

An Uncontrolled Experiment

Much of the current information on the aquatic hazard of antibiotics is limited to acute toxicity testing, which is not as useful for understanding the effects of long-term, low-level concentrations of antibiotics in the environment (Brooks et al., 2009; Park and Choi, 2008). Although the levels of antibiotic exposure necessary to affect survival, growth, and reproductive rates are regularly tested, in general toxicological assays do not allow for the effective prediction of ecological responses to environmental contaminants (Brooks et al., 2009; Park and Choi, 2008). Additionally, experiments typically focus on one antibiotic at a time, whereas organisms are often exposed to mixtures of different compounds and these mixtures may have synergistic or antagonistic interactions (Brooks et al., 2009; Kolpin et al., 2002).

Source: Blog.Cleveland.com

Scientific Implications of the Proposed Solution

The Science Behind Amending the Drug Approval Process

The new approval process for nontherapeutic application of drugs in animal agriculture focuses on a basic presumption: changing the current patterns of antimicrobial use will influence the incidence and prevalence of resistant bacteria (Jansen et al, 2006). The safety standards, which apply to approvals of new animal drugs as well as a retroactive review of previously approved drugs, address the problem of antibiotic resistance in two distinct ways. Firstly, by preventing the widespread use of new drugs, the Act aims to proactively reduce the rate at which resistance develops. Secondly, by retroactively restricting drugs that had previous approval, it attempts to restore the effectiveness of drugs that are currently used heavily in food animal production.

Rate of the development of resistance

Antibiotics provide selective pressure for the emergence and spread of resistance. Decreased use of antibiotics lowers that selective pressure and thereby reduces the pace of emergence and spread of new forms of bacterial resistance. Resistant genes are pervasive even when antibiotic usage is greatly reduced (Levin, 2000). As a result antibiotics should be applied judiciously when resistance is low (Jansen et al. 2006). Microbial evolutionary responses to antibiotics cannot be stopped, but they can be managed by using antimicrobials judiciously (Hogberg et al., 2010)

Reversibility of resistance

While there is a definite correlation between antibiotic use and the development of resistance in microbial communities, it is much less clear how reducing the use of antibiotics will affect established antimicrobial resistance (Johnsen, et al 2011). Increasing evidence from laboratory and empirical studies reveals that with long-term, low-dose exposure to antibiotics, antimicrobial-resistant bacteria are able to overcome the fitness costs conferred by resistance to become strong competitors even in the absence of antimicrobials (Andersson, 2003; Jansen et al. 2006; Summers, 2006; Schulz zur Wiesh et al. 2010). This suggests that post hoc reductions of antibiotics may not reverse the spread of resistance.

Moreover, as was discussed in the section describing the complex adaptive mechanisms by which resistance spreads, resistant genes can be transferred amongst bacterial communities and between different species of bacteria such that resistance can spread to bacteria that do not carry the associated fitness cost (Summers, 2006). Therefore, even if antibiotics are reserved for therapeutic use, antimicrobial resistance could remain in the system for years (Harbottle, et al. 2006). The degree to which this holds true varies according to the particular context, the antibiotic under consideration, and the preponderance of resistance within the current system (Harbottle, et al. 2006).

The critical implication of these findings is that antimicrobial-resistant bacteria can be pervasive and persistent (Levin et al., 2000; Andersson, 2003). This holds true particularly for environments where antibiotics are still widely used for nontherapeutic purposes; lower levels of antibiotics in the system can allow resistant bacterial strains to maintain a high equilibrium level of resistance (Summers, 2006). Moreover, there are very few documented examples where antibiotics have been completely removed from the environment, so it is uncertain how quickly resistance levels would decline in the complete absence of antibiotics that select for the resistant gene (Johnsen, et al. 2003).

The Environmental Pervasiveness of Resistant Genes

Research about the long-term effects of antimicrobial resistance confirms the difficulty of reversing resistance and similarly indicates that a reduction in antibiotic use does not necessarily translate to a reduction in resistance levels (Levin et al. 2000). One reason cited for this disparity is that relatively low levels of drug use can maintain significant equilibrium frequencies of resistant bacteria by providing the selective pressure necessary for maintaining resistance levels (Levin et al. 2000).

