

# Antibiotics on the Farm: Agriculture's Role in Drug Resistance

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## Abstract

The discovery of antibiotics in the early 20th Century was a major breakthrough for human health, markedly reducing the infection threat from minor cuts, surgery, and cancer treatment. The more antibiotics are used, however, the faster bacteria adapt and become resistant to them. Antibiotic resistance is now spreading so rapidly, and the development of new antibiotics has slowed so much, that there is talk of a nightmarish post-antibiotic future where even minor injuries could once again become deadly if infection sets in. The threat is growing worldwide, but it is a particular problem in poor countries where respiratory infections and diarrheal diseases remain leading causes of death, especially among children.

While the misuse of antibiotics in human health is a key factor in accelerating the emergence of drug resistance, farmers also use large amounts of antibiotics in livestock. Moreover, many administer these drugs in feed

and water at low doses for extended periods to promote growth and prevent disease in their animals. Those are ideal conditions allowing drug resistant bacteria to thrive. Many industrialized countries are taking steps to address this risk, but there are often loopholes. And livestock production is growing rapidly in developing countries where antibiotic use is lightly regulated.

Policymakers desperately need more information about antibiotic use and resistance in humans and animals so they can assess the risks of this behavior for human health, and determine how aggressive they need to be with policies to change it. At the same time, there is growing evidence that the economic benefit to livestock producers of using antibiotics may be less than thought. Given what is at stake in keeping antibiotics effective, it is prudent to couple improved data collection with steps to reduce the use of medically important antibiotics in farm animals.

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## Introduction

The discovery of antibiotics in the early 20<sup>th</sup> Century was a breakthrough for human health.<sup>1</sup> Before that, even minor injuries could be deadly if an infection set in. But the more we use antibiotics, the faster bacteria adapt and become resistant to the drugs' effects. The Centers for Disease Control and Prevention estimate that 2 million people get sick and 23,000 die each year in the United States from antimicrobial resistant infections. Globally, the number could be more than 700,000 people (O'Neill 2014, pp. 8-9). Drug resistance is now spreading so rapidly that there is talk of a nightmarish post-antibiotic future where minor cuts could again become lethal and surgery and cancer treatment would be far riskier.

Antibiotic resistant bacteria are a threat to all of us. But the greatest danger is in poor countries where respiratory infections and diarrheal diseases remain leading causes of death, especially for children.<sup>2</sup> The second- and third-line drugs to which doctors turn when initial treatments fail are also generally more expensive. Having to use them strains the resources of already weak public health systems in developing countries and leaves the poor with few options (Center for Global Development 2010, pp. 17-19). The O'Neill review on antimicrobial resistance (2014), commissioned by UK Prime Minister David Cameron, projects that, if current trends continue, 10 million more people would die prematurely each year from drug resistant infections. The global economy would also be \$60 trillion to \$100 trillion smaller by 2050 and developing countries in Africa and Asia would bear the brunt of these burdens.

Several years ago, a CGD working group examined the large human and economic costs associated with drug resistance, particularly for developing countries (Nugent et al. 2010). That report documented how overuse and misuse of antibiotics in human health contributes to the problem.<sup>3</sup> Doctors often prescribe antibiotics for ailments that are not bacterial in nature and patients do not always take medications as directed. These practices kill off the more susceptible bacteria and allow the more resistant bacteria to survive and thrive. Consuming substandard or fraudulent drugs, which are a problem in many developing

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<sup>1</sup> Antibiotics are part of the broader antimicrobial drug category and some studies and data sources use the broader label. The key concerns, especially with respect to agricultural uses, relate to antibiotics, however, and that is the focus here.

<sup>2</sup> The World Health Organization presents data on the top ten causes of death in 2012, by income group, here: <http://www.who.int/mediacentre/factsheets/fs310/en/index1.html>, accessed February 9, 2015; see also Center for Global Development (2010, p. 3).

<sup>3</sup> The CGD report, like the O'Neill review, also examines public health threats that are not only bacterial in nature, including HIV/AIDS and malaria.

countries, has the same effect. The CGD report called for urgent global action to combat the problem, focusing on surveillance of resistance, research, and ensuring drug quality across the supply chain. That report did not address antibiotic use in animals, however. This paper fills that gap.

While the inappropriate use of antibiotics in human health is a key factor in accelerating the emergence of drug resistance, livestock producers in some countries use large amounts of antibiotics in low doses for extended periods to promote growth in their animals.<sup>4</sup> That is a recipe for accelerating resistance. And many of the drugs used in animals are the same as those used in human health, or are in chemically related classes of drugs. Intensive, high-density livestock operations, which are expanding rapidly, also routinely use antibiotics to prevent disease. By 2005, large, intensive livestock operations “account[ed] for three-quarters of the world’s poultry supply, 40% of its pork, and over two-thirds of all eggs” (Naylor et al. 2005; p. 1621). And “virtually all of the growth in livestock production is occurring in industrial systems,” especially in more lightly regulated developing countries (*ibid.*).

The evidence that antibiotic use in agriculture creates a pool of resistant bacteria in farm animals is not in dispute. The key questions relate to the magnitude of the risk to human health, and the productivity effects of antibiotic growth promoters. Importantly, some recent research suggests that the economic gains for farmers from using antibiotics are less than previously thought. Unfortunately, the failure to systematically monitor antibiotic use and resistance in humans and animals remains a key barrier to sound analysis and well-informed policy (WHO 2014). Thus, the first policy priority is the creation of harmonized surveillance systems in priority countries. Collecting and analyzing the needed data will take time, however. In the meantime, many countries, including the European Union and the United States, are taking steps to end the routine use of antibiotics for growth promotion. In 2015, the World Health Organization will also launch a global action plan to combat antimicrobial resistance.

This paper synthesizes research and available data on the use of antibiotics in livestock, and the potential costs and benefits of that use. It reviews recent policy actions to reduce this use and reviews in some depth recent research on the economic impact of antibiotic use in livestock. A key contribution of the paper is to put production of the global public bad of

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<sup>4</sup> Antibiotics are also used for disease prevention in aquaculture and horticulture, but the total amounts are small relative to livestock; see Hollis and Ahmed (2013, p. 2475).

antibiotic resistance in the context of national agricultural policies that perversely subsidize the livestock sector in all too many countries.

## **Setting the Stage: Livestock Subsidies, Consumption, and Trade**

Even in rich countries that have reformed their agricultural policies, the meat and dairy sectors often receive high levels of subsidies and other government support for producers. Increasingly, governments in developing countries are also supporting meat and dairy producers. One key difference is that consumption and production in developing countries are growing rapidly, as well.<sup>5</sup> Overall, the Food and Agriculture Organization of the United Nations projects that the consumption of animal products will increase more than 70 percent by 2050, with most of the growth in developing countries. Trade is also growing rapidly, which creates new avenues to transmit antibiotic resistance globally.

Figure 1a shows trends in per capita meat consumption over the past three decades. While the United States is by far the largest meat consumer on a per capita basis, average consumption is flat as is that of the European Union. Consumption in the large emerging markets—Brazil, China, and Russia (after the Soviet Union’s collapse)—is growing rapidly as a result of rising incomes that allow consumers to add more animal products to their diets. India currently consumes very little meat but, among developing countries, it is a large and growing consumer of dairy products. And the FAO projects that India’s poultry consumption will increase by “a staggering 850 percent” by 2030 (Robinson and Pozzi 2011, p. viii).

To meet growing demands for animal products over the years, major producers have long been moving to larger, more specialized and intensive production models (NRC 1999; Center for a Livable Future 2013, p. vii). To get the flavor of what this means, consider the changes in US livestock operations over the past five decades. The average number of cattle and chickens on American farms and ranches doubled; the inventory of the average pork producer increased from 49 animals in 1964 to 1,100 in 2012. And these averages vastly understate the degree of concentration. For example, two-thirds of hogs and pigs are produced on just 5 percent of swine operations, with an average of 15,000 animals per farm (table 1). More intensive production is more efficient, but it also contributes to air and water

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<sup>5</sup> See Elliott (2013, pp. 10-11) for a discussion of these trends. After the paper was published, India submitted a long-delayed report on its agricultural subsidies to the World Trade Organization. Those data suggest that India’s support to agriculture is comparable to China’s and following a similar upward trend.

pollution. And, increased livestock densities makes disease management a critical concern, often leading to an increased demand for antibiotics.

The intensive production model is also spreading rapidly in emerging economies. China is the world's largest meat producer by far (figure 1b) and one recent report estimates that the share of Chinese pork produced by "factory farms" rose from 2.5 percent in 1985 to 22 percent in 2007 (Schneider 2011, pp. 6-7). A researcher at the Chinese Academy of Sciences (CAS) cited estimates that China consumes a total of 150,000 to 200,000 metric tons (MT) of antibiotics each year (roughly ten times US levels), and that about half of the total goes to livestock (mostly pigs) (Larson 2015, P. 704). At the end of 2014, the China Central Television (CCTV) network reported that large amounts of antibiotics, "up to four times the legal limit in the United States," were found in China's major rivers and in some cities' tap water.<sup>6</sup> A pharmaceutical company admitted to dumping antibiotics in rivers near its production facilities. But CAS researchers, using genetic analysis, identified farms as the major source (Larson op cit.). In 2011, China's Ministry of Agriculture announced plans to ban the use of antibiotics to promote growth in livestock and to require a veterinary prescription for antibiotic use. China's food system has been scarred by a number of scandals in recent years, however, and it is unclear how effectively this regulation will be implemented.<sup>7</sup>

India also loosely regulates antibiotic use in people and animals and it has a growing drug resistance problem. *The New York Times* reported in late 2014 that 58,000 infants had died in India the previous year antibiotic treatments failed.<sup>8</sup> According to the chair of the neonatology department at a prominent New Delhi hospital, over the previous five years, the share of babies they were seeing with infections that were multidrug resistant had grown from almost none to nearly all of them. The article quoted one researcher as saying that the problem was due to "India's dreadful sanitation, uncontrolled use of antibiotics and overcrowding coupled with a complete lack of monitoring." The article also noted that antibiotic use is common in the rapidly growing poultry industry and it pointed to a study that found antibiotic residues in 40 percent of chicken samples.

