A Global Treaty to Reduce Antimicrobial Use in Livestock

Kimberly Ann Elliott, Charles Kenny, and Janeen Madan

Abstract

While the misuse of antimicrobials in human health is a key factor accelerating the emergence of drug resistance, we should not overlook the role of agriculture. In the livestock sector, a significant portion of antimicrobials are provided in subtherapeutic doses over long periods of time to speed growth and prevent disease, rather than to treat illness. Currently, the United States and countries across Europe are major users of antimicrobials in livestock, but there is rapid growth in key developing countries. Following the recent discovery of a bacterial gene in pigs and people that conveys resistance to a last resort antibiotic drug, addressing agriculture's contribution to antimicrobial resistance is more urgent. Moreover, the fact that the gene was discovered within a relatively short time in both China and the United States underscores the global nature of the problem. Drug resistant superbugs do not respect borders. To date, however, there has been little concrete action at the global level.

This paper makes the case for a global treaty to reduce antimicrobial use in livestock. We propose that negotiations could begin with the two dozen or so key countries that account for the majority of global antimicrobial use in farm animals. This could help make significant inroads into the problem, even as those countries work to expand the treaty's membership. Drawing on lessons learned from the Montreal Protocol on Substances that Deplete the Ozone Layer, the paper outlines a framework for a global treaty to reduce livestock's contribution to the health threat posed by the spread of antimicrobial resistant bacteria.

Kimberly Ann Elliott, Charles Kenny, and Janeen Madan. 2017. "A Global Treaty to Reduce Antimicrobial Use in Livestock." CGD Policy Paper. Washington, DC: Center for Global Development. http://www.cgdev.org/publication/global-treaty-reduce-antimicrobial-use-livestock

The authors would like to thank Rachel Silverman and an anonymous reviewer for their helpful feedback.

CGD is grateful for contributions from the UK Department for International Development in support of this work.

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CGD Policy Paper 102
January 2017

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Introduction

Each use of antibiotics in humans or animals gives bacteria an opportunity to evolve resistance to those life-saving drugs. Globally, antimicrobial resistance (AMR) already kills hundreds of thousands of people a year.[1] If left unchecked, AMR could cause 10 million deaths a year by 2050 along with a cumulative loss of $100 trillion to the global economy (The Review on AMR 2016). In contrast, the policy recommendations to slow AMR's spread outlined by The Review on AMR—commissioned by former UK Prime Minister David Cameron—have an estimated price tag of up to $40 billion over a decade.

The AMR threat is attracting increased attention from policymakers worldwide. In 2014, President Obama issued an Executive Order on Combatting Antibiotic-Resistant Bacteria. The World Health Organization (WHO) released its Global Action Plan on Antimicrobial Resistance in 2015. The Group of 7 (G-7) declared AMR a global health priority in 2015 and the Group of 20 (G-20), under Chinese leadership in 2016, affirmed the urgent need to tackle this issue. And in September 2016, the United Nations General Assembly (UNGA) convened a high-level meeting on AMR, only the fourth time a global health issue has been on the agenda at UNGA. World leaders adopted a resolution reiterating the WHO action plan in calling on member countries to develop, fund, and implement national multi-sectoral plans. The resolution also directed the Secretary General to establish an interagency coordination group to facilitate global action on AMR.[2]

The agriculture sector's widespread use of antibiotics in livestock plays an often underappreciated role in the global AMR problem. Farmers routinely use large amounts of antimicrobials in healthy farm animals because they can promote faster growth and prevent disease in large, crowded, production systems. In the United States, for example, livestock producers use between 70 to 80 percent of all antibiotics sold (by volume) across the country (Sneeringer et al. 2015, p. 5; Van Boeckel et al. 2015). Intensive livestock production systems—driven by rising demand for meat, eggs, and dairy—are also expanding rapidly across middle-income countries. Estimates suggest that antimicrobial use in pigs, chickens, and cattle will double in Brazil, Russia, India, China, and South Africa between 2010 and 2030 (Van Boeckel et al. 2015). Crucially, many of the antimicrobial drugs used in farm animals are the same as, or chemically related to, drugs used in humans. That opens the path to drug resistant bacteria that threaten human health as well.

Yet, evidence suggests that modern agricultural management practices can be similarly productive without the widespread use of antimicrobials, while also reducing the risk of creating antibiotic resistant superbugs.[3] Addressing agriculture's role is thus low-hanging

[1] Antimicrobials are used to treat infectious diseases—they kill or inhibit the growth of microorganisms including bacteria (antibacterial), viruses (antiviral), fungi (antifungal), and protozoa (antiprotozoal). Antibiotics are the largest, and most widely studied class of antimicrobials. In animal agriculture, the misuse and overuse of antibiotics is a primary challenge; but there is also growing concern over the use of antifungals in crop culture. Throughout this paper, we use the term "antimicrobial resistance" to reflect drug resistance from increased use of antibiotics, as well as other drugs such as antifungals. For more information, see Review on AMR 2016 and 2015.

[2] More on the September 2016 UNGA High-Level Meeting on AMR is here: http://bit.ly/2e4qT2w and http://wapo.st/2drueaz.

[3] See http://bit.ly/2e93ssu.

fruit, offering an opportunity to make relatively rapid progress in significantly reducing overall antimicrobial use and slowing the spread of AMR at low cost. Reducing irrational and inappropriate use of antibiotics by humans will also be necessary. But changing the behavior of sick patients who want to feel better, or of doctors who feel pressure to move on to the next patient, may be more challenging.

This paper discusses the scale and nature of the problem of antimicrobial use in the livestock sector worldwide; provides an overview of the recommendations to tackle livestock's contribution to the AMR challenge put forth by the 2016 Review on AMR, and outlines the role for a global treaty to reduce antimicrobial use in livestock.

Drug resistant superbugs do not respect borders—people and animals cross them all the time and meat is widely traded between countries. Thus, the nature of the problem is global and global cooperation is needed to move the needle on the AMR issue (Woolhouse and Farrar 2014; Ardal et al. 2016; Review on AMR 2016). This paper's contribution is to propose a specific framework for international collaboration, modelled on the Montreal Protocol on Substances that Deplete the Ozone Layer, and outline what a global treaty to reduce antimicrobial use in animals might look like. The negotiations might well begin with a small number of key countries, but as with the Montreal Protocol, it would ultimately need to be universal to fully address the problem.

Linking Agricultural Use to Human Health

Many farmers routinely use antibiotics in subtherapeutic doses to promote growth and prevent disease in farm animals. The low doses and widespread use combine to allow drug resistant bacteria to survive and thrive. Drug resistance can then spread to humans through a number of channels, especially since many of the drugs used in animals are the same as, or related to, drugs used in humans. But the epidemiological processes are complicated and still not fully understood. The frequency of drug resistant infections in humans that can be traced to livestock practices is also unknown because of weak, or missing, surveillance systems.[4]

Nonetheless, experiments as early as the 1970s showed that chickens excreted drug resistant *E. coli* bacteria soon after antibiotics were added to their feed. And farm employees subsequently developed populations of *E. coli* bacteria resistant to the same drugs. Resistance can also spread to people further away through contamination of air and water. Furthermore, many more people can be exposed to resistant bacteria through handling or consumption of raw or undercooked meat. The US Food and Drug Administration (FDA) monitors antibiotic resistant bacteria in meat, and detected multi-drug resistant salmonella bacteria in 20 percent of chicken and 36 percent of turkey samples in 2015.[5] That same year, the FDA also discovered ciprofloxacin resistant salmonella in a pork sample—the first time inspectors had detected resistance to that critically important drug.

[4] See Elliott (2015) for a summary and the sources cited therein for details.

[5] Data for 2014-2015 are from the FDA's National Antimicrobial Resistance Monitoring System (NARMS), available here: http://bit.ly/2dZW4y2.

In an alarming new discovery in November 2015, scientists detected *E. coli* bacteria in both people and pigs in China that were resistant to colistin—a widely used feed additive in that country. Not long after, a gene conveying colistin-resistance was found in bacteria in people and pigs in the United States, even though the United States does not permit agricultural uses of the drug.[6] Doctors rarely prescribe the drug for people because of its severe side effects, but it is a last resort antibiotic for some diseases.[7] These discoveries ratcheted up the urgency and underscored the global nature of this problem.