The management of resistance became a serious concern in the United States in the 1970s, when research demonstrated that the elimination of antibiotic use in agriculture resulted in declining antibiotic resistance, but also a decrease in health and performance (Gustafson, 1991). When antibiotics were re-introduced in low doses, the level of resistance immediately increased to the same level of swine that had continuously received antibiotics (Gustafson, 1991). Nearly all studies conducted since then have produced similar results (Harbottle et al. 2006; Hogberg et al. 2010). Reduction in resistance due to decreased antibiotic application almost always comes at a cost to animal health. These reductions therefore require significant increases in therapeutic antibiotic use, and the decline in resistance often returns to previous levels once antibiotics are re-administered. This demonstrates the pervasiveness of the problem, and that it may be inappropriate to expect significant reductions of resistance beyond isolated communities when antibiotic use (and therefore resistance) is still pervasive in the broader environment.

Controversies Related to Antibiotic Resistance and Restricting Nontherapeutic Drug Use

The complexity of antibiotic resistance has led to various controversies concerning both the problem and the solution that the Act proposes. While there is strong evidence regarding the development of resistance and the impact of the nontherapeutic use of antibiotics in animal agriculture on the proliferation of this resistance, the consequences of the Act's proposed solution remain uncertain.

Scientific Controversies related to antibiotic resistance

Transfer from Animals to Humans

The claim that resistant bacteria from food-producing animals cause antibiotic resistant infections in humans is disputed. It is agreed that resistant bacteria can transfer from animals to humans, but there is controversy on whether agricultural activity is the dominant source of human infections. Alternative explanations for the spread of resistant infections include transmission from international travel or poor hygiene, and that antibiotic use in humans is responsible for the observed resistance (Casewell et al, 2003). Evidence to support or restrict the use of antimicrobials in food animals due to a specific effect on human health is lacking in many cases. A report published by the Institute of Food Technologists states that "[t]here are very few data regarding food animal-to-human transfer of antimicrobial resistance to indicate more frequent or severe infections or increased morbidity and mortality (Institute of Food Technologists, 2006)."

Scientific Controversies related to the proposed legislation

Changes in resistance from a reduction in nontherapeutic use

To shed light on potential outcomes of banning nontherapeutic use of critical antibiotics we can look to the policies enacted in Denmark. In 1998, the Danish government banned the use of antibiotic growth promoters during the finishing stage of pork production. In 1999, they banned all antibiotic growth promoters, followed later that year by a European Union ban on nontherapeutic use of several critical antibiotics used as growth promoters in animals (Hayes and Jensen, 2003). Although the ban has been enforced, data demonstrating significant improvements in the effectiveness of critical antimicrobials is lacking (Danish Veterinary and Food Administration et al. 2009).

At the start of the ban, the sharp decrease in antibiotics used for growth promotion caused many negative health effects in the animals (Hayes and Jensen, 2003). This led to an increase in the therapeutic use of antibiotics (Hayes and Jensen, 2003; Figure 5). For example, Tetracycline use in Denmark went from 12,100 kg in 1998 to 27,900 kg in 2001, which led to problems related to Tetracycline resistance in humans (Hayes and Jensen, 2003).

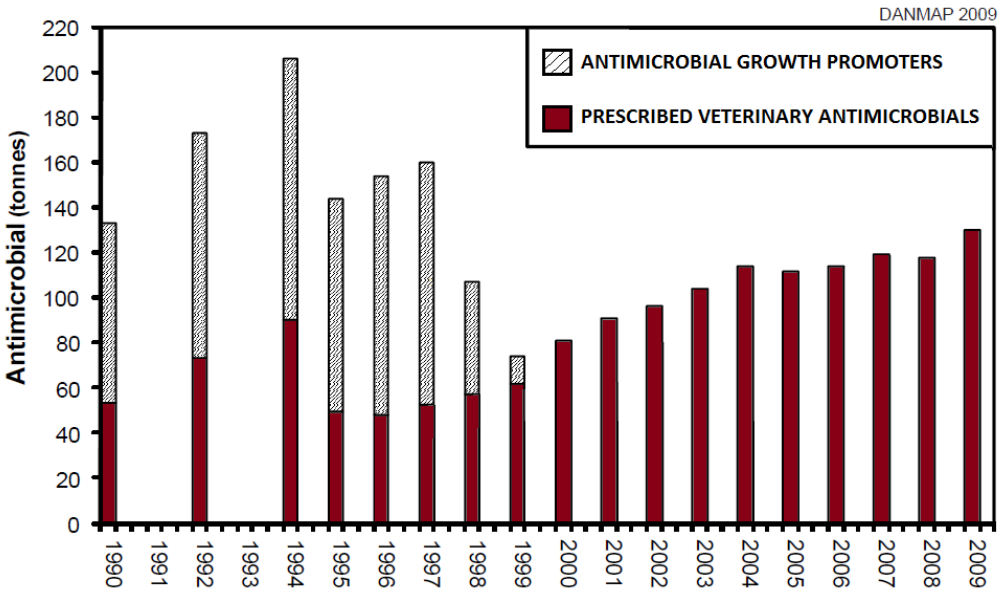


Figure 5. Consumption of prescribed antimicrobials and growth promoters in animal production, Denmark. *(DANMAP 2009)*