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<sup>6</sup> See <http://blogs.cfr.org/asia/2015/01/16/maxine-builder-antibiotics-in-chinas-rivers-an-emerging-health-threat/>, accessed February 9, 2015.

<sup>7</sup> Ibid. Also see the special topic page on "China Food Scandals" on the South China Morning Post website here: <http://www.scmp.com/topics/china-food-scandals>. In addition to concerns about resistance, antibiotic residues in meat and other food products can be a problem in countries with relatively weak regulatory systems.

<sup>8</sup> [http://www.nytimes.com/2014/12/04/world/asia/superbugs-kill-indias-babies-and-pose-an-overseas-threat.html?\\_r=0](http://www.nytimes.com/2014/12/04/world/asia/superbugs-kill-indias-babies-and-pose-an-overseas-threat.html?_r=0), accessed February 9, 2015.

These trends make addressing the externalities associated with livestock production, including antibiotic resistance, particularly important and urgent. Far from addressing those externalities, table 2 shows that key countries protect and subsidize their meat and dairy producers. These figures understate the degree of producer support, including in the United States, because they do not include support for livestock as a group or for agriculture as a whole, such as irrigation and energy subsidies.

More important, these data miss the implicit subsidies that arise from the failure to control or tax the negative spillovers associated with livestock production. In addition to antibiotic resistance, these can include local problems, such as air and water pollution, and other global public bads, such as large greenhouse gas emissions (FAO 2006). The rest of the paper focuses on antibiotic use primarily in the United States and Europe because data and research are more readily available. But the growth in livestock production and antibiotic use in the large emerging markets underscores the need for global cooperation.

## **Antibiotic Use on the Farm**

In the 1940s, researchers inadvertently discovered that animals given feed containing certain antibiotics grew faster and needed less feed per pound of meat produced (called feed efficiency). Although the mechanism by which this happens is not fully understood, the US Food and Drug Administration (FDA) approved the use of antibiotics as a feed additive without a prescription shortly thereafter (Mathew et al. 2007, p. 116). Regulators across Europe followed a similar path (Cogliani 2011, p. 274). As a result, farmers began routinely administering small doses of certain antibiotics for extended periods of time to all or most of their animals. Unfortunately, that is the recipe for stimulating the growth of drug resistant bacteria (WHO 2012, p. 51).

As livestock producers moved to more intensive production systems, they also began using antibiotics to prevent disease in healthy animals (prophylaxis), as well as to treat disease.<sup>9</sup> The European Union now bans antibiotic growth promoters (AGPs) and the United States is phasing them out. But both still allow the use of antibiotics for disease prevention. Since many drugs approved for disease prevention are the same as those previously approved for growth promotion, producers could continue to use antibiotics largely as they had been, just under another name.

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<sup>9</sup> Rushton et al. (2014, pp. 10-11) provide more detail on antibiotic uses in various types of animals.

Data on antibiotic use in farm animals are sparse, but, where we have data, the numbers are strikingly large. The figure most commonly seen in the press is that 80 percent of American antibiotic use is in farm animals. The Centers for Disease Control and Prevention (CDC) concluded in a recent report that more than half the total antibiotics used in the United States each year are used in livestock (CDC 2013, 11). According to industry surveys in Europe in the late 1990s, about half of total antibiotic use there was also for animals (Follet 2000, p. 151). In Denmark, even after the government banned AGPs, the total volume of antibiotics used in animals was twice as high as that prescribed for humans (National Food Institute, 2012, p. 11). Overall, the available data reveal that drug companies sold or distributed around 10,000 MT of antibiotics for use in food animals in 2012 in the United States, and 8,000 MT in Europe.<sup>10</sup>

To understand the links between agricultural uses of antibiotics and potential threats to human health, however, we need to know far more than just the aggregate numbers. We also need to know how farmers are using antibiotics—in which animals, when, and for what purposes. The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) provides one model. Denmark started monitoring antibiotic use and resistance in animals and humans in the mid-1990s, earlier than most. The DANMAP reports include data on which antibiotics are used in which animal species in what amounts and they integrate this information with data on use and resistance in human health.<sup>11</sup> Surveillance in most of the rest of Europe is improving, but still has far to go. The United States collects some highly aggregated data, but lags far behind in providing detail on how farmers use antibiotics in livestock. We know relatively little about antibiotic use in agriculture in the rest of the world.

## **Europe**

The European Medicines Agency published the initial report from the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project in 2010 (EMA 2014, pp. 22-23). The report provides data on antimicrobial use in the livestock sector by country, drug class, and mode of administration and the EMA is working to add species-specific data. The 2014 ESVAC report covered 24 EU member countries, plus Iceland and

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<sup>10</sup> Neither figure includes ionophores, a class of antibiotics never approved for use in human health and not known to contribute to resistance problems. The total figure for US use as reported by the US Federal Drug Administration is just under 15,000 MT, which includes ionophores (FDA 2014).

<sup>11</sup> National Food Institute (2012) summarizes the Danish approach and illustrates the effects of changes in Danish policy. The DANMAP website, with all of the reports, is <http://www.danmap.org>, accessed January 14, 2015. Rushton et al. (2014, p. 121) report that Sweden and Norway have similar systems.



Norway, up from just 9 in the first report. In addition to total volumes, the ESVAC project also reports antimicrobial use per “population correction unit” to control for differences in animal numbers and sizes. This makes it possible to roughly compare usage across countries.

Figure 2 shows the most recent ESVAC results for selected countries, as well as trends for some that have been reporting to ESVAC longer. What is striking is the variation across countries, which correlates with differences in policy as I discuss below. These data alone do not shed much light on AGP use because the ESVAC reports began after the EU’s 2006 ban. A European industry survey in the late 1990s found that only a third of antibiotic use in livestock was for growth promotion (Follet 2000, p. 151). But that is lower than what Danish and Dutch national data shows for the late 1990s (figures 3-5).

The ESVAC reports do include important information on antimicrobial delivery methods. In 2012, more than a third, on average, were included in “premixes” prepared by feed mills, and more than half were in the form of oral powders or solutions that producers often add to feed or water themselves (EMA 2014, p. 25). In other words, farmers are still mostly administering these drugs in forms that are appropriate for preventing disease in whole herds or flocks of mostly healthy animals, rather than to treat sick animals.

## **United States**

In 2008, Congress required drug producers to report to the FDA on sales and distribution of antimicrobials for use in food-producing animals. Congress also directed the FDA to issue a summary public report that protects companies’ proprietary information.<sup>12</sup> From 2009 through 2013, the reports were just a few pages long with one table listing the total volume of drugs for use in animals by antimicrobial class. The 2014 report, by contrast, was 56 pages long and it provides a bit more information on how these drugs are used in American agriculture. There is still no way, however, to know how much of the total was used to promote growth, prevent disease, or to treat sick animals. And, as in Europe, we also do not know how much farmers used in pigs versus chickens or cattle.

According to the 2014 report, the total volume of antimicrobials sold or distributed for use in food animals in 2012 was 32 million pounds, an increase of 16 percent over 2009. The

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<sup>12</sup> Under the confidentiality requirements of the law, the FDA can only report independently on “categories with three or more distinct sponsors of approved and actively marketed animal drug products.” The effect is that some data are reported in highly aggregated categories. In particular, the FDA cannot report separately on antibiotics approved for growth promotion because of this confidentiality rule.

report also reveals that 61 percent of those drugs were in “medically important” drug classes, meaning they are also used in human health. The other 39 percent were mostly in the ionophore class, which are not used in human medicine and which have not been linked to resistance problems. Of the medically important drugs, 97 percent were sold over the counter and 94 percent were administered either through feed or water.

We also know that two-thirds of the medically important drugs had FDA approval to be used for “production purposes,” that is growth promotion and feed efficiency. But many of those same drugs are approved for therapeutic purposes (treatment or prophylaxis). A 1995 study by the (now defunct) Office of Technology Assessment estimated that 90 percent of the antimicrobials used in livestock were used prophylactically or for growth promotion (OTA 1995, chapter 7; Union of Concerned Scientists 2001). That is consistent with the share administered in feed or water.

### **Emerging Markets and Global Consumption Trends**

In a recent paper, Thomas P. Van Boeckel, Ramanan Laxminarayan, and colleagues provide rough estimates of global antimicrobial consumption in agriculture. Using projections of the rapidly growing consumption of animal products, mainly in developing countries, they also estimate how much antimicrobial consumption might grow by 2030 if policies do not change. The authors use statistical models to combine data on “livestock densities, economic projections of demand for meat products, and current estimates of antimicrobial consumption in high-income countries to map antimicrobial use in food animals for 2010 and 2030” (Van Boeckel et al. 2015, p. 1). They estimate that global antimicrobial use in livestock in 2010 was between 60,000 and 65,000 MT and that it could rise by two-thirds by 2030 if nothing is done. They project that antimicrobial use in Brazil, China, India, Russia, and South Africa will roughly double.