The good news is that curbing the use of antibiotics in animals can apparently reverse resistance trends in at least some cases, thereby helping to preserve the effectiveness of medically-important drugs. In 2005, for example, chicken farmers in Quebec, Canada stopped using an antibiotic in the cephalosporin class (Dutil et al. 2010). Tests of supermarket chicken tracked a decline in cephalosporin-resistant salmonella from 60 percent to 10 percent of samples in the first year after the ban. Tests of bacteria from human subjects showed drug resistant isolates fell from 40 percent of the total to near zero over two years.

As we discuss in the following sections, the costs to livestock producers associated with reducing antimicrobial use appear to be manageable in many situations. Thus, agriculture offers an opportunity for relatively rapid progress in addressing the AMR challenge.

Gauging the Scale of Livestock's Role in the AMR Challenge

Ideally, we would use data on consumption of antimicrobials by country and by species in standardized units that control for differences in animal population size and composition to inform our analysis. But, data on antimicrobial use across countries and disaggregated by type of use are spotty at best. The European Union collects total antimicrobial consumption in livestock per kilogram of animal mass from most of its member countries (plus Norway and Iceland), which allows for comparisons across countries.[8] EU authorities are also working to disaggregate data on consumption by species. The United States currently collects data on the volume of sales only, disaggregated by drug class. Both EU and US sources also provide some information on the route of administration—whether producers provide these drugs in feed or water, or by injection. Given the large gaps in data, especially for much of the rest of the world, one clear priority for international action, therefore, is to improve and expand data collection.

Figures for the value of the antibiotics market are also difficult to find, and even more difficult to interpret. But they are important to consider in analyzing the potential economic costs of policy reform. Globally, analysts estimate that the antibiotics market is worth *$40*

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[6] More details are here: http://bit.ly/2emxY1I, accessed September 30, 2016.

[7] The Pew Charitable Trusts provide a useful explainer here, http://bit.ly/2dfQ6bt, accessed September 30, 2016; see also: http://bit.ly/1Hg4KdM and here: http://bbc.in/1Lnpk76.

[8] EU officials developed a standardized "population correction unit" (PCU) to account for differences in the composition of animal populations across countries. See http://bit.ly/1M1ZwCv.

billion to $45 billion, just 4.5 percent of the total pharmaceutical market.[9] While most of the *volume* of antibiotics used is in livestock, a considerable share of the market *value* is in more expensive drugs for human use. An animal health research and consulting firm estimated that the value of the medicinal feed additives market in 2011 (including classes of antibiotics not used at all in human medicine) was just under $6 billion, with roughly one-half and one-third in the US and European markets, respectively. Another study estimated that the Asia Pacific region accounted for an estimated $1.8 billion of the market for animal antimicrobials, which is more than estimated for the entire rest of the world by the above analysis,[10] But other market research reports find lower values for this market.[11] For the purposes of our research, the essential point is that the numbers are relatively small and that addressing the implications of policy reform for the animal health sector should be manageable.

We turn now to what we can glean from the limited data available on how and where livestock producers use antimicrobials in their operations. It varies considerably by type of production. Intensive operations, with large numbers of animals raised in a relatively small space—often called confined animal feeding operations, or CAFOs—are more likely to use antibiotics for growth promotion and disease prevention than extensive operations, where animals graze or are fed crop residues or household scraps rather than purchased feed. Intensive production systems are prevalent across high-income countries and rare in poorer countries. For example, the share of poultry produced in intensive systems can vary from ten percent in the poorest countries to 95 percent in the richest (Gilbert et al. 2015). On the other hand, extensive production—which is more common in poorer countries—uses relatively small amounts of antibiotics, mostly for therapeutic purposes (Grace 2015). The result is far lower antimicrobial use in poor countries. In dairy cattle in rural Peru and Zambia, for example, antibiotics are infrequently used and almost exclusively to treat sick animals.[12]

In terms of global trends in antimicrobial use in livestock, one rough estimate based on the limited data available showed that the five largest users in 2010 were China, the United States, Brazil, Germany, and India. Together these countries accounted for 51 percent of estimated global antimicrobial consumption by livestock of 63,000 metric tons (Van Boeckel et al. 2015). These countries also account for half or more of global meat production. Left unchecked, Van Boeckel et al. (2015) project that global antimicrobial use in the livestock sector will increase by two-thirds by 2030 to 105,000 metric tons. Most of the increase will come in the large emerging markets, where meat consumption is growing rapidly and livestock production is becoming more intensive.[13] By 2030, the ranking of the top five consumers will shift slightly, with Mexico replacing Germany as the fifth largest consumer, and China's share of global consumption rising from 23 to 30 percent.

[9] Figures are from http://bit.ly/2dfW24c and http://bit.ly/2cp2bxp, accessed September 27, 2016.

[10] Rushton et al. (2014) discuss both studies, as well as the caveats.

[11] http://bit.ly/2e4ubTq, accessed September 27, 2016.

[12] Small dairy farmers in Peru obtain antibiotics from vets (at district vet offices, for example) and from local feed stores (Redding 2014). A study in Zambia reported that 90 percent of farmers purchased antibiotics from established small or big veterinary drugs shops; 35 percent without a prescription (Mainda et al. 2015).

[13] Van Boeckel et al. (2015) estimate that about two-thirds of the global increase in antibiotic use is due to increased meat consumption and the other third to increasingly intensive production methods.

The authors use the limited data available from high-income countries, mainly in Europe, which are disaggregated by species, to estimate the average amount of antimicrobials used in intensive production systems (in milligrams per kilogram of animal mass). They combine these calculations with national level estimates of animal mass, by species, to calculate total antibiotic use at the country level.[14] The underlying data for these national-level averages vary significantly, but there is a basic pattern in use by species-type that holds across most countries: the highest levels of antibiotics per unit of animal mass are used in pigs, followed by chickens and, at generally lower levels, cattle (see Table 1). Average use in cattle may be lower in part because antibiotics are used mainly for disease prevention at particular stages of the animal's life—in large feedlots when beef cattle are being fattened for slaughter and during the "dry" period when dairy cattle are not producing milk. Beef cattle operations also vary more in the intensity of production than those for either pigs or poultry.