Considering the complexities behind the development of resistance, particularly the resilience of resistant bacteria, banning antibiotics used for growth promotion may not be sufficient to reduce levels of antimicrobial resistance. This concern is supported by findings from several governmental agencies. The vast majority of studies across antimicrobial classes and animal species do not show significant changes in observed levels of resistance after reductions in antibiotic use (Hayes and Jensen, 2003; Danish Veterinary and Food Administration et al. 2009). For example, overall resistance levels of *Escherichia coli* towards seven different classes of antibiotics observed in cattle and pigs have neither increased nor declined significantly since restrictions began in Denmark (DANMAP 2009; Figure 6). The patterns of resistance among drugs are heterogeneous, though the general trend indicates little change to resistance levels. Perhaps the modest reductions in total quantities of antimicrobials observed in Denmark could only maintain the level of resistance, rather than facilitate the reduction of resistance. There are very few instances where resistance levels were significantly reduced over time (Danish Veterinary and Food Administration et al. 2009).

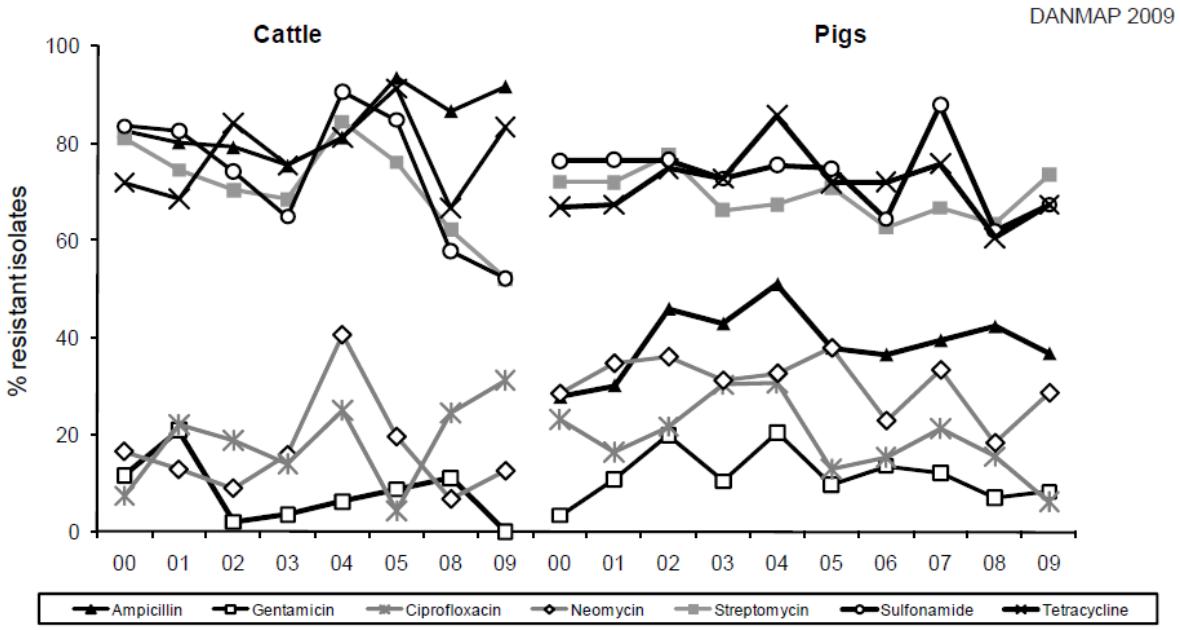


Figure 6. Trends in resistance to selected antimicrobial agents among Escherichia coli from diagnostic submissions from animals, Denmark.
(DANMAP 2009)

The findings in Denmark have also been observed in many other European countries and can largely be attributed to the fact that overall reductions in the use of antibiotics have been small (Casewell et al. 2003, Wierup 2001, Phillips 2007).