In 2010, the authors estimate that the top five consumers of antimicrobials for livestock production were China, the United States, Brazil, India, and Germany. By 2030, the authors project that the rankings will be similar, except that Mexico will replace Germany as the fifth largest overall consumer and China’s share of the global total will rise from 23 percent to 30 percent. Other developing countries will see even faster growth in antimicrobial consumption for livestock, including Indonesia, Nigeria, and Vietnam (*ibid.*, p. 2). Note,

however, that other estimates for China suggest that the estimates for both current and future consumption in that country, and globally, may be significantly understated.<sup>13</sup>

## **Antibiotic Resistance on the Farm: Risks to Human Health**

Thus, farmers and ranchers routinely use large amounts of antibiotics in farm animals and do so in ways that create ideal conditions for the emergence of drug resistance. Many of those drugs are either the same as those used in human medicine or are chemically related (FAO/WHO/OIE 2007). These drug resistant bacteria can move then from animals to humans through a variety of channels<sup>14</sup>:

- To farmers, their families, or employees through direct contact with animals
- To those groups, their neighbors, or others through soil and water contamination (for example, if farmers use manure for fertilizer) or via airborne particles
- To consumers via contaminated meat

Bacteria also pass resistance genes back and forth, creating another mechanism by which antibiotic resistance could be transferred to human pathogens (Rushton et al. 2014, pp. 16-21; and Ward et al. 2014 for a specific example of gene transfer).

In an early study exploring links between antibiotic resistance in animals and humans, researchers from Tufts University gave poultry a feed mix that was supplemented with tetracycline. Within just a week, almost all the intestinal flora in the chickens were resistant to that antibiotic. Within a few months, a third of fecal samples from human residents on the farm showed they also had higher levels of tetracycline resistant bacteria than their neighbors (80 percent versus 7 percent) (Levy et al. 1976). Marshall and Levy (2011) summarize the evidence from well over one hundred research studies from around the world that showing increased prevalence of drug resistant bacteria in animals routinely fed antibiotics and in workers and family members on those farms.

Surveillance systems in the United States and European Union also reveal relatively high rates of drug resistant bacteria in meat samples, particularly poultry. As part of the National Antimicrobial Resistance Monitoring System (NARMS), the FDA has been monitoring

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<sup>13</sup> See Larson (2015) and Zhu et al. (2013).

<sup>14</sup> The CDC has a graphic and website discussing the links here, <http://www.cdc.gov/foodsafety/from-farm-to-table.html>, accessed March 23, 2015.

bacteria in retail meats since 2002.<sup>15</sup> The most recent data (for 2011) showed, for example, that 50 percent of retail chicken samples had campylobacter bacteria that were resistant to tetracycline and 20 percent that were resistant to ciprofloxacin. About half of the salmonella isolates from poultry meat were multi-drug resistant.<sup>16</sup> The European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Agency issue a joint summary report on the prevalence of antibiotic resistant bacteria in animals, humans, and food. As in the United States, EU surveillance showed that the highest levels of antibiotic resistance bacteria were usually in poultry meat—around of 70 percent of salmonella isolates from chicken and turkey samples showed resistance to ciprofloxacin. There were also high levels of resistance to certain antibiotics in campylobacter bacteria in poultry meat.<sup>17</sup>

In a particularly intriguing case from Canada, researchers found a strong correlation between changes in antibiotic use in chicken hatcheries and changes in drug resistant salmonella in retail chicken samples and humans (Dutil et al. 2010). In 2005-07, because of public concerns about rising resistance, Quebec chicken hatcheries voluntarily stopped injecting eggs with an antibiotic from the cephalosporin class that is chemically related to a critically important human drug. The prevalence of resistant Salmonella bacteria in retail chicken dropped from over 60 percent to 10 percent in the first year after the ban; in humans the prevalence dropped from 40 percent to almost zero over two years. The incidence of drug resistant infections in humans also dropped sharply, albeit from very low initial levels.

Finally, the environment is a potentially important route for transferring drug resistance from animals to humans, as illustrated by the antibiotic-laden rivers in China. But Laxminarayan et al. (2013, p. 1069) argue that it is understudied relative to the food-borne pathway. One recent effort to fill this gap is MacEachran et al. (2015). The authors found that particulate matter collected downwind of cattle feedlots in the Southern High Plains of

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<sup>15</sup> NARMS also tracks changes in the susceptibility to antibiotics of certain intestinal bacteria found in ill people (the CDC) and food animals (USDA). The data is available at: <http://www.cdc.gov/narms/>, <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm>, <http://www.ars.usda.gov/Main/docs.htm?docid=6750>, accessed January 14, 2015.

<sup>16</sup> The 2014 FDA news release is available here: <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm409035.htm>; and an interactive data display is here: <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm416741.htm>, both accessed February 9, 2015.

<sup>17</sup> The 2015 report is here, <http://www.efsa.europa.eu/en/efsajournal/pub/4036.htm>, accessed March 23, 2015; the ECDC also collects data on human antibiotic consumption (ESAC-Net) and resistance (EARS-Net), <http://www.ecdc.europa.eu/en/activities/surveillance/Pages/index.aspx>, accessed January 14, 2015.

Texas carried traces of antibiotics, as well as genes encoded for antibiotic resistance, that were not present in upwind samples.

Overall, there is a growing body of evidence that antibiotic use in food animals is linked to the emergence of drug resistant bacteria in food animals. The Marshall and Levy (2011) literature review finds scattered, but compelling, evidence for the transfer of resistance from animals to humans. The key unknown is how often resistant bacteria lead to serious infections in humans (OTA 1995, chapter 7). Mathew et al. (2007, p. 126) provide a useful summary and analysis of the issues and conclude:

*It is well established that agricultural use of antibiotics results in increased prevalence of antibiotic resistant bacteria in farm environments, thus contributing to the global pool of resistant organisms. However, what risk this poses to human health has not been clearly established.*

A National Research Council report (1999 p. 8) concluded similarly that:

*A link can be demonstrated between the use of antibiotics in food animals, the development of resistant microorganisms in those animals, and the zoonotic spread of pathogens to humans. The incidence of the spread of human disease in that way is historically very low, but data are seriously inadequate to ascertain whether the incidence is changing.*

More than a decade after that report, the systematic data on antibiotic use and resistance in animals and humans that we need to thoroughly assess the risks is still lacking (WHO 2012, p. 50; Laxminarayan et al. 2013, p. 1061, 1069-70). As Landers et al. (2012) conclude from their extensive review of the literature, antibiotic use in livestock is “widespread, yet poorly characterized.” For example, distinctions between therapeutic, subtherapeutic, and prophylactic uses are not clear and definitions across countries and monitoring systems differ. Overall, the authors find that neither the human risks nor the animal production benefits of antibiotic use are well-studied (ibid., p. 5). Even with better data, the link between antibiotic use in food animals and resistant infections in humans is difficult to make definitively because the biological and ecological processes involved are extremely complex (Laxminarayan et al. 2013, pp. 1069-71).

The dilemma for policymakers is that antibiotic resistance is spreading rapidly *now* and the costs of losing antibiotics as a treatment option would be enormous, while it will take years to collect the necessary data and do further research. Over the past two decades, many countries have created mechanisms to monitor antibiotic use and resistance, and more are doing so. But many countries and the World Health Organization have also concluded that

the risks of waiting are too great and they are taking precautionary steps to reduce antibiotic use in agriculture.

## **Evolving Policies on Antibiotic Use in Agriculture**

One of the first official reports to examine the potential human health hazards of antibiotic use in animals was the Swann Committee in the United Kingdom in the late 1960s. Because of the paucity of hard data, the committee recommended the creation of surveillance programs to track antibiotic use and resistance, as well as precautionary restrictions on the use. The European Union regulators moved earliest and have gone furthest in restricting the use of antibiotic growth promoters. American regulators have been more constrained by the politics of agricultural policy in this country and only recently moved to restrict the use of antibiotic growth promoters. President Obama launched a national strategy to combat antimicrobial resistance in September 2014, but the provisions on agricultural uses are still relatively restrained.

Relatively little is known about policies governing antibiotic use in farm animals in other countries. The World Organization for Animal Health (OIE) conducted a survey of member countries in 2012 on the topic and received responses from 152 of 178 member countries.<sup>18</sup> Of those, half reported that they had banned AGPs; another 19 percent reported having restrictions on AGPs and 30 percent had no restrictions. The OIE did not reveal which countries were in which categories and there is no information on how those with bans are implementing them. Moreover, 70 percent of respondents reported having no official system to collect data on antibiotic use, so it would be impossible to assess the impact of any restrictions. A US Congressional Research Service report from 2011 compiled information on policies restricting AGPs and identified only New Zealand as having banned them. The researcher found information indicating Japan, South Korea, and Thailand either had or were considering restrictions on the use of antibiotics in farm animals (Johnson 2011, p. 12).

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<sup>18</sup> A presentation from the OIE Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals is here, [http://www.oie.int/eng/A\\_AMR2013/Presentations/S2\\_4\\_Fran%C3%A7oisDiaz.pdf](http://www.oie.int/eng/A_AMR2013/Presentations/S2_4_Fran%C3%A7oisDiaz.pdf), accessed January 13, 2015.