Table 1: Use of antibiotics across countries by species

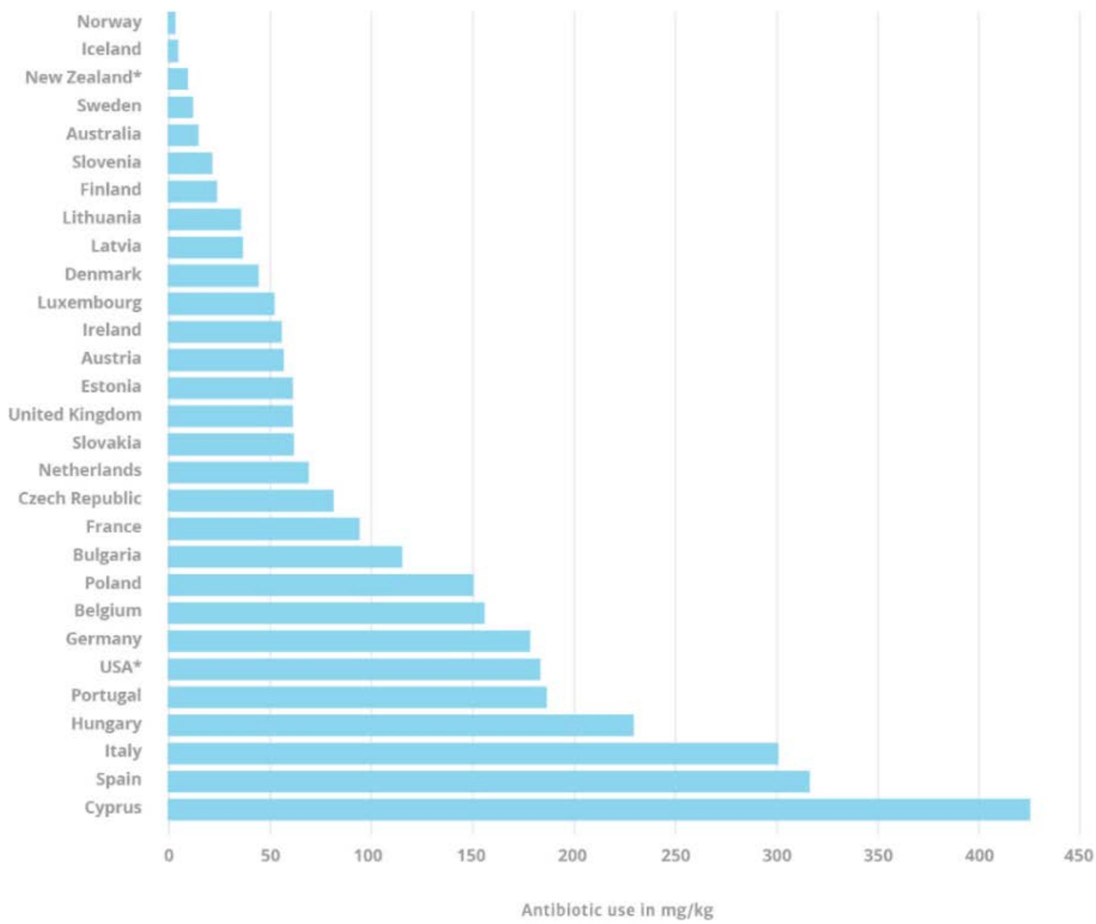
Mg of active ingredients per kg of animal mass, 2010 or closest available			
	Cattle	**Chickens**	**Pigs**
Estimated average in intensive systems	**45**	**148**	**172**
Belgium	57	150	169
Denmark	36	4	57
France	19	108	147
Netherlands	185	109	119
Netherlands-alt	25 *(excluding veal)*	45	53
UK	6	204	204
UK-alt	7	76	279

Notes: Van Boeckel et al. (2015) report mg/PCU figures for France and the UK; others calculated using total antibiotic sales by species from Van Boeckel et al. (2015) and PCU estimates by species from ESVAC (2013). For the Netherlands-alt figures, antibiotic sales are from Netherlands Veterinary Medicines Authority (2016) and PCU estimates are from EVSAC. The reported UK figure combines data on pigs and poultry; the alternative estimate uses data from the British Poultry Council to roughly estimate them separately.

Some of the Van Boeckel et al. estimates differ rather substantially from what EU countries report to the European Surveillance of Veterinary Antibiotic Consumption (ESVAC) project. Figure 1 shows the wide range of use levels, per population corrected unit, as reported by European countries to ESVAC and for a few others as calculated by The Review on AMR (2016). Comparing the two sets of estimates for countries where they overlap, the Van Boeckel et al. estimates are generally higher for countries with the lowest reported use, and lower than the EU for countries with the highest reported use levels. That suggests that the overall magnitude of the estimates may not be too far off, but that the country-specific estimates should be used with caution. For our purposes, the main message from the Van Boeckel et al. research is the large projected increase in use if the world continues with a business-as-usual approach.

[14] See Van Boeckel et al. (2015) for details.

Figure 1: Antibiotic use in agriculture for select countries



Source: Review on AMR, 2016. Data are from the European Medicines Agency (2011) and from national governments of the United States, Australia, and New Zealand.
Notes: * Animal biomass estimated based on number of animals. All figures are given in milligram (mg) purchased for every kilogram (kg) of livestock biomass and do not include ionophores and oligosaccharides.

Another factor that varies across countries is the use of antimicrobials in agriculture that are particularly important for human health. Overall, however, this appears to be relatively low. In the United States, 70 to 80 percent of the total volume of antibiotics sold each year are used in animals, and the FDA reports that 60 percent of those are "medically important," meaning they belong to the same class as drugs used in human health. Moreover, most of the antibiotics used in agriculture are older penicillins and tetracyclines, which are relatively cheap, but also still commonly used in human health.

The FDA has identified three classes of medically-important antibiotics that it regards as "critically important." These include third generation cephalosporins, fluoroquinolones, and macrolides. The WHO maintains a longer list of "critically important" antibiotics, but it has tagged the same three, along with fourth generation cephalosporins, as priorities for attention and funding in the battle against AMR (FDA 2003; WHO-OIE-FAO 2007). According to the most recent FDA (2015) report on antibiotic sales for use in farm animals, these three classes of drugs accounted for around 5 percent of total sales.[15] Across 26 EU countries, antibiotic sales for food-producing animals in these three priority classes added up to about 10 percent of the total (7.4 percent of which was accounted for by macrolides) (see

[15] The FDA report does not break out cephalosporin sales by generation.

Table 2).[16] But within the 26 EU countries, this varied considerably—macrolide use in animals, for example, accounted for between 0 and 12.4 percent of total sales (WHO-OIE-FAO 2007; ESVAC 2015).

Table 2: Sales of "critically important" antibiotics

Drug Class	EU (26 countries) (2013)				United States (2014)
	Median	Min	Max	Percent of total sales across 26 countries	Percent of total sales
3rd-4th generation cephalosporins	~0.2	0.1	1.3 (Luxembourg)	Lumped with several classes that sums to 2.7	< 1
Macrolides	~5.5	0 (Iceland, Norway)	12.4 (Portugal)	7.4	4
Fluoroquinolones	~0.1	0.1 (Iceland)	7.9 (Slovenia)	1.9	< 1

Source: Authors' calculations based on data from EVSAC 2015 and FDA 2015.

The data are not detailed enough to know the purposes for which food producers use these antibiotics, but the information on routes of administration gives us some clues. Drugs provided in food or water are often used for growth promotion or disease prevention, rather than treatment. US producers provide some macrolides to livestock in feed or water, while fluoroquinolones and cephalosporins are not administered by this route (FDA 2015, p. 36). The ESVAC report provides more details: 84 percent of third and fourth generation cephalosporins are delivered by injection; 78.1 percent of fluoroquinolones are in oral solutions (mixed in water) with the balance by injection; while most macrolides are in forms suitable for delivery in feed or water and only 6.4 percent are delivered via injection (EVSAC 2015).

Scaling the Economic Costs of Reducing Use in Livestock

A number of countries have already taken steps to ban the use of antimicrobials for growth promotion—51 percent of 152 countries recently surveyed, with another 19 percent having partially banned such use (Rushton et al. 2014, p. 11). This suggests fairly widespread acceptance that the costs of this step are manageable. The data from European surveillance programs, however, show that overall antibiotic use might not be significantly reduced—or can turn back up—if authorities do not also address routine prophylactic (i.e., preventive) uses. But analysis of the European experience, as well as controlled trials by animal researchers in the United States, suggest that the costs of further reducing routine use will not be as great as farmers fear.

[16] More information is here: http://bit.ly/1w8L8QF, accessed November 10, 2016.

The effects of antimicrobial growth promoters (AGPs) depend on a variety of factors related to animal characteristics and production practices. These include animal age and the presence of environmental stressors, such as nutrition, crowding, sanitation, hygiene, and temperature. Adding antibiotics to feed has the largest impact when animals are growing slowly because of other stressors—helping to improve weight gain by as much as 70 percent in suboptimal environments, compared to an effective zero response rate where these stressors are not present (Elliott 2015).

As livestock producers move towards reduced antimicrobial use on their farms, there are a number of alternative approaches and practices to maintain overall good health of their animals. These include using vaccines to protect herds against disease; improved diagnostics that enable farmers to separate sick animals and prevent the spread of disease; improved animal husbandry practices and hygiene conditions to reduce disease; and increased use of probiotics or prebiotics and other non-antibiotic growth promoters (Review on AMR 2015; Rushton et al. 2014).