[Case Study:

Complete Ban of Avoparcin & Resistance Reversibility]

There are very few instances where a reduction in antibiotic use in food animal production resulted in decreased resistance. Some research suggests that resistance levels are maintained because the overall reduction of antibiotic use is not enough (Casewell et al. 2003, Wierup 2001, Phillips 2007). It is extremely rare for an antibiotic to be completely removed from use (Johnsen et al. 2011). Antibiotic restrictions in food animal production are often qualified such that a restriction might only apply to a particular species of animal, a specific stage of the animal's development, or for a specific type of nontherapeutic use such as growth promotion (Danish Veterinary and Food Administration et al. 2009).

However, as part of their effort to track resistance development in DANMAP, Danish scientists collected revealing data from a scenario where the food animal drug avoparcin was banned outright (Figure A).

In 1995, Danish poultry farms banned the growth promoter avoparcin, which had been heavily used in animal production in many European countries for decades (Johnsen et al. 2011). The ban was first instituted because the use of avoparcin in food animal production led to high proportions of resistant *Enterococci faecium* bacteria, which can cause life-threatening infections in humans (Johnsen et al. 2011). Moreover, avoparcin conferred complete cross-resistance to clinically important antibiotics such as vancomycin and teicoplanin, which are considered to be antibiotics of last resort for treating *Enterococci faecium* gastro-intestinal infections (Johnsen et al. 2011). Once these findings were revealed, the European Union followed suit, enacting an outright ban of avoparcin in food animal production in 1997 (Danish Veterinary and Food Administration et al. 2009). After the avoparcin ban, surveillance data from Denmark demonstrated that the proportion of resistant *Enterococci faecium* bacteria declined rapidly in the first three years from 80% to 2% (Danish Veterinary and Food Administration et al. 2009, Johnsen et al. 2011; Figure A).

The successful reversal of antimicrobial resistance levels has been attributed to the virtual elimination of the antibiotic from the environment, which allowed for selective pressures to eliminate the resistant strain of bacteria (Johnsen et al. 2011).

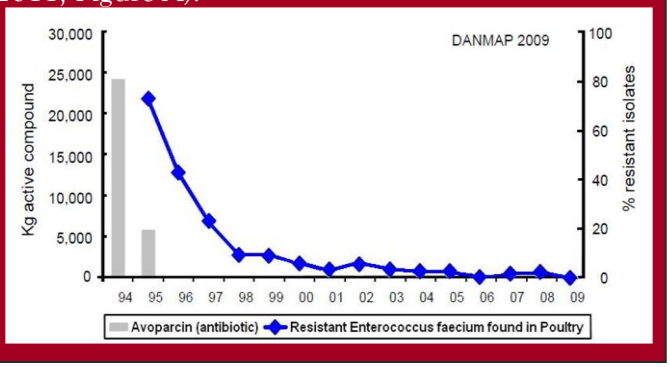


Figure A. (Right) The consumption of avoparcin and the trend in occurrence of resistance to avoparcin among *Enterococcus faecium* bacteria from poultry

Resistant Infections and Reduced Antibiotic Use

The ban of antibiotics in Denmark and Sweden did not lead to a reduction in the prevalence of antibiotic-resistant infections in humans (Casewell et al, 2003). Drug resistance to Vancomycin is still observed in Denmark years after an institutional ban for nontherapeutic purposes, and human resistance to Vancomycin has increased (Casewell et al, 2003). Increased Vancomycin resistance may be due to the increased use of this antibiotic for treating Methicillin-resistant *Staphylococcus aureus* (MRSA) (Casewell et al, 2003). The ban of nontherapeutic use of antibiotics in Denmark led to an increase in the use of therapeutic antibiotics in food-producing animals, particularly those antibiotics that are often used in human medicine (Hayes and Jensen, 2003). Increased resistance to these critically important antibiotics suggests that banning nontherapeutic use can possibly aggravate the problem of resistant bacteria in humans (Hayes and Jensen, 2003; Figure 7). After enacting a ban in 1999, the Netherlands experienced similar consequences – a doubling in the use of therapeutic antibiotics in the past decade without a decline in total use of antibiotics or a visible reduction in resistant bacterial infections in humans (American Veterinary Medical Association, 2011).