## **Europe Follows a Precautionary Path**

Not long after the release of the Swann report, European regulators withdrew approval to use penicillins, tetracyclines, and streptomycin to promote growth in animals (Cogliani et al. 2011, p. 278). Farmers could still use these drugs to treat infections in animals and regulators allowed antibiotics approved only for animals to continue being used as feed additives to promote growth. But the latter drugs were often chemically related to antibiotics used for human health. When evidence of resistance to those antibiotics in animals, and of related drugs in humans, began to emerge, European countries gradually tightened the restrictions in the 1990s and 2000s.

In 1986, Sweden became the first country to ban AGPs. Interestingly, the government acted at the behest of the Federation of Swedish Farmers, which was concerned about the reaction from consumers following a report on the heavy use of antibiotics in agriculture (Cogliani 2011, p. 275). Antibiotic use in farm animals dropped by almost half. A decade later, Danish researchers began to document the heavy use of antibiotics in animals and to investigate the links to resistance in animals and humans. Denmark's first step, in 1995, was to prohibit veterinarians from profiting from the sale of antibiotics to farmers. That immediately cut therapeutic uses of antibiotics by almost half, and overall use by a third (Aaerstrup 2012, pp. 465-66). That same year, the government created a system for monitoring antibiotic use and resistance in humans and animals.<sup>19</sup> Danish officials followed with bans on using particular drugs as AGPs as resistance concerns emerged. Danish pork producers then voluntarily phased out the use of all antibiotic growth promoters in 1998-99 and the government followed with a formal ban in 2000 (Aaerstrup 2012; Levy 2014).

Other EU member countries, and ultimately the European Union, followed. In 1999, EU regulators prohibited the use of all remaining "medically important" antibiotics for growth promotion. In 2006, the European Union prohibited the use of any antibiotic for growth promotion purposes. For a few countries, where data are available from ESVAC, we can see the impact of these restrictions on antibiotic use (figure 2). Sweden and Denmark, which took action well before 2005, are at the bottom and use is relatively stable. Cogliani et al. (2011, p. 277) report that the British government undertook education campaigns and encouraged farmers to phase out AGPs well before the EU ban went into effect and use in that country was also relatively low by the mid-2000s. Germany, Italy, and Spain only

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<sup>19</sup>Aaerstrup found that veterinarians were earning as much as a third of their income from selling antibiotics to farmers (Levy 2014, p. A162).

recently began reporting to ESVAC and the data show that antibiotic use remains at far higher levels in those countries. Antibiotic use in France and the Netherlands was at much higher levels than Denmark, Sweden, and the UK prior to the EU ban in 2006. In France, antibiotic use declined steadily but in the Netherlands it actually went up slightly immediately after the ban.

The trends in several of these countries show that antibiotic use for prevention or treatment often increased after authorities imposed restrictions. Figures 3-5 illustrate these trends for Sweden, Denmark, and the Netherlands, where at least some data on AGP use is available before and after the bans. In each case, overall use of antibiotics declined after AGPs were banned, but therapeutic use increased, at least for a time. Thus, regulators often found they needed to take additional steps to rein in antibiotic use in livestock.<sup>20</sup>

The Swedish monitoring report shows total antibiotic use in farm animals falling from 45 MT, of which 17 MT were feed additives, to 25.8 MT in the first year of the AGP ban (National Veterinary Institute 2000, p. 13). Therapeutic usage then rose to around 30 MT, reportedly because of an increase in the treatment of disease in piglets. The government worked with producers to change management practices to improve animal health and, after the mid-1990s, antibiotic resumed falling and settled at around 11 MT. In Denmark, therapeutic use increased steadily through the 2000s, despite declining swine mortality in the late 2000s (Aerstrup et al. 2010). In 2010, Danish authorities introduced the “yellow card” system to identify food producers using quantities of drugs above certain thresholds and get them to action to reduce consumption.<sup>21</sup> In the Netherlands, after the AGP ban initially produced no change in antibiotic use, the government prohibited the use of antibiotics to prevent disease and set a goal of reducing overall use by 50 percent. They also worked with producers to change husbandry practices and the goal of a 50 percent reduction in antibiotic use was achieved a year early.

### **US Policymakers Move, but Cautiously**

In the mid-1970s, the FDA undertook a review of the safety of using medically important antibiotics to promote growth in farm animals, the first step toward regulating them.

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<sup>20</sup> Cogliani et al. (2011) summarizes lessons from the EU experience; see also Aerstrup (2012) on Denmark and Maryn McKenna on the Netherlands, here <http://modernfarmer.com/2014/06/abstinence-method/>, accessed February 13, 2015.

<sup>21</sup> The Danish Ministry of Food, Agriculture and Fisheries explains here, [http://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/25\\_PDF\\_word\\_filer%20til%20download/Yellow%20Card%20Initiative.pdf](http://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/Yellow%20Card%20Initiative.pdf), accessed March 26, 2015.



Congressional appropriators directed the FDA to suspend its regulatory actions and commission the National Academy of Sciences to study the issue instead.<sup>22</sup> That study concluded that the potential hazard to human health from AGPs was “neither proven nor disproven,” and that a single study to settle the issue was “technologically impractical.” Congressional appropriators directed the FDA to keep its regulatory efforts on hold while further studies were being done (ibid.).

Nearly 40 years later, amidst lawsuits and petitions trying to force its hand, and threats of lawsuits from industry interests if it acts, the FDA is still struggling with how to regulate antibiotic use in farm animals.<sup>23</sup> The FDA has begun moving, albeit using “voluntary guidance” because the agency believes it will be faster than the formal regulatory process. And in 2014-15, the Obama administration raised the priority of the issue and launched a national strategy to combat antibiotic resistance. The provisions on livestock use, however, do not go much beyond what the FDA is already trying to do.

The FDA took its first step in 2003 when it announced that it was unlikely to approve the use of medically important antibiotics in animals in the future. The guidance had no effect on past drug approvals, however, and no apparent effect on use. Figure 3 patches together data from the Animal Health Institute (a veterinary drug industry association) and recent FDA reports. It shows continued increases in the total volume of antibiotics being sold or distributed for use in animals after 2003.

In 2004-05, the agency prohibited the use in poultry of enrofloxacin because of concerns about the increasing prevalence of drug resistant campylobacter infections in humans. Enrofloxacin is a fluoroquinolone, a class of second-line drugs, including ciprofloxacin, that the World Health Organization has identified as critically important for human health (WHO 2012b). In 2012, the FDA also banned off-label (unapproved) uses of third and fourth generation cephalosporins after studies showed that routine injections of chicken eggs

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<sup>22</sup> This legal brief from the Center for Science in the Public Interest summarizes the background of FDA attempts to regulate antibiotic use in agriculture, [http://www.cspinet.org/ar/petition\\_3\\_99.html](http://www.cspinet.org/ar/petition_3_99.html), accessed March 23, 2015.

<sup>23</sup> These articles indicate the pressures that the FDA is under, <http://www.theatlantic.com/health/archive/2012/01/the-failure-of-the-fda-why-were-still-using-antibiotics-on-livestock/251442/>; <http://www.healthline.com/health/antibiotics/politics-pork-and-poultry-why-legislation-has-not-passed>, accessed March 23, 2015.

at hatcheries was promoting Salmonella resistance.<sup>24</sup> These drugs are also on the WHO list of critically important drugs.

In 2011 and 2013, the FDA issued two voluntary guidance documents to discourage the use of antibiotics for growth promotion in food animals. In the first document (#209), the FDA, for the first time, formally declared that “the use of medically important antimicrobial drugs for production purposes in food-producing animals does not represent a judicious use of these drugs.” The second guidance document (#213) followed up by asking drug producers to change the labels on medically important antibiotics to remove growth promotion as an approved use by 2016.<sup>25</sup> As of early 2014, drug companies accounting for virtually all veterinary antibiotic sales had announced their intention to cooperate and to change their labels accordingly.<sup>26</sup>

The second guidance document also asked drug producers to change their drug labels to require veterinary oversight for the remaining approved uses of antibiotics. But there is a large potential loophole because the document allows veterinarians to continue to prescribe antibiotics for group-level use to prevent disease. A recent analysis by the Pew Charitable Trusts (2014, p. 2) shows that there is significant overlap in the recommended dosages of drugs approved for growth promotion and for disease prevention:

*About one-quarter of medically important antibiotics (66 of 287) can be used in at least one species for disease prevention at levels fully within the range of growth promotion dosages and with no limit on the duration of treatment. FDA classifies 29 of these 66 antibiotics as critically important in human medicine, and 37 as highly important.*

Moreover, the experiences in Denmark and, in particular, the Netherlands show that, without close monitoring and enforcement, the overall level of antibiotic use may not drop when authorities ban AGPs. The Danish case also suggests that giving veterinarians increased oversight responsibilities may not be effective if they profit from the sale of drugs to farmers. In the United States, many veterinarians have financial ties to drug companies

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<sup>24</sup> See FDA background information here, <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm421527.htm>, accessed February 11, 2015; see also Center for a Livable Future (2013, p. 9).

<sup>25</sup> FDA guidance #213, which also discusses #209, is here: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf>. Levy (2014) also discusses the history of the FDA’s efforts to reduce AGP use and why it opted for a voluntary approach.