According to a growing body of research, the utility of AGPs in high-income countries has actually been falling over the past 30 years as production practices have improved. These trends suggest the impact of a ban on antimicrobial use for growth promotion would be small in high-income countries, to the point that savings on feed costs may outweigh benefits from weight gain (WHO 2003; Graham et al. 2007). The experience from Denmark shows that antibiotic use can be cut relatively quickly, while also maintaining high production levels (figure 2; the Netherlands has had a similar experience). Economic analysis on the Danish case suggests the slightly slower growth of pigs after the AGP ban might have raised farm-gate meat prices by one percent.[17] In addition, analysis by the US Department of Agriculture (USDA) suggests that "use of antibiotics for purposes other than disease treatment is associated with a 1 percent to 3 percent increase in the productivity of a farm (not statistically distinguishable from no effect)."[18]

At the same time, costs of a ban on AGPs could be higher in middle-income as well as some low-income countries that are moving to intensive production systems, but without the modern management practices that are common in higher income countries. Therefore, widespread adoption of alternatives will require education and public awareness campaigns. And some alternatives will be more easily adapted to developing country conditions than others. For example, high prices for vaccines could inhibit use in low-income countries. And, in general, the costs of switching to alternatives are not fully understood (Grace 2015). In the poorest countries, antimicrobial use of any kind is comparatively rare, especially for disease prevention and growth promotion.[19] The research thus suggests that the most difficult challenges will arise in middle-income countries with growing livestock industries

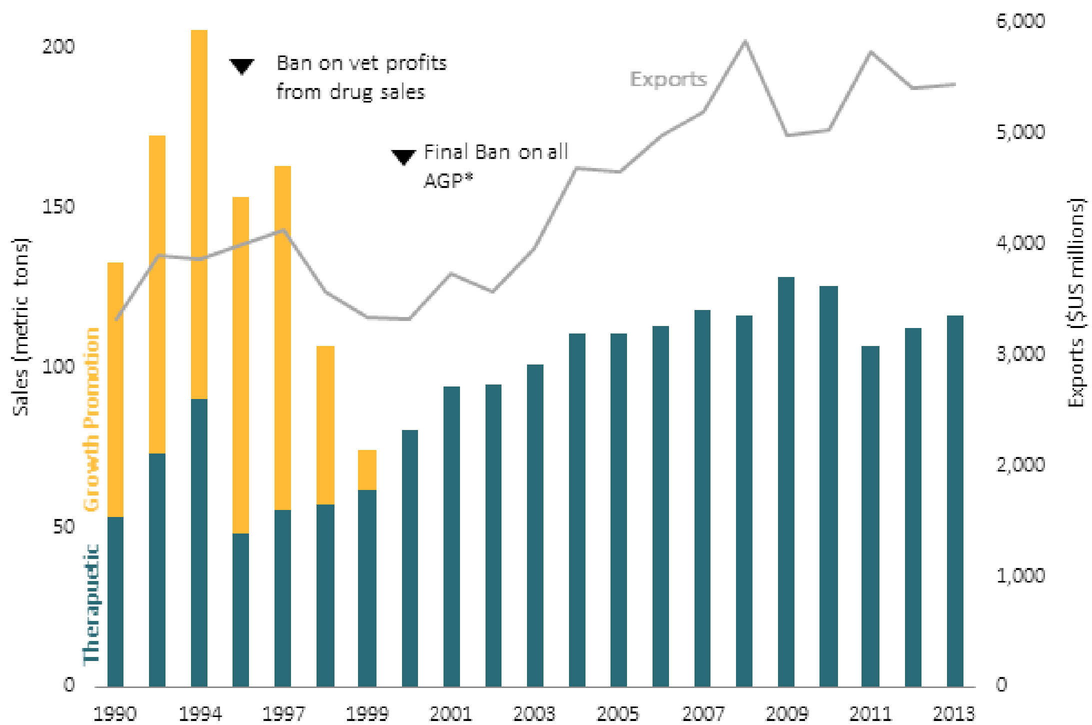
[17] Research on the economic impacts of antibiotic use in livestock is summarized in Elliott (2016) and Laxminayaran et al. (2015).

[18] The 2015 USDA report is available here: http://bit.ly/1PVVdLH.

[19] On a species-by-species basis, the study results suggest the total economic loss per pig produced of removing AGPs might amount to $1.34. Given there are approximately one billion pigs produced globally each year this adds up to a (low end) global cost of just over $1 billion; estimates on the number of pigs are from FAOSTAT at: http://bit.ly/1MLO4ZG.

that are increasingly intensive, and where extension services and regulation of the sector are relatively weak. By contrast, producers in the poorest countries cannot afford antibiotics, and those in the richest countries have access to alternatives.

Figure 2: Sales of active ingredients of antimicrobials for food-producing animals and exports of meat products in Denmark



*AGP = Antimicrobial Growth Promoters.
Sources: Antimicrobial sales: 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: UN Comtrade (SITC Revision 1).

Overall, the evidence, sparse as it is, suggests that the scale of the challenge is small compared to the global cost of losing antimicrobial effectiveness, or to other global challenges like climate change. Laxminarayan et al. estimate that a ban on AGPs might lead to an overall loss in global meat production of 1 percent to 3 percent, equivalent in value to $13 billion to $44 billion globally (2015).[20] The authors calculated the economic impacts for these high and low cost scenarios based on evidence of declining effectiveness of AGPs in modern management systems. In the absence of more detailed data on the reasons farmers use antibiotics, the authors also conservatively assume that all use in all countries is for growth promotion. In reality, however, only a certain proportion of antibiotics are used for growth promotion, and this varies widely across countries.

[20] In developing countries, overuse occurs alongside a lack of access to veterinary antibiotics. Some argue that limiting antibiotic use without adequate alternatives for livestock farmers could have unintended consequences (Grace 2015).

Using the costs estimated by Laxminarayan et al., we calculate that the value of lost meat production as a share of Gross Domestic Product (GDP) globally would be equal to 0.02 and 0.06 percent (see Table 3). In dollar terms, lost meat production is smallest for low-income countries, while upper-middle-income countries, mainly China and Brazil, experience the highest losses. As a share of national income, losses are lowest in high-income countries and highest in low-income countries, where the agriculture sector is a far larger share of national income. However, the estimate for low-income countries is particularly likely to be exaggerated since, for now at least, there is only limited use of antibiotics for growth promotion. Within countries, equity concerns should also be limited because the impact will be focused on larger, more intensive operations, though that also increases the potential for a few large operators to organize to oppose reforms. Overall, these costs seem manageable, and far less than the estimated costs associated with human deaths and resulting lost economic output if the AMR challenge is left unchecked (The Review on AMR, 2016).

In addition to modest overall costs on the supply side, consumer concern about this problem is growing and producers are increasingly responding to market pressures to reduce antibiotic use, even absent regulatory pressures. Increased consumer awareness has been a key factor in prompting Danish pork producers and major US poultry producers, such as Perdue, to voluntarily phase out the use of antibiotics. In the United States, Perdue—the fourth largest poultry producer—now uses vaccines, probiotics, and even oregano instead of antibiotics to promote growth and prevent disease in its flocks.[21] Some of the world's largest fast food chains, such as McDonald's, are also requiring suppliers to reduce antibiotic use.[22]

Table 3: Estimated loss in total meat production from AGP withdrawal by country income group

Income group	# of countries	Total loss in meat production value, 2014 (USD millions)		Average loss as share of GDP, 2014 (percent)	
		Low estimate	High estimate	Low estimate	High estimate
High-income	61	2,922	10,817	0.01	0.02
Low-income	30	1,273	2,954	0.34	0.79
Lower-middle-income	48	3,386	8,762	0.06	0.15
Upper-middle-income	49	5,866	21,303	0.03	0.11
GLOBAL	**188**	**13,446**	**43,836**	**0.02**	**0.06**

Notes: Estimate ranges are based on a low growth response to AGP scenario (data from the 2000s) and a high growth response scenario (1980s data). Calculations for GDP are based on data for 2014 in current USD millions. Country income groups are based on World Bank classifications as of July 2016.

Sources: Data for meat production loss are from Laxminarayan et al. 2015. Agriculture value added and GDP for 2014 are from the World Bank, accessed July 2016.

[21] Tom Philpott, "How Factory Farms Play Chicken with Antibiotics," *Mother Jones,* May/June 2016, accessed online at http://bit.ly/1NvC8R2.

[22] Information on McDonald's commitment on responsible antibiotic use is at: http://bit.ly/2drvbjh.