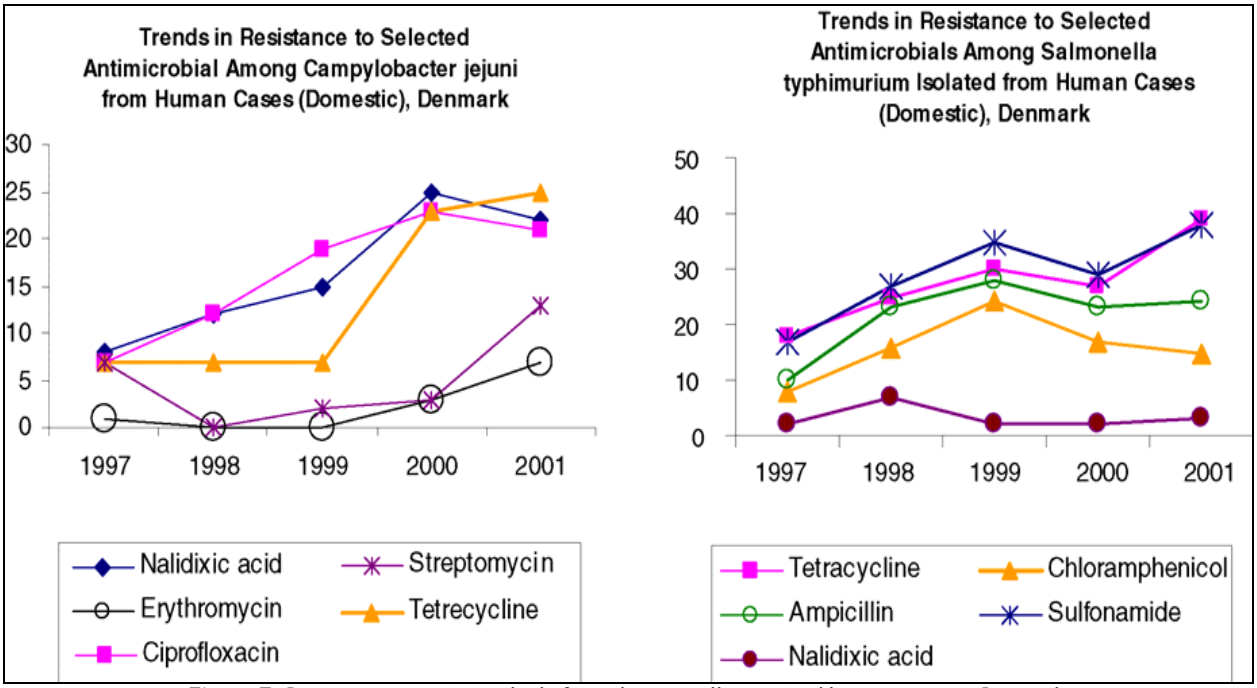


Figure 7: Resistance to antimicrobials from domestically acquired human cases in Denmark
Source: Hayes and Jensen, 2003

Measuring the Efficacy of the Solutions

As the results in Denmark show, measuring the success of restrictions on the use of antibiotics in livestock is complex and difficult. However, the key indicators for determining success are clear – the amounts of antibiotics being sold and used in farms, the amounts, types and changes in resistance found on farms, the rates and amounts of resistant bacteria in human populations, and the effectiveness of antibiotics in human populations. Fortunately, monitoring the effectiveness of this policy can be accomplished by utilizing an existing infrastructure of agencies.

National Antimicrobial Resistance Monitoring System

The infrastructure for measuring antibiotic resistance at the national level was first implemented in 1996. It was the collaboration of the Food and Drug Administration (FDA), the Centers for Disease Control (CDC) and the United States Department of Agriculture (USDA) (Torrence, 2001). Together they created the National Antimicrobial Resistance Monitoring System (NARMS). The objectives of NARMS are multi-lateral, including measuring the susceptibility of enteric organisms, providing specific data about the host and nature of the isolate, providing temporal data, communicating data to healthcare professionals to promote responsible use of antibiotics, and prompt identification of bacterial antibiotic resistance patterns. Annual reports of these data are maintained and available through the Food and Drug Administration (FDA) online database (Torrence, 2001).

Veterinary and Human Components

The activities of NARMS are organized in two branches: veterinary and human. The veterinary branch collects bacterial isolates from animals at farm sites. These samples are then sent to the Department of Agriculture's Russell Research Center in Atlanta, Georgia. (Torrence, 2001) Control, clinical, and slaughter-based samples are taken from various national laboratories with a focus on specific bacteria types including, *Salmonella*, *Escherichia coli* and *Campylobacter* (Torrence, 2001). For the human component of NARMS, public health laboratories in each state collect and serotype pathogen samples and send them to the Center for Disease Control Laboratory in Atlanta, Georgia for testing for susceptibility (Torrence, 2001). In contrast to the results from the animal populations, the results in humans are fairly representative of the overall population in the United States (Torrence, 2001).