<sup>26</sup> The FDA press release is here: <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390738.htm>, accessed January 14, 2015.

and, unlike medical doctors, there are no regulations requiring veterinarians to disclose these relationships.<sup>27</sup>

The Obama administration should address this gap, but as of early 2015 it had not. Neither President Obama's national strategy to combat antibiotic resistance, nor the report of the President's Council of Advisors on Science and Technology (PCAST 2014, p. 2) that inspired it, address veterinarians' potential conflicts of interest or propose steps much beyond the FDA's current approach. The July 2014 PCAST report recommends action in three areas:

- Improved surveillance to quickly identify and contain antibiotic resistant infections
- Prudent use, in both human health and agriculture, to conserve the efficacy of existing antibiotics for as long as possible
- Incentives to encourage the development of new antibiotics and alternative treatments

With respect to antibiotic use in livestock, the report notes that this is "a matter of very serious concern." But it merely encourage the FDA to vigorously implement the new voluntary guidance documents and to monitor progress by tracking total sales for livestock, which the FDA already does. Some in Congress have introduced legislation authorizing the FDA to go further and collect farm-level data on antibiotic use.<sup>28</sup>

The report also recommends that the US Department of Agriculture use its extension services to educate farmers about the new guidance, and veterinarians about their enhanced oversight role. The president's 2016 budget request, which requested almost doubling funds for combating antibiotic resistance overall, included money for educational programs as recommended and for research into alternatives for growth promotion and disease prevention in farm animals.<sup>29</sup> But the national strategy falls short on collecting more

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<sup>27</sup> Duff Wilson and Mimi Dwyer for Reuters at <http://www.reuters.com/article/2014/12/23/farmaceuticals-vets-idUSL1N0U60Y220141223>, accessed February 11, 2015.

<sup>28</sup> See, for example, <http://www.reuters.com/article/2014/09/16/us-farmaceuticals-chicken-congress-idUSKBN0HB1YZ20140916>, accessed February 2, 2014.

<sup>29</sup> The President's executive order is here <http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria>, and Maryn McKenna discusses the budget proposal here, <http://www.wired.com/2015/01/white-house-budget/#more-1719199>, accessed February 12, 2015.

information about antibiotic use in farm animals and on ensuring that the incentives facing veterinarians are aligned with the strategy's public health goals.

## **Economic Effects of Restricting Antibiotic Use in Agriculture**

Given the uncertainties about the magnitude of the risks to human health, additional aggressive steps to reduce antibiotic use in livestock are more questionable if the economic benefits of that use are large. Recent studies, however, suggest that improvements in livestock management reduce the need for antibiotics, and that any remaining economic benefits are small when farmers follow good practices. There is also more evidence on real-world impacts from Sweden and Denmark, where the governments implemented AGP restrictions decades ago. A few experimental studies from animal scientists and others in the United States also find small or even no net production benefits from using antibiotics in modern management systems.

The studies that previously found relatively large growth effects from using AGPs were generally done before 1990. Laxminayaran et al. (2015) review these studies, as well as a number of the more recent analyses, and they find that the economic benefits declined over time. With improved nutritional and hygienic practices, and improved breeds, these authors find that the benefits are small in modern livestock production systems (pp. 4-5). Many of the more recent studies have been conducted by Kansas State University researchers on pork operations in the United States. Professor Steve Dritz says the researchers “started to reevaluate the use of antimicrobials and found that the [growth] responses are much lower in magnitude than earlier claims” (Larson 2015, p. 704).

More direct evidence on the impact of restricting antibiotic use is becoming available as more countries implement AGP bans, though the data still have large holes. Only nine countries cooperated to produce the first European report on antimicrobial consumption in livestock and that data source begins only in 2005—just one year before the ban on all AGPs went into effect. Cogliani et al. (2011) surveyed the available research as of a few years ago and concluded that “in general, animal food production in these countries continues to thrive, *with appropriate adjustments in practices to ensure continued animal health and safety*” (emphasis added, p. 274). It is important to note, however, that this survey does not provide any data on production costs before or after the bans.

More detailed research in Sweden, Denmark, and the United States suggests the following effects of restricting AGP use in farm animals:

- Little or no impact on productivity or costs in poultry production
- Some increased disease in young pigs, but little or no impact on productivity in older pigs
- The costs associated with adjustments in management practices appear to be small, with some important exceptions

Wierup (2001) examined the Swedish experience and found “no negative clinical effects” of the AGP ban in beef, turkeys, or pigs at slaughter. Farmers also used some of the antibiotics approved as growth promoters to prevent a particular disease in chickens (necrotic enteritis), however, and antibiotic use did not fall in that sector until producers made changes in diets and the living environment to prevent the disease. Wierup (p. 187) also found little impact on older pigs, but he did find increased mortality and lower feed efficiency among piglets. A decade after the ban, he found that, on average, it took an additional day and a half for a young pig to reach 25 kilograms. Feed efficiency was actually higher, however, among “progressive” producers. Wierup reports that researchers had found similar results following AGP bans in Denmark, Finland, and Norway (p. 189).

The World Health Organization convened an expert group in 2002 to examine the Danish case in detail. The resulting report (WHO 2003, pp. 6-8) broadly confirmed Wierup’s findings for Sweden. In poultry, Danish farmers used ionophores, a class of antimicrobials not used in human medicine, to control disease and there was no increase in mortality. Average growth was also the same after the ban, though feed efficiency dropped a bit over 2 percent.<sup>30</sup> The expert group concluded, however, that the extra cost of more feed was offset by the lower cost of not having to add AGPs to the feed (WHO 2003, p. 41).

The WHO report and Aaerstrup et al. (2010) also confirm Wierup’s findings that there was little impact of removing AGPs on older pigs (finishers), but some negative impact on younger pigs. Aaerstrup et al. found little or no impact on total pig production, average weight gain, or feed efficiency in older pigs. Mortality was increasing for both older and younger pigs prior to the ban and the authors find no statistically significant change in the trend after the ban took effect. One puzzle is that therapeutic use of antibiotics continued to increase modestly even after mortality in swine dropped. One explanation is that the price of antibiotics in this period was dropping.

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<sup>30</sup> Emborg et al. (2001), cited in Aaerstrup (2012, p. 466), find no decline in either the total of chickens produced or the amount of feed used.

The experts contributing to the WHO report on Denmark also conducted an economic analysis that focused on available data: relative weight gain, feed efficiency, mortality, and feed and other variable costs. They found that the extra costs associated with the AGP ban were relatively modest, perhaps 1 additional euro per pig, or 1 percent (WHO 2003, p. 7). Using a general equilibrium model of the Danish economy, researchers found that the AGP ban might have caused a decrease in pig production of 1.4 percent, but a small increase in poultry production of 0.4 percent because of substitution effects. The impact on the Danish economy as a whole was minimal (*ibid.*, p. 8). The report notes that the expert group did not have data on potentially larger, one-time costs related to changes in production systems, such as the costs of modifying buildings or constructing new ones. But a communication from the Danish Bacon and Meat Council asserted that these broader changes in production systems were due to factors other than the AGP ban (WHO 2003, p. 42).

Some US researchers, and poultry companies, have come to similar conclusions about the low costs of eliminating AGPs in poultry production. Engster et al. (2002) conducted controlled trials for the Perdue poultry company in Maryland and North Carolina. The experiment involved removing AGPs from some flocks but not others that were housed under the same conditions and fed the same diet. Both sets of flocks continued to receive ionophores to prevent disease. There were no more disease outbreaks in the treatment flock compared to the control group, mortality was just 0.2 percent higher and there were only small drops in weight gain and feed efficiency in the treatment group. As with the WHO (2003) analysis, when Graham et al. (2007) compared the cost of the small losses in growth and feed efficiency to the higher cost of antibiotic-supplemented feed, the net economic effect for producers of dropping AGPs was slightly positive.

Results from a number of experiments by Steve Dritz and other researchers at Kansas State University support the conclusions from these other studies regarding the benefits of AGPs in pork production. The KSU researchers found few benefits in older pigs, but some in younger pigs that are more susceptible to disease.<sup>31</sup> Overall in studies estimating the economic benefits of using antibiotics in swine, Kansas State researchers found that certain antibiotics in the feed of nursery pigs could raise producer incomes by a \$1-3 per pig (Sotak et al. 2010). Dritz told a reporter that new production methods are so effective in preventing

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<sup>31</sup> The university reports the results of its research in annual Swine Day progress reports that are available at <http://www.asi.k-state.edu/species/swine/research-and-extension/>, accessed February 11, 2015.

disease that he tells pork producers “that most uses of antibiotics for growth promotion or feed efficiency really [do] not make sense anymore.”<sup>32</sup>

To put things in perspective, a US National Research Council committee in 1999 conducted a broad study of the benefits and risks of using antibiotics in food animals. As part of that study, the committee tried to assess the economic cost for livestock producers of a ban on the subtherapeutic use of antibiotics.<sup>33</sup> Like Wierup, who found that “progressive” farmers had better outcomes after Sweden banned AGPs, the committee pointed to US studies finding that farmers with better management practices had less need for antibiotics and that these farmers could gain from a ban. As others have concluded, the committee noted (p. 181):

*This raises the interesting possibility that a ban on subtherapeutic drug use would actually result in an economic incentive to improve animal care and could result in a more efficient industry in the long term. However, the process required to reach that point would be painful for those producers forced out of business.*

Given the heterogeneity among producers, the committee decided that trying to estimate an average cost for producers made little sense. They focused on the cost to consumers instead. The committee concluded that a ban on the subtherapeutic use of antibiotics in chickens, turkeys, beef, and pork would cost between \$5 and \$10 per person year, or \$0.34-\$0.75 per family per week.<sup>34</sup>

Other indications of the competitive impact of the AGP ban comes from export performance. When the AGP restrictions were imposed there, Denmark was the world’s leading pork exporter. It remained so until 2008, a decade after the AGP ban, when German and American exports began to edge past those of Denmark (figure 4). The Netherlands is also a major meat exporter and, after a dip during the global recession in 2009, Dutch exports recovered strongly, despite sharp falls in antibiotic use (figure 5).