Despite emerging efforts to monitor and quantify the AMR challenge, there remain a number of caveats and unknowns regarding its nature and scale:

- There is a fuzzy line between using antibiotics for growth promotion and for disease prevention. Many drugs approved for prophylactic use are the same as those used for growth promotion. This may help to explain the limited impact of the AGP ban in the Netherlands and Denmark until additional steps were taken (as summarized in Elliott 2015).
- Only 42 out of 154 surveyed countries have a system in place to collect data on antibiotic consumption by farm animals (Rushton et al. 2014, p. 12).
- The risk of resistance developing as a result of using antimicrobials for growth promotion or prophylaxis in animals is widely accepted. There is also growing evidence linking resistance in animals to resistance in humans. However, the scale and severity of the risk that use in livestock will lead to more deadly infections in humans remains a matter of debate.
- There is no globally accepted list of antimicrobials essential to human health for which agricultural use should be curtailed or eliminated.

These unknowns—along with the complex nature of the AMR challenge—call for a response that allows for existing knowledge gaps and uncertainty and provides for flexibility to adjust the policy response as needed.

The Review on AMR Recommendations

Recognizing the urgency of the AMR problem, the UK government commissioned *The Review on Antimicrobial Resistance*, chaired by Lord Jim O'Neill, which released its final report in May 2016. While the review also focuses on the human and environmental aspects of the AMR challenge, the report proposes a series of international actions in three broad areas to reduce the use of antimicrobials in agriculture:

- **Set 10-year targets to reduce overall antimicrobial use (2018 to 2028) in agriculture and aquaculture**. The report lays out multiple options for this. The first involves a common target with different phase-in periods for different groups of countries, depending on levels of development. An alternative proposal is to set targets on a country-by-country basis. The report suggests a target of 50 mg/kg for high-income countries—the current level in Denmark. The report suggests governments could use regulation, taxation, and/or subsidies to achieve targets.
- **Restrict or ban certain antibiotics that are of critical importance for human health**. Improved systems of veterinary oversight are needed to monitor and control the use of antimicrobials in agriculture, especially in low- and middle-income countries.
- **Harness transparency and consumer concern** by requiring food producers to report on antibiotic use and possibly setting standards for a "responsible use" label.

To begin to fill the knowledge and evidence gaps, the report lays out three priority actions for 2016: further research on the transition costs to lower antibiotic use across a range of countries/regions; improved surveillance and a harmonized approach for data collection; and the creation of an expert group to agree on a list of antibiotics that are critical for human health and where agricultural uses should be banned or tightly regulated.

The Montreal Protocol Precedent

The AMR challenge shares a number of similarities with a previous global challenge around ozone depleting substances. In the 1970s, scientists were becoming increasingly concerned that ozone holes in the upper atmosphere could form and become so large as to expose significant numbers of people to dramatically increased risks of sunburn, cataracts, and skin cancers. The suspected cause was chlorofluorocarbons (CFCs)—a family of chemicals used in everything from aerosol sprays to coolants for refrigerators and cooling systems in buildings and automobiles. The risk was large, but at the time policy debates began the science was still in the theory stage and no ready alternatives to CFCs existed (Benedick 1998, chapter 1). As DeSombre (2000, p. 49) summarized it, international negotiations began "under conditions of uncertainty, over both the existence and extent of environmental harm and the costliness of taking action to mitigate it."[23]

In 1985, representatives from key countries—led by the United States—signed the Vienna Convention, which highlighted the need for global action and provided the legal framework for parties to address ozone depletion, but specified no actions beyond cooperation on data collection, information exchange, and scientific research.[24] That was followed two years later by the Montreal Protocol on Substances that Deplete the Ozone Layer, which established initial abatement targets, leaving it to individual parties to determine how to achieve those targets (by using taxes or regulation, for example). The convention-protocol model, along with embedded processes for amendments and adjustments, provided flexibility to begin modestly, and then ratchet up commitments as new scientific information and alternative products became available. Treaty membership also evolved over time, with mainly advanced economies signing on at the beginning and important developing countries, including China and Korea, joining relatively early with others joining gradually over the years.

The processes for amendments and adjustments are central to the treaty's flexible model. Amendments to the Montreal Protocol require a two-thirds vote and apply only to parties ratifying them. A series of amendments were adopted in 1990, 1992, 1997, and 1999 that added new substances to the proscribed products list, created a Multilateral Fund to assist developing countries, and revised phase-out schedules for some substances. Adjustments also require a two-thirds vote, with a majority of both developed and developing country

[23] In a speech subtitled "The Improbably Montreal Protocol," the chief US negotiator for the Protocol, Richard E. Benedick (2009, p.14), noted similarly that: The proposed treaty would unquestionably inflict substantial near-term economic costs solely to prevent speculative future dangers—dangers that rested on scientific theories rather than on proven facts.

[24] More information about the Vienna Convention and Montreal Protocol are available at: http://bit.ly/1LK3Z9l and http://bit.ly/2bYreTW.

members, but adjustments apply to all parties regardless whether they ratify them or not. Adjustments accelerated the phase-out timelines for some chemicals as alternatives became available more quickly than expected. For example, the initial target for industrialized countries to reduce use of "major CFCs" by 50 percent of 1986 levels by 1999 was changed to a complete phase-out by 1996 (DeSombre 2000, p. 55). In the end, members reduced production of ozone depleting substances far further and faster than originally envisioned (Benedick 1998, Appendix D). Today, almost all CFC production has been eliminated and atmospheric ozone concentrations began to recover around 2006.

It was a happy coincidence fostered by domestic regulatory action in the United States that some of the leading producers of ozone depleting substances were also developers of replacement products. This regulation in the United States (prior to the Montreal Protocol) was a key policy lever for incentivizing industry actors to develop alternatives and to support international regulation. American firms initially wanted to ensure that they would not be at a competitive disadvantage under US regulation. The industry in Europe was slower to adjust and opposed many of the more far-reaching proposals from US negotiators initially. However, research for alternatives only really got underway after the threat of significant global regulation of CFCs was on the table, and in particular as excise taxes on ozone depleting substances were ramped up in the United States and across the European Union. This helped reduce the relative cost of alternatives compared to CFCs. It also lowered later cost of compliance for developing countries. And firms in advanced countries supported treaty implementation because they now had a world market for their non-CFC alternatives.

A number of provisions encouraged participation by developing countries, many of whom were skeptical because of the potential costs. Countries below a low consumption threshold of ozone depleting substances of 0.3 kg per capita per year were given a 10-year grace period before they had to begin implementing their commitments. In the interim, those below the threshold could increase production or use up to the annual 0.3 kg/capita threshold. In addition to that flexibility, DeSombre suggests that the Multilateral Fund—created by an amendment in 1990 in London—"was the element that allowed for universal participation in the agreement, and facilitated the process of moving away from ozone depleting substances in developing countries" (2000, p. 70). This fund, with cumulative contributions from developed countries of $877million by 1999, was designed to help developing countries with the incremental costs of developing and adopting alternative technologies. Countries could apply to the Fund for financing, much of which was used to purchase equipment, chemicals, and technical expertise from developed countries (DeSombre 2000, p. 62).

Benedick (1998, pp. 243-44) agrees that the Multilateral Fund was important in facilitating implementation, but he also points to trade measures as a key factor encouraging developing countries to ratify the treaty. Amendments, also approved in London, required an immediate ban on imports of CFCs from non-parties and a ban on exports of CFCs to non-parties applied within a few years. Within three years, parties were to develop a list of products *containing* banned substances, and the import of these products from non-parties would be banned.

The Montreal Protocol as a Model for Reducing Antibiotic Use in Livestock

The challenges posed by phasing out ozone depleting substances and reducing antimicrobial use in the livestock sector share a number of similarities—as well as some differences—that could inform a global treaty to address antimicrobial use in livestock.

High net benefits of action: Best estimates of the costs and benefits of a phase out were very uncertain at the start of the process of negotiation over ozone depleting substances, but suggested a very high global economic return to their reduction (Benedick 1998, p. 63). Similarly, we have seen that the best estimates available today suggest high global returns to curbing antimicrobial use. AMR could cost the global economy up to $100 trillion cumulatively by 2050 (Review on AMR 2016). By comparison, the price tag of implementing the review's ten policy recommendations for overall reductions (not just in agriculture) is estimated at $40 billion over a decade. Moreover, unlike CFCs and other ozone depleting substances, which were used in a wide variety of industries across high-income countries, the proposal for a global treaty would affect just one relatively small sector. Impacts in poorer developing countries, where the agricultural sector is a larger share of total GDP, would be limited because the overall use of antimicrobials in livestock is relatively low.