Other Monitoring Programs

Two other government programs designed for the surveillance of resistance and use of antibiotics collect data on a broad range of antibiotics and pathogens in humans: the Emerging Infections Programs (EIPs) and the National Healthcare Safety Network (NHSN) (Friedan, 2011). These programs are run by the Center for Disease Control and Prevention (CDC). The Emerging Infections Programs (EIPs) involve laboratories, healthcare facilities, academic institutions, and 10 state-based health departments performing surveillance of resistance at the community, healthcare facility and national level (Friedan, 2011). The National Healthcare Safety Network (NHSN) compiles data from national networks and currently has 2,500 hospitals participating in the program (Friedan, 2011). The surveillance of the NHSN is achieved via an online tool that allows hospitals and state departments to track healthcare-associated infections and submit data on resistance (Friedan, 2011).

Limitations to Effective Measurement

The scope of these programs and the infrastructure supporting them is currently limited. Although the control and clinical samples collected from national laboratories can be considered representative of the animal population, sampling efforts vary through time, by species, number, and geographical region. The variation is likely due to the voluntary nature participation (Torrence, 2001).

Further challenges related to the EIP and NHSN include considerable variation among the antibiotic stewardship programs that contribute data (Jacob, 2010). For these programs, data is compiled by hospitals and communities that lack the infrastructure and staff to facilitate accurate measurement (Jacob, 2010). Additionally, the data does not include all healthcare associated infections, only certain infections within a particular healthcare facility (Jacob, 2010). The variability in measuring consumption of antibiotics also leads to challenges in measurement. The data on antibiotic consumption is typically compiled in aggregate and related only to select types of infections (Jacob, 2010).

In order to effectively measure the success of the Act a substantial investment will be needed in developing the infrastructure for measurement. A national guideline should also be established for recording and submitting information from every farm, hospital and outpatient clinic in the country. A real time, unified database run by a single government agency with the specific mandate to collect and analyze the data is essential. The only way to judge the actual success of the legislation will be to design and implement a system by which it can be measured.

Alternative Solutions to Facilitate Success

The limited effectiveness of Denmark's restriction on growth promoting antibiotics in animal agriculture, and the issues with effective monitoring of resistance, demonstrate the difficulty the Act would have in reducing bacterial resistance to critical drugs. As a focused legislative action, the Act does not directly address a more comprehensive solution to the fundamental issues driving the use of antimicrobial drugs in animal agriculture or what should be done in their absence. An understanding of an effective solution is dependent on examining other principal factors.

Livestock management without nontherapeutic antibiotics

Husbandry

Animal husbandry has undergone significant change over the last 60 years. The use of antimicrobial drugs in conjunction with technological advances has allowed animal agriculture to become industrialized, with many more animals being raised in intensive farming operations such as confined animal feeding operations (CAFO). In order to release farmers from dependence on continuous antibiotics, better husbandry practices – including both management and technological changes – are essential.

The first tool of better husbandry is to improve basic management practices to control infectious disease. Livestock management should aim to limit the opportunities for exposure between animals and between farms, rather than use antibiotics on healthy animals to prevent sickness. Minor changes, such as improved sanitation, waste management, swift quarantine procedures, suitable temperature, ventilation, and water quality are enough to reduce the need for widespread antibiotics (McEwen and Fedorka-Cray, 2011). Danish farmers have adapted to their country's ban on nontherapeutic antibiotic use with frequent cleaning of housing, improved ventilation and water quality, additional space, as well as experimenting with feed quality and additives made up for the lack of routine antibiotics on most farms (Pew, 2011). Organic practices, which do not use any antibiotics, show a substantial decrease in resistance.

Source: Flicker

A recent study looked at two different types of bacteria on conventional and organic poultry farms and tested them for resistance against multiple types of antibiotics. The percentage of bacteria that were resistant to more than three different types of antibiotics was significantly higher on conventional farms when compared to organic farms – with 84% compared to 17% for one of the bacteria tested (Sapkota et al., 2011). These organic management practices employ a simple model to decrease the need for antibiotics: cleaner conditions, more space, and more focused attention on animal health.