Finally, to get a sense of the impact globally and on developing countries, Laxminarayan et al. (2015, pp. 27-33) estimate parameters for high and low growth responses to antimicrobial use from their review of the literature on AGPs in livestock production. They then combine

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<sup>32</sup> Dan Charles for National Public Radio at <http://www.npr.org/blogs/thesalt/2013/11/04/241603861/why-are-pig-farmers-still-using-growth-promoting-drugs>, accessed February 11, 2015.

<sup>33</sup> As noted above, there is no consensus definition of what constitutes subtherapeutic or nontherapeutic use of antibiotics in farm animals. The NRC committee defined it as any use that is not to treat symptoms, so it includes disease prevention as well as growth promotion.

<sup>34</sup> Based on the consumer price index for food, those figures would be roughly 50 percent higher today.

those parameters with estimates of antimicrobial consumption by country, from Van Boeckel et al. (2015) to estimate the impact on livestock production of restricting antimicrobial use. They find that it would be relatively small in the aggregate, just 1.3 percent to 3 percent, with relatively larger negative effects in developing countries with less modern management systems. On the high end, in some developing countries like Sudan and Bangladesh, the loss in meat production might be 5 percent. The authors estimate meat production might be lower by 1 percent to 3 percent in Brazil and China, and probably around 1 percent in the United States.

Thus, even in developing countries the costs would be relatively modest. The authors calculate that the value of the total, global reduction in meat production might be \$44 billion under the most pessimistic assumptions. And even if that figure is an order of magnitude too low, it would still be a tiny fraction of the \$60 trillion in economic losses that the O’Neill review estimated could occur by 2050 if the world does not address antimicrobial resistance (O’Neill 2015).

Finally, it is important to remember that some of the early moves to restrict AGPs in Sweden and Denmark were taken by or at the behest of livestock producers who were concerned that consumers would lose confidence in their product. Others producers, including in the United States, also see an opportunity to meet a growing consumer demand for healthier food choices. The Perdue poultry company, after examining the results of the studies it commissioned showing a minimal impact from withdrawing AGPs (above), introduced a line of antibiotic-free chicken that now accounts for a third of the chicken it sells. Organic chicken is another 5 percent while the remainder receives medically important antibiotics only if needed to treat disease (Sharpe 2014).

In the United States, some large meat buyers, such as McDonald’s and Chick-fil-A, have also adopted policies to reduce antibiotic use among their suppliers.<sup>35</sup> And, at the end of 2014, the six largest US school districts—Chicago, Dallas, Los Angeles, Miami-Dade, New York City, and Orlando County—announced that they would demand antibiotic-free chicken

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<sup>35</sup> Some public health advocates criticized the McDonald’s policy, which allowed continued prophylactic use, as too weak. See <http://www.bloomberg.com/bw/articles/2014-01-02/animal-antibiotics-fda-rules-criticized-as-weak-as-mcdonalds>, accessed February 2, 2015. McDonald’s website says that the policy is currently under review: [http://www.aboutmcdonalds.com/content/dam/AboutMcDonalds/Sustainability/Sustainability%20Library/antibiotics\\_policy.pdf](http://www.aboutmcdonalds.com/content/dam/AboutMcDonalds/Sustainability/Sustainability%20Library/antibiotics_policy.pdf); for Chick-fil-A’s policy: <http://www.chick-fil-a.com/Food/Ingredients>, accessed February 2, 2015.



when they renew contracts with meat suppliers in coming years.<sup>36</sup> Thus, increasing consumer concerns about animal welfare and human health effects are forcing some producers to reconsider how they operate, even in the absence of government regulation.

### **International Efforts: Mostly Talk, Little Action So Far**

The World Health Organization published a set of Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food in 2000. This was followed in 2001 by a Global Strategy for Containment of Antimicrobial Resistance, which included “rational use in animals” as one of the five most important area for action, along with surveillance, rational use in humans, infection prevention and control, and innovation in drugs, diagnostics, and other tools (WHO 2012, p. 2). Also in 2001, the Codex Alimentarius Commission, which sets global standards for food safety, asked the Food and Agricultural Organization and the World Organization for Animal Health (OIE from the French), along with WHO, to hold a joint expert consultation on these issues.<sup>37</sup>

Recommendations from WHO’s 2001 global strategy for reducing the risk from the use of antimicrobials in food animals include:

- Require obligatory prescriptions for all antimicrobials used for disease control in food animals
- Terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans
- Create national systems to monitor antimicrobial usage in food animals
- Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs
- Monitor resistance to facilitate identification of emerging health problems and actions to protect human health

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<sup>36</sup> See <http://www.reuters.com/article/2014/12/10/us-antibiotics-chicken-education-idUSKBN0JO00320141210>, accessed February 2, 2015.

<sup>37</sup> See the description and documents at <http://www.fao.org/food/food-safety-quality/a-z-index/antimicrobial/en/>, accessed January 21, 2015.

- Develop guidelines for veterinarians to reduce overuse, misuse of antimicrobials in food animals

As noted above, there has been progress on several of these recommendations in Europe and in the United States. But there are important loopholes and therapeutic uses of antibiotic in animals remain high in most countries where data are available.

The 2014 WHO report on global surveillance shows that systems to track antibiotic resistance remain spotty in coverage and inconsistent in how they measure and report resistance. A WHO Secretariat report to the 2014 World Health Assembly noted that only 29 member states, mostly in Europe, reported having national action plans to tackle antimicrobial resistance (WHO Secretariat 2014, p. 2).

One important result of the joint FAO/OIE/WHO consultations is that WHO and OIE published lists of critically important antimicrobial drugs for human and animal health, respectively.<sup>38</sup> In addition, a joint experts report (FAO/OIE/WHO 2007, p. viii) identified three classes of critically important drugs for human health (quinolones, 3rd and 4th generation cephalosporins, and macrolides), and three foodborne pathogens (*Salmonella* spp. and *Campylobacter* spp., and the commensal bacteria, *Escherichia coli*) that should be priorities for research and risk assessment.

Nevertheless, there has been relatively little action in the decade since WHO announced its global principles and global strategy to contain antibiotic resistance. Underscoring that fact, a strategic and technical advisory group convened by the Director General in 2013 called for “urgent renewal and expansion of action to tackle this growing public health threat.” The experts group also called on WHO to take the lead in developing and coordinating a global action plan to combat antibiotic resistance (WHO Secretariat 2014, pp. 2-3). Among the next steps identified by the advisory group were for WHO to “develop global standards for data collection and reporting, and facilitate development of national and regional surveillance networks” (ibid., p. 4).

The WHO secretariat will present the Global Action Plan to member states for adoption at the 2015 World Health Assembly. One of the key deliverables is that members should adopt national action plans to address resistance within two years. The OIE also created an ad hoc

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<sup>38</sup> The lists can be found online here [http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf), and here <http://www.oie.int/doc/ged/D9840.PDF>, accessed February 13, 2015.

group to examine how to create a global database on antimicrobial use in animals.<sup>39</sup> President Obama's national strategy for combating antibiotic resistance also has an international component, calling for coordination with WHO, OIE, and the FAO, as appropriate, to improve surveillance of antibiotic resistance in animals and food-borne pathogens around the world. It also calls for collaboration to "harmonize international data submission requirements and risk assessment guidelines related to the licensure and/or approval of veterinary medicinal products including antibiotics, vaccines, and diagnostics, to the extent possible" (White House 2014, pp. 31-32).

## **Conclusions and Recommendations**

The development of antibiotics was a huge boon to human health and the costs of their loss due to widespread resistance would be enormous. Even minor infections or injuries could again become life-threatening, as could surgery and cancer treatment. Moreover, those costs would be borne disproportionately by the poor, and particularly by children who are at most at risk from diarrheal and respiratory infections that could otherwise be treated with antibiotics. Developing country health systems are also already stretched thin and they are least able to afford the more expensive second- and third-line antibiotics to which doctors must turn when older drugs fail.

The magnitude of the threat to human health from antibiotic use in farm animals remains unknown. There is clear evidence that routine, subtherapeutic use of antibiotics increases the prevalence of resistant bacteria in farm animals and that resistant bacteria can infect humans through direct contact or via the food chain. What is not known is how often that occurs. Even less is known about the risks of environmental exposure. That it is partly due to the large number of steps in the food chain and the complexity of the processes involved in the evolution of resistance. But the lack of knowledge is also due to the failure in most countries to systematically monitor antibiotic resistance and use.

The WHO has been calling for the creation of surveillance systems for more than a decade, yet they remain rare. Most countries in Europe are now collecting this data and creating mechanisms to harmonize and integrate it, as well as taking steps to reduce antibiotic use. While the FDA is taking steps to reduce antibiotic use for growth promotion in farm

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<sup>39</sup> There is an OIE conference presentation here, [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2014/03/WC500162570.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/03/WC500162570.pdf), accessed March 25, 2015.

animals, it will be difficult to monitor the effectiveness of that policy without significantly enhanced data collection. And for developing countries, there is almost no information.