Global externalities: There would be high returns to collective action because the overuse and misuse of antimicrobials in farm animals, much like the production of ozone depleting substances, contributes to large, negative environmental and public health externalities that are global in their impact. A global treaty with binding commitments would help overcome the collective action problem and preserve the effectiveness of existing antimicrobials, contributing an important global public good. The goal of the Montreal Protocol process was to phase out use of (most) ozone depleting substances, but with flexibility to make exemptions for essential uses (DeSombre 2000, p. 57 and Green 2009, p. 263). Similarly, it appears the global consensus is moving towards eliminating the use of antimicrobials for growth promotion in livestock and restricting use of certain medically-important drugs to human use, while also sharply reducing overall use. Livestock producers could still use antimicrobials to treat disease, which could pose problems for enforcement relative to the Montreal Protocol, in which case most uses were phased out completely.

Scientific uncertainty: Protecting the ozone layer was "the first time the international community had taken formal steps to address an environmental threat before scientific certainty was established regarding the cause" (Green 2009, p. 258). But that uncertainty caused many countries to be cautious and to take only limited steps at the beginning. With AMR, there is ample evidence that antimicrobial use in livestock expands the pool of antibiotic-resistant bacteria and that these bacteria can spread to humans through direct contact with animals, the environment, or contaminated meat. What is unknown is how often resistant bacteria cause infections in humans (Laxminarayan et al. 2015, p. 2). Farmers, like many CFC producers and consumers before them, may resist paying costs for an uncertain, global benefit.

Alternatives uncertain but under development: CFCs were in widespread use when talks began and there were no alternatives on the immediate horizon for many applications. Other than the use for aerosol sprays, alternatives were expected to be expensive. Unlike ozone depleting substances, there are ready alternatives to using antibiotics for growth promotion and disease prevention. A growing body of evidence shows that better management practices sharply reduce the need for antimicrobials, while a range of substitutes and alternative approaches are already under development; but the costs under different circumstances (i.e., different production systems across a range of countries) remain unclear.

Favorable market structure and the role of regulation in creating incentives to develop alternatives: Market structure facilitated reduction in the case of CFCs and may do the same with antimicrobials. There were a relatively small number of large producers of ozone depleting substances which made reporting and monitoring easier. Many producers were also involved in developing alternative chemicals. And competitive concerns of firms in countries like the United States, with domestic regulations in place, contributed to support for an international agreement to level the playing field and to open up a large market internationally for US companies that developed alternatives (DeSombre 2000, p. 60). Similarly, in the United States, there are only 26 major manufacturers of antibiotics that are used in animal health. Many are also involved in producing alternate technologies that would help reduce the need for antibiotics in livestock management, not least vaccines. Major players in the animal antimicrobials market include Zoetis Inc. and Merck Animal Health, for example. Both are also involved in a global animal-vaccine market which may be worth an estimated $7.2 billion by 2020, an increase from $5.5 billion in 2010. Animal vaccines accounted for one half of product approvals in 2015 for Zoetis Inc.; and Merck Animal Health introduced a vaccine for bacterial intestinal infections in pigs in 2016.[25] Table 4 summarizes some of the key differences and similarities in how industry structure could affect the prospects for international policy reform.

Growing public awareness: Public concerns about the impacts of the ozone hole as well as the threat of AMR also play a role as a stimulus for public, and private, sector action. In response to mounting consumer pressure in the 1970s, DuPont—one of the major manufacturers of ozone depleting substances—began research on non-CFC propellants for aerosol spray cans (DeSombre 2000, p. 59). Even before the US government passed the ban, the market for these CFCs had fallen by two-thirds (Benedick 1998, pp. 27-28). In parallel, there is growing public awareness about AMR, due in part to recent discoveries of antimicrobial strains in humans and animals that are resistant to a last-line antibiotics, such as colistin. Even prior to that, a growing demand among consumers for healthier food and increased awareness about how foods are produced, was driving major US poultry producers and marketers to phase out the use of antibiotics, just as similar concerns had done earlier with meat producers in Europe.

[25] These trends are discussed in a Bloomberg article, available here: http://bloom.bg/2aVPatC.

Table 4: Industry structure issues affecting regulation of ozone depleting substances and antimicrobials in livestock

Role in value chain	Ozone Depleting Substances	Antimicrobials in livestock
Producers	Chemical producers: • Highly concentrated • Involved in developing new technologies • US firms subject to early regulation interested in level playing field; new markets for alternatives	Drug producers: • Relatively concentrated • Involved in some, but not all alternatives • Interest in larger markets, new drugs not necessarily consistent with conservation of current drugs • Animal drugs relatively small part of overall portfolio for many firms
Users	Manufacturing firms: • Concerned about potential for higher costs of alternatives • Users highly dispersed	Feed mills/retailers: • May be involved in developing, selling alternatives • Highly dispersed? "Integrators" who rely on contract farms to produce meat that they retail; often exert control over feed, other production decisions (particularly prominent in poultry and pork) Animal veterinarians: • Control prescriptions when OTC banned • Have farmers as clients • May profit from drug sales or drug company incentives • Highly dispersed
Final consumers	Highly dispersed and usually no direct link to product Exception that proves rule: aerosol sprays in US where consumers pushed for alternatives to CFCs	Restaurant/fast food chains may be large enough to have market power over production process Meat consumers are highly dispersed, but shunning can be costly; willingness to pay more uncertain

Global equity: The relative costs to phase out CFCs were potentially higher for developing countries in the case of ozone depleting substances. The same is true in the case of antimicrobial use in animals (see Table 3), and the treaty would have to address that, as the Montreal Protocol did. Moreover, in both cases, the cost to developing countries of not responding to the issue would be considerable, thus encouraging participation in a global agreement. For example, 90 percent of the estimated 10 million AMR-related deaths per year by 2050 will be in developing countries (Review on AMR 2016).

In sum, as with ozone depleting substances, we believe an international agreement to restrict antimicrobial use is feasible and would help overcome the global collective action problem that could otherwise inhibit effective action. The Montreal Protocol provides a possible model to design a global treaty that would help manage livestock's contribution to the AMR challenge. Note that a treaty around use of antibiotics would differ from the Montreal Protocol in at least one significant way. A treaty on antimicrobial use in livestock could only be one element of the international response to the overall AMR challenge. It would have to be embedded in a broader multisector, "One Health," response that also addresses human health uses. That said, a Global Treaty to reduce the consumption of antimicrobials by farm animals responds to an important component of the global AMR challenge.

Options for Negotiating a Global Treaty on Antimicrobial Use in Livestock

Building on lessons learned from the Montreal Protocol process and current knowledge about the AMR threat, we outline options for negotiating an effective global treaty to reduce the use of certain antimicrobials in livestock and protect drugs that are critically important for human health. The three key elements of such a treaty are flexible tools to reduce use that can be easily adapted to reflect new evidence or the pace of development of alternatives; incentives for key countries, including developing countries, to participate early on and the flexibility to bring in other countries over time; and provisions for data collection, monitoring, and enforcement. Under each of these three elements, we discuss various options negotiators might consider, as summarized in figure 3 (see panels A, B, and C).