Biosecurity

Biosecurity refers to the application of health measures to prevent the introduction of new infectious diseases into herds and avoid further proliferation (Barcelo and Marco, 1998). Biosecurity encompass both an augmentation to husbandry practices, which were mentioned above, and an incorporation of new technologies (Barcelo and Marco, 1998). One operational model that reduces the horizontal transmission of disease in livestock facilities is referred to as "all-in/all-out". In facilities practicing this technique, cohorts of livestock are kept together throughout their lives, and when the animals are moved the entire facility is emptied, cleaned, and disinfected (Armbrecht, 1999). This leads to better sanitation and lower disease transmission in pig farms (Armbrecht, 1999). A biosecurity measure used in dairy cattle is teat dipping, which involves capping a cow's teats with a secure cover and sanitizing solution after milking in order to prevent infection. Teat dipping is very effective, with significant reductions in infections, and has great potential for use in organic dairy as an alternative to antibiotics (Berry, 2002). The implementation of these and other biosecurity measures must be stepped up in the absence of antibiotics to decrease the risk of infection in livestock.

Vaccines

Vaccinations can be used as alternatives to antibiotics to prevent bacterial and viral infections in livestock. Rather than use antibiotics to kill bacteria present in an organism, vaccines stimulate the immune system to produce natural defenses against infection. This is done by injecting, feeding, or spraying livestock with live attenuated viruses or bacteria or killed viruses or bacteria. Infecting animals with small amounts of the virus or bacteria usually establishes a permanent immunity, which will prevent sickness in the future - protecting both the individual and the population from disease (NOAH, 2002). Unlike antibiotics, vaccines only have to be administered once or at low frequencies in order for immunity to develop for a specific virus or bacteria.

Examples of the effectiveness of vaccines against bacterial infections in poultry, cattle, and swine are widespread. One of the most extensive uses of vaccines on feed animals has been with *Salmonella*, which has seen a substantial increase in antibiotic resistance and has resulted in many human infections (Barrow, 2000). Poultry, swine, sheep and cattle can all be infected with different types of *Salmonella* and vaccines are widely used. The extensive use of live, attenuated *Salmonella* vaccines has been especially successful in poultry (Barrow, 2000). These dermally administered host-specific

vaccines induce a strong immunity against future infection for a variation of *Salmonella* that produces typhoid-like symptoms. Vaccines for the *Salmonella* variation that is related to food poisoning have not been used extensively in the past, but recent research has shown new treatments to reduce the level of infection - leading to its licensing by a number of European countries (Barrow, 2000). While cattle have experienced significant variation in success with *Salmonella* vaccines, swine and sheep have exhibited promising responses (Barrow, 2000). Though success is varied, vaccines do not lead to the development of antimicrobial resistance in bacteria, and therefore help to alleviate that risk to human health.

Probiotics

Probiotics promote the healthy growth of livestock while limiting the possibility of antibiotic resistance. They work by promoting the growth of benign lactic acid bacteria in the gut flora early in an animal's life so that it is less vulnerable to bacterial infection due to the bacterial competitive exclusion in the gut (Reid and Friendship, 2002). In cattle, use of probiotics was connected to reduced *Salmonella* and *E. coli* infections (Callaway et al., 2008). Controversially, some *enterococci* (*E. faecium*) have even been applied as probiotics in chickens, resulting in higher feed conversion efficiency and egg laying intensity (Reid and Friendship, 2002). In swine there is evidence to show that probiotics can alter fecal bacterial flora, reducing diarrhea and improving weight gain (Reid and Friendship, 2002). While a number of anecdotal studies show positive effects of probiotics, many were not quantitative, so there is a dearth of statistical and clinical evidence to bolster the case for increased use of probiotics (Patterson and Burkholder, 2003).