Thus, the first and most obvious step to take is to, finally, devote the resources necessary to create and strengthen harmonized systems to track antibiotic use and resistance in animals in key countries. Improved surveillance is the key to being able to spot emerging resistance problems and respond in a targeted, rather than scattershot, fashion. Donors, WHO, and the OIE should ramp up financial and technical assistance to developing countries to create and strengthen these systems. The WHO and OIE need to move more vigorously to provide platforms to publish this data in a harmonized format so that trouble spots can be identified and resources targeted to where they are most needed to slow the emergence of resistance.

In the United States, several additional steps are necessary. First, Congress should pass legislation authorizing the FDA to collect and publish more detailed information on the use of antibiotics in farm animals. The most recent FDA report on antibiotic use in farm animals is a step forward, but researchers also need to know how drugs are being used, in what doses, for how long, and in what species. The NARMS program also needs to expand its sampling and the FDA needs to find ways to link more detailed antibiotic use data with the resistance data from NARMS.<sup>40</sup>

Second, while the FDA actions to discourage AGP use is another step forward, there are loopholes. The Obama national strategy addresses one of them with its proposal to fund educational programs to help livestock producers adapt their husbandry practices so that routine, prophylactic use of antibiotics is not necessary. In the meantime, FDA guidance allows farmers to continue using antibiotic to prevent disease and it relies on veterinarians to oversee that use. The experience in Denmark, as well as common sense, suggest that veterinarians profiting from selling antibiotics or having financial ties with drug companies is unhelpful. Congress should ensure that the FDA has the authority to address this issue.

Finally, the problem is global one and with many developing countries increasing meat and dairy production sharply, this is a critical time to develop global policies to guide the prudent use of antibiotics in livestock, and to build capacity in developing countries to regulate that use. The WHO, FAO, and OIE should develop text for an international convention to constrain the use of antibiotics in agriculture. Indiscriminate antibiotic use in farm animals to

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<sup>40</sup> See APUA's recommendations for improving NARMS the last time it was reauthorized here, [http://www.tufts.edu/med/apua/index\\_168\\_274705518.pdf](http://www.tufts.edu/med/apua/index_168_274705518.pdf), accessed February 11, 2015.

promote growth or to prevent disease resulting from inferior management practices could be considered production subsidies of a sort. It is true that many of the world's poor need to consume more protein to get all the nutrients they need. But many others, especially in the United States, consume far more animal products than is healthy. Lower meat prices due to explicit and implicit subsidies to livestock production are not the way to solve the undernutrition problems of the world's poor.

Getting acceptance for prudent antibiotic use policies in emerging markets could be difficult as long as advanced countries continue to provide government subsidies and protection for meat and dairy production. Advanced countries need to reform those policies, as well as address the implicit subsidies that are created when regulations do not address the negative externalities associated with meat production, including antibiotic resistance.

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**Table 1 Animal Densities on the Largest Operations, United States (2012)**

	Larger operations as a share of total, by species	Large operations: share of all animals, by species	Average number of animals on large operations
Dairy cattle	3%	44%	4,300
Beef cattle	1%	51%	5,200
Swine	5%	67%	15,000
Chickens (for meat)	19%	68%	911,000

*Source:* United States Department of Agriculture's National Agricultural Statistics Service, 2012 Census of Agriculture.

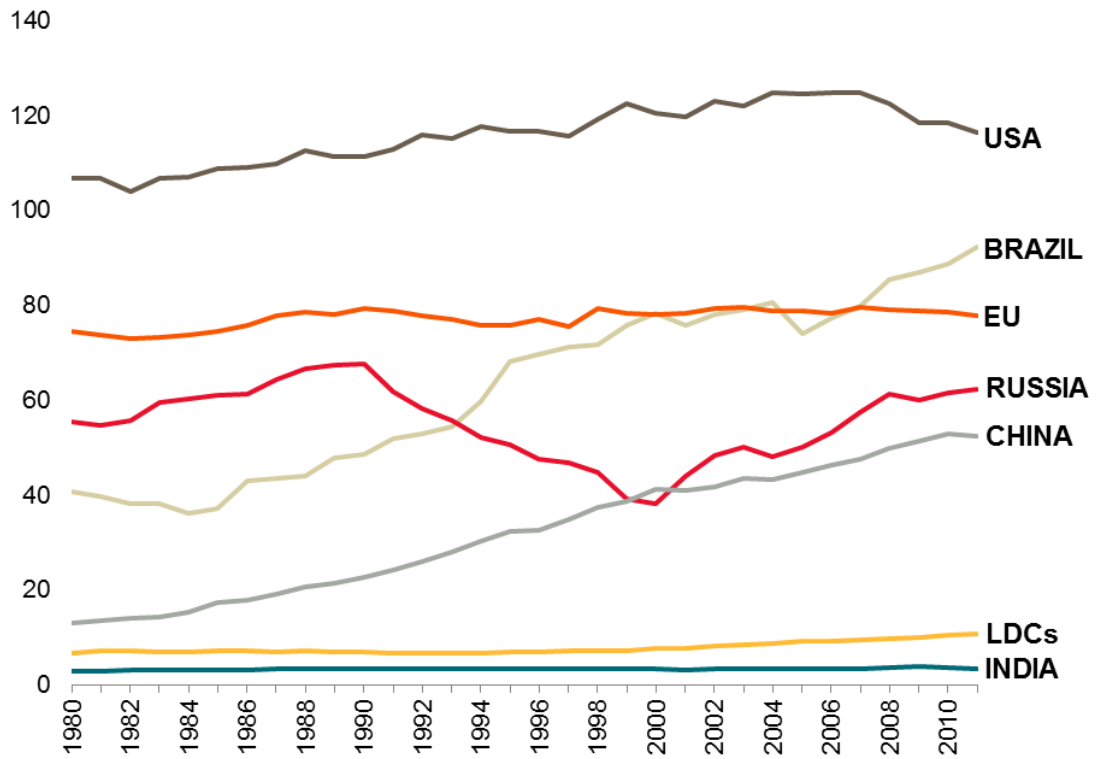
**Table 2 Government Support for Producers by Commodity, Average 2011-2013 (as a percent of gross farm receipts)**

Commodity	EU	Japan	Korea	US	Brazil*	China*	Russia*
Beef & Veal	29	38	31	0	1	13	26
Milk	6	61	51	6	15	24	18
Pigmeat	1	64	55	0	4	13	52
Poultry Meat	18	10	42	0	0	2	19
Wheat	0	48		7	5	23	-11
Soybean	0	48	89	4	1	14	
Maize	0			4	2	9	-54

\*Average 2010-2012

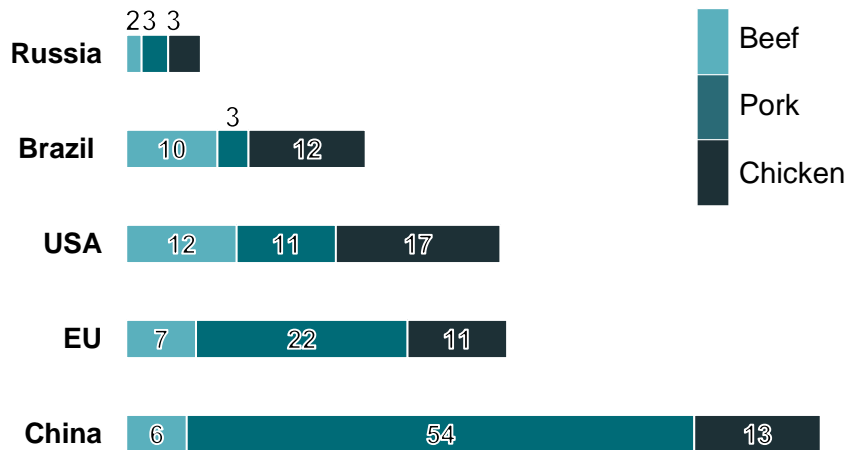
*Source:* Organisation for Economic Co-operation and Development, Producer and Consumer Support database.

**Figure 1a Per Capita Consumption of Beef, Pork, and Poultry (Kilograms)**



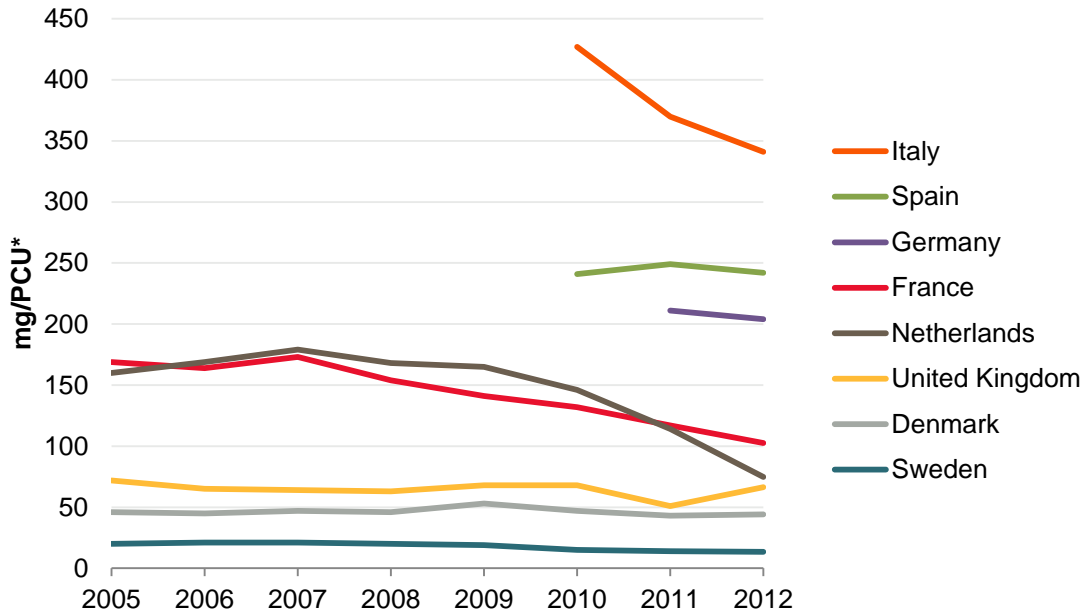
Source: Food and Agriculture Organization of the United Nations Statistics Division, FAOSTAT: Food Supply database.

**Figure 1b Top Livestock Producers (Beef, Pork, and Chicken), Millions of Metric Tons (2013)**



Source: Food and Agriculture Organization of the United Nations Statistics Division, FAOSTAT: Production database.

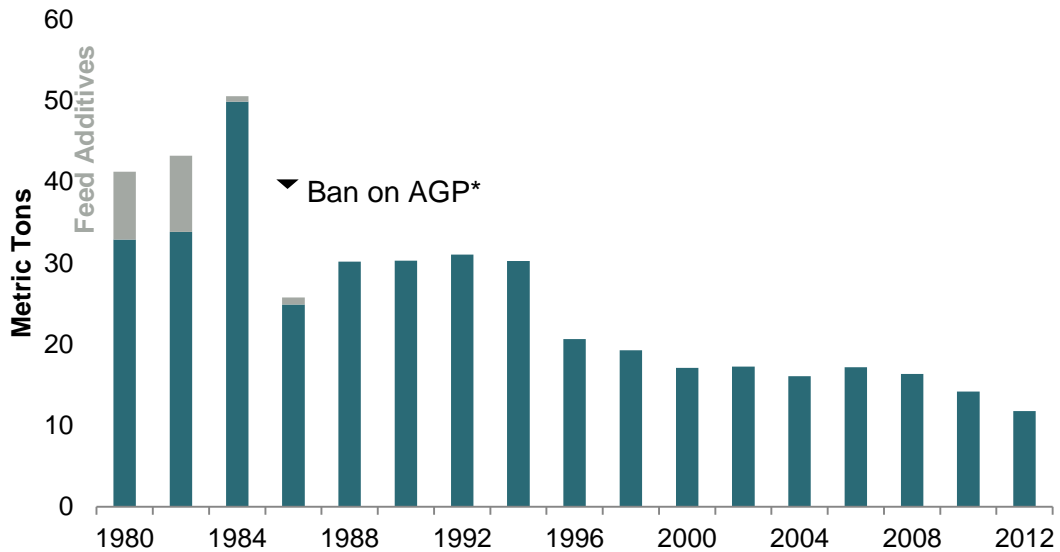
Figure 2 Sales of Active Ingredients of Antimicrobials in Selected Countries



\*PCU: Population Correction Unit

Source: European Medicines Agency, 1st – 4th EVSAC Reports.

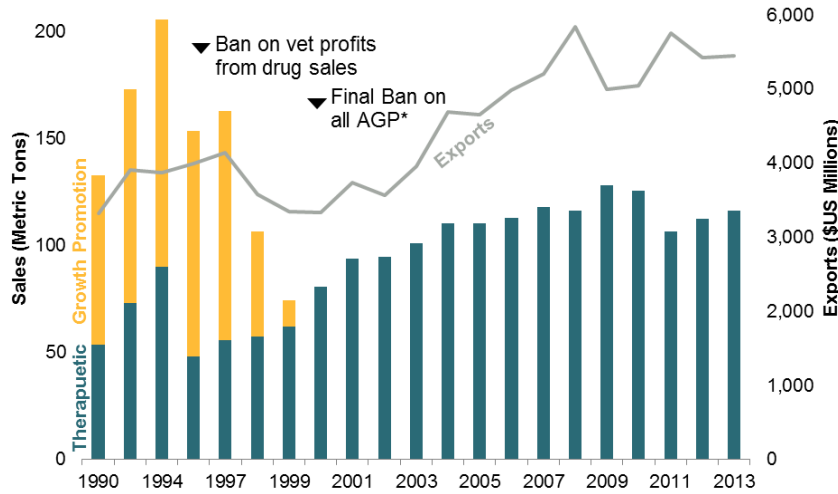
Figure 3 Sales of Active Ingredients of Antimicrobials for Food Producing Animals in Sweden



\*Antimicrobial Growth Promoters.

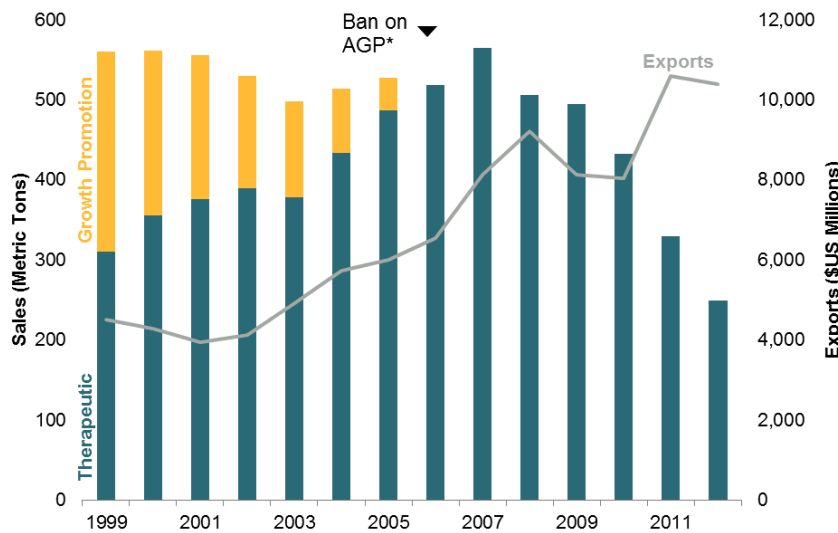
Source: 1996-2012 Swedish Veterinary Antimicrobial Resistance Monitoring 2013 Report; 1980-1996 Wierup, Martin. 2001.

**Figure 4 Sales of Active Ingredients of Antimicrobials for Food Producing Animals and Exports of Meat products (SITC 01) in Denmark**



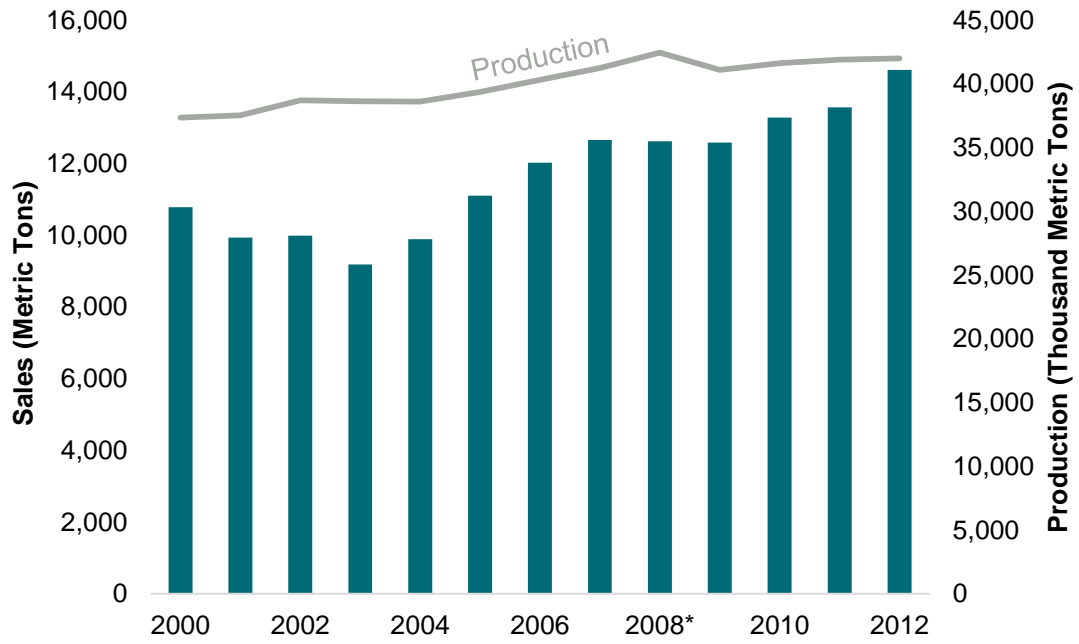
\*Antimicrobial Growth Promoters. *Source:* DANMAP, 2013 Report on the Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark Report; Exports Value, UN Comtrade (SITC Revision 1).

**Figure 5 Sales of Active Ingredients of Antimicrobials for Food Producing Animals and Exports of Meat products (SITC 01) in the Netherlands**



\*Antimicrobial Growth Promoters. *Source:* Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands, 2012; Export value, UN Comtrade (SITC Revision 1).

**Figure 6 Sales of Active Ingredients of Antimicrobials for Food Producing Animals and Production of Poultry and Red Meat in the United States**



\*Calculated based on simple average of 2007 and 2009.

Source: Antimicrobial data: 2000-2007 from Animal Health Institute Surveys, 2009 - 2012 from Food and Drug Administration, Department of Health and Human Service, 2014 Summary Report. Production data: United States Department of Agriculture's World Agriculture Supply and Demand Estimates Report.