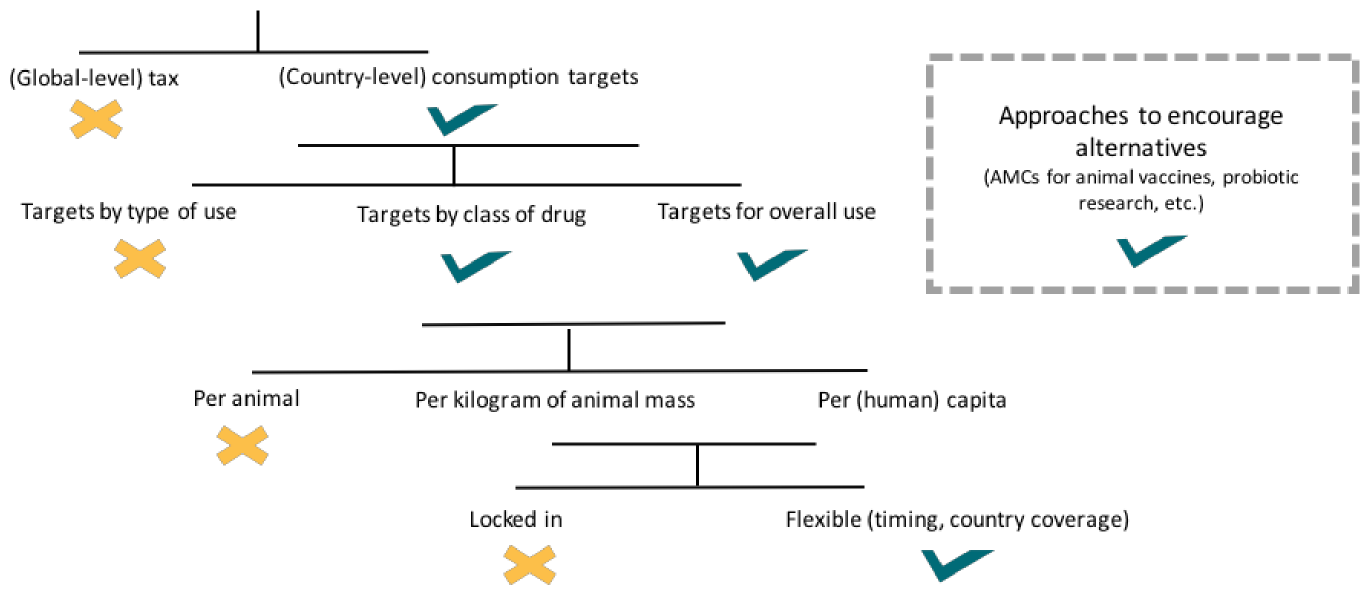
Given that AMR is a global problem that cannot be contained nationally or regionally, universal adoption is the ultimate goal. At the beginning, however, a relatively small number of countries could take the lead and have a large impact. According to the 2010 estimates calculated by Van Boeckel et al. (2015) 42 countries account for 90 percent of global antimicrobial use in livestock, and just 20 countries for 75 percent of global use.[26] Setting up an initial treaty regime with the United States, European Union, Brazil, China, India, Mexico, Russia, and a few others could make significant inroads into the global problem, and it would be similar to the way in which the Montreal Protocol evolved.

[26] The twenty countries are Thailand, Denmark, United Kingdom, Sudan, Australia, Argentina, Japan, Italy, Poland, Netherlands, Canada, France, Mexico, Russian Federation, Spain, Germany, India, Brazil, United States and China. Thomas Van Boeckel kindly provided the country-specific data on antibiotic use from their 2015 paper.

Before turning to the three key elements of the proposed treaty, there is another key element for success that we do not address directly within the scope of this paper: incentives to develop alternatives to antimicrobials for growth promotion and disease prevention. As with the Montreal Protocol, a treaty that successfully reduces demand or increases costs for an existing technology—in this case AGPs—will create incentives for the market to produce alternatives. Moreover, in countries with modern, intensive livestock production systems, there are already a number of alternatives available. However, there could be a need for additional incentives to develop alternatives adapted for developing country situations—a point we address below.

1. Tools to reduce use

Figure 3 (panel A): Options to reduce use in livestock



Source: Authors.

When governments want to discourage consumption of a "global public bad," they can introduce a tax or set quantitative limits or conditions on use. Economists generally regard taxes as more efficient because they allow the market to allocate the now relatively scarce good to its most valued uses. In this case, we think it would be difficult in practice to set a global tax that could reliably achieve the needed reductions in antimicrobial use in the livestock sector. Antibiotic prices vary widely across countries, making it difficult to determine an appropriate global tax rate that fits all contexts. Individual countries might choose taxes as part of their domestic strategy for reducing overall use, however.

For pragmatic reasons, we agree with the Review on AMR's recommendation to set targets for reducing such use, and discuss three potentially complementary approaches: banning the use of antimicrobials for growth promotion in livestock; banning or restricting the use of specific drugs that are critically important for human use; and sharply reducing overall use by eliminating inappropriate uses. A ban on using antibiotics to promote animal growth might seem like a logical place to start, especially since the European Union, United States, and a number of other countries have already taken steps to do that. But relying solely on such a ban would be a mistake in our view since it would be difficult to enforce. Many of the same drugs used for growth promotion are also used for disease prevention; and past experience with bans on AGPs suggests that overall antimicrobial use in livestock often does not fall, or it rebounds after an initial drop. Such a ban might be useful to create a global norm, but it should not distract from the core task of reducing overall antimicrobial use in the livestock sector.

A more important priority should be the rapid reduction in the routine use of specific antibiotics in livestock feed or water that are critical to human health. The list could start with the three classes (third and fourth generation cephalosporins, fluoroquinolones, and macrolides) that the FDA has identified as critical and that the WHO also identified as priorities. Like the Montreal Protocol, the treaty should build in flexibility to adjust the list as more information on livestock use, resistance, and alternatives becomes available. Negotiators should also take early action to ban the use in livestock of last resort drugs, such as colistin.

In setting global targets to reduce overall antimicrobial use in livestock, negotiators need to decide how to measure use and what the targets should be. The decision on how to allocate the smaller pool of legitimate antimicrobial use across countries is an ethical as well as a practical issue. The Montreal Protocol used a per capita CFC consumption measure as a cutoff between countries to determine the timing of treaty obligations and access to financing. Proposals for a carbon 'cap and trade' regime also frequently suggest pollution allowances on a per capita basis. This is on the understanding that 'the right to pollute' regarding a global public good should be equally distributed amongst the world's (human) population. A similar logic could apply to antimicrobial use in livestock: a country limit on grams of antibiotic use in animals in per (human) capita.

The alternate (and more widely discussed) set of measures involve targets related to livestock numbers (per animal, per kilogram of weight). The advantage of such a measure it that a low cap can be used as a method to largely force the abandonment of subtherapeutic dosing in livestock. Countries will want to preserve their limited allocation to treat sick or injured animals. A measure designed on a per (human) capita basis might allow countries with low livestock-to-human population ratios to potentially continue subtherapeutic use under a cap that might constrain even therapeutic uses in countries with a high livestock-to-human ratio. At the same time, reduced use of antibiotics in livestock can be achieved in two ways: less antibiotics per animal or fewer animals overall. A measure related to use per animal rewards only one of those two approaches. Countries with (or moving toward) relatively small livestock populations per (human) capita might regard that as unfair and it provides no incentive to accelerate that progress. These countries could benefit if they are allowed to trade their 'pollution rights' in terms of credits to use antibiotics in livestock. 'Cap and trade' would also reduce the risk of therapeutic uses potentially being capped in countries with relatively larger livestock populations, but it would also have to come with safeguards that prevent the mechanism undermining the goals of the treaty (see discussion in next section).

Whether a per (human) capita or per livestock measure of antimicrobial use is adopted will depend not least on the relative winners and losers under each model and their importance to successful treaty negotiation, the presence or absence of trading usage rights under the model, and the priority on ending subtherapeutic uses amongst other factors. We believe that the practical issues with a per capita ban—especially that it would only work to full effect to reduce subtherapeutic use worldwide if combined with 'cap and trade,' which raises other concerns—suggests that a livestock-based measure of use is likely to be more tractable.

However, measures based directly on livestock numbers are a challenge because of current data limitations and because the composition of livestock populations differs widely across countries. Setting targets that reflect these differences might be optimal, but is not currently possible given the paucity of data. Setting the target as a quantity of drug per animal would be problematic because animal weight can vary significantly from country to country and by type of production system. The UN Food and Agriculture Organization (FAO) reports data on meat production across the world, but setting the target per kilogram of meat would leave out egg and dairy production.

For pragmatic reasons mainly related to data availability, the approach we focus on here is based on the methods adopted by the European ESVAC project, adapted by Van Boeckel et al. (2015), and recommended by the Review on AMR. The methodology involves the calculation of a population correction unit (PCU)—a standardized measure of milligrams of active antimicrobial substance per kilogram of (population corrected) animal mass that can be compared across countries. This technique provides a measure that controls for differences in animal populations and production systems across countries. The mg/kg target would then be multiplied by the sum of PCUs for each country to come up with the overall allocation of antimicrobials that each country can use in its livestock sector. As more data on actual antimicrobial use by species is collected and made available, it may be possible to develop more refined measures and even species-specific targets. Therefore, we propose adopting a treaty structure that is similar to the Montreal Protocol, where flexible features would allow for adjustments as new data and evidence become available.

Setting an appropriate target and defining it in the context of global antimicrobial use in livestock is complex. Because different countries have different animal mixes along with different proportions of extensive farming, setting a single target defined on a per unit basis will be more challenging for some countries than others to meet. The Review on AMR recommends a target, at least for high-income countries, based on the current level of use in Denmark (50 mg/kg). This target, based on the information that we have available, seems reasonable. Denmark is relatively concentrated in pork products, and pigs are relatively heavy users of antibiotics, compared to chickens or cattle. On the other hand, a 50 mg/kg target may produce an overall allowable use allocation that is too high for a country with more chickens or cows, another reason that the treaty should build in flexibility to adjust targets.

Basing a global target on the Danish level would also result in allocations that are considerably above current usage levels in countries (especially low-income countries), where extensive farming systems are more prevalent. As livestock sectors in those countries develop, there may be pressures to increase antimicrobial use up to that level, or even beyond, so it would be useful to incorporate incentives for these countries not to go down a path of routine antibiotic use for growth promotion or disease prevention. We discuss some options for this in the next section.

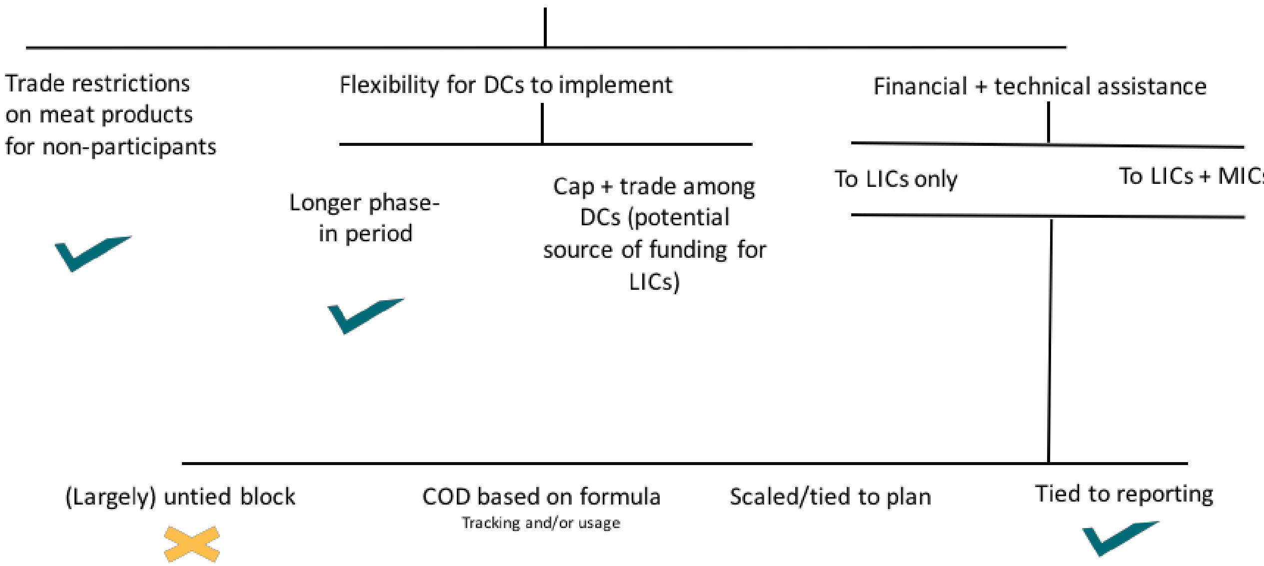
Given the scientific and economic uncertainty, flexibility in implementation would facilitate achievement of a formal, binding agreement to reduce overall use. The Review on AMR recommends 10 years for countries to reach the 50 mg/kg target. As with the Montreal Protocol, the treaty should include a mechanism to accelerate the goal if science suggests the costs of waiting are higher than we currently estimate, or adoption of alternatives becomes cheaper. It would also be useful to have interim targets to ensure that countries do not wait to begin the process of switching to alternatives. For example, countries might commit to reduce use by 50 percent over the first five years.

There should also be flexibility, at least at the early stages of the process, in what countries needs to be at the negotiating table. The process might begin with a critical mass of four or five countries agreeing among themselves to lead the way. In their discussion on the need for a combination of quick wins and long-term efforts, Ardal et al. (2016) suggest a few large markets could informally agree to reserve critically important antimicrobials for human use only, while a global treaty is being negotiated. As with the Montreal Protocol, this could help incentivize and speed up the development of alternatives, thereby lowering the costs of compliance for followers.

Given the uncertainty around the level of antimicrobial use that allows for necessary treatment but effectively ends subtherapeutic uses for production purposes, as well as the ongoing need for research and consensus building about the global scale of the AMR challenge in livestock, the treaty would certainly want to incorporate an amendment and adjustment process, including a qualified super-majority process to accelerate timelines or adjust targets. Additional treaty requirements might involve requiring prescriptions and veterinarian involvement for antimicrobial prescriptions, but with safeguards against veterinarians profiting from the sale of antimicrobials and a ban on advertising antimicrobials for non-therapeutic uses. Overall, however, it is best to leave the specifics of how to reach the targets for responsible use to individual treaty members, as was done in the context of the Montreal Protocol.

2. Incentives for countries to participate

Figure 3 (panel B): Options for incentives for countries to participate



Source: Authors.

The Montreal Protocol used three main approaches to encourage countries, especially developing countries, to participate: restrictions on trade with nonparticipants; flexibility in implementation; and a Multilateral Fund to provide financial and technical assistance to help developing countries with the incremental costs of moving to new technologies. A global treaty to reduce antimicrobial use in livestock will likely need to incorporate each of these elements in some form, as well.

The Montreal Protocol used restrictions on trade in CFCs, or products containing CFCs, to prevent non-parties from offsetting the progress made by treaty participants. In the current case—given limited data and the importance of using antibiotics for legitimate health purposes—it may be preferable to focus on meat trade instead of antimicrobials. Most countries already regulate drug residues in meat and increased scrutiny by treaty parties of meat imports from non-parties would be warranted. In addition, parties may want to consider restrictions on meat imports from countries that decline to participate in a global treaty. Benedick (1998, p. 243) notes that participation in the Montreal Protocol increased markedly after the London Conference clarified the scope of the trade measures.

Additional flexibility in implementing the Montreal Protocol's commitments was another incentive for developing countries to join. As with that case, countries unable to take on antimicrobial use commitments in the near term might be granted a grace period before they have to start implementing reductions, and then might have additional time to phase them in. Another option to provide flexibility, and possibly generate financing for lower income countries, would be to incorporate a tradeable permit regime. Countries might be allocated a stock of credits to use antimicrobials based on their (livestock) population and agreed international usage targets, which they could use for legitimate national antimicrobial use or trade to countries which were using more than their allocated antimicrobial allowance in the livestock sector. Over time, the number of permits would be reduced as part of a process of overall antimicrobial use reduction. Given that production systems in high-income countries mostly already embrace modern management practices, the adjustments there should be relatively rapid. The treaty might even exclude those countries from using tradeable permits. The major buyers of permits would likely be middle-income countries where a large proportion of livestock production is already intensive, but where modern practices are perhaps not as prevalent. And low-income countries—since they mostly still have extensive livestock production systems and low antimicrobial use—would be able to sell permits and use the proceeds to beef up their systems for data collection and surveillance. Such a scheme would have to be limited, however, since AMR could spread globally from even a small number of countries not embracing responsible antimicrobial use.

Finally, whether from a tradeable permit scheme