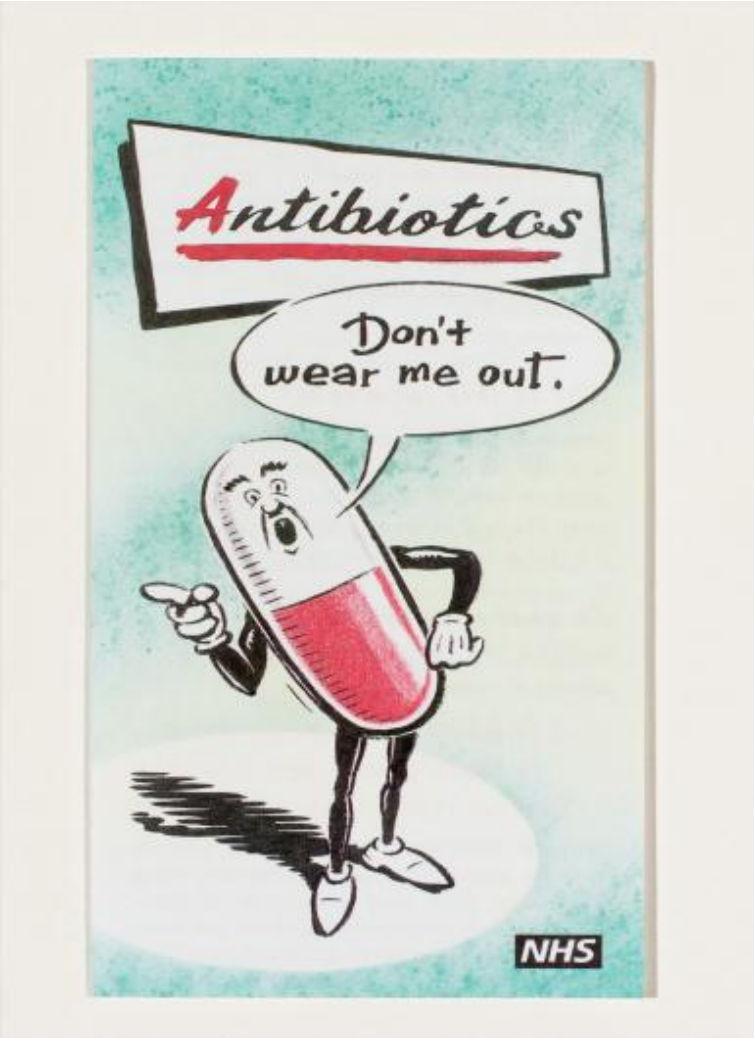
"We've listened to the concerns, studied the issue, and the bottom line was we thought it was the right thing to do to discontinue the use of [fluoroquinolone] antibiotics in poultry"

~ Walt Riker, Vice President of Corporate Communications, McDonalds Corporation

Private sector participation

Support from the private sector will be important in decreasing the use of nontherapeutic antibiotics. Some companies have been important proponents for ending the nontherapeutic use of antibiotics in animal agriculture. Such voluntary, market-based actions can complement political efforts to address the problem of antibiotic resistance by shifting demand to alternative products. McDonald's, for instance, is the largest purchaser of meat in the world and phased in its Antibiotics Use Policy in 2004, which prohibits the use of antibiotics that are in the same class as those used in human medicine for growth promotion purposes (McDonald's, 2003). In addition to this, McDonald's suppliers must comply with sustainability guidelines in the therapeutic application of antibiotics (McDonald's, 2003). After the implementation of this policy,

Tyson Corporate, McDonald's top supplier, reduced antibiotic use by 90% and poultry producers in the US lowered their antibiotic use by an estimated 223,600 pounds (Environmental Defense Fund, 2010). Other companies have similar policies, including Chipotle, Bon Appetit, and Compass Group (Environmental Defense Fund, 2007). In conjunction with pressure from retailers, some suppliers have also shifted towards antibiotic growth-promoter free production. For example, Smithfield Foods, the world's largest pork producer and processor, ended the use of antibiotics as growth promoters in 2002 (Smithfield Foods, 2009). These proactive measures taken in the absence of political and legal action demonstrate how the judicious use of antibiotics in animal agriculture is important to industry and already perceived to be a way of limiting resistance.



Source: Science Museum UK

Conclusion

The goal of the Preservation of Antibiotics for Medical Treatment Act is simple: protect the effectiveness of our antibiotics by curbing the growth of bacteria resistant to these drugs. The effects of banning the use of nontherapeutic critical antibiotics in livestock, however, are complex and difficult to predict. Denmark's experience with banning growth promoting antibiotics, but not those used daily for prophylaxis, did not lead to a significant reduction in use or resistance. In contrast, an absolute ban of the drug avoparcin yielded a rapid decline in levels of antibiotic resistance. The Act proposes a solution between these two scenarios – a ban on treating healthy animals with critical antibiotics for both growth promotion and disease prevention, but allowing for the treatment of sick animals. With no past models, it is uncertain whether implementation will lead to an increase in therapeutic use, as in Denmark, or if a complete restriction on nontherapeutic treatment will be sufficient to reduce resistance levels.

Despite uncertainty, action is necessary to protect important antibiotics and human health. Better husbandry practices, vaccines, and action from the private sector in combination with the Act could potentially lead to major reductions in antibiotic use. Since it is clear that overuse leads to increased resistance, any reduction in antimicrobial treatment might mitigate resistance. The synthesis of these measures would help, but it is important to recognize that contemporary industrial farming is unsustainable without the use of antibiotics. As long as demand for abundant, inexpensive meat continues, antibiotics will play a major role in animal agriculture, bacterial resistance will continue to spread, and critical antibiotics will lose effectiveness. Rethinking systems of meat production could be the only comprehensive solution.

Source: www.Care2.com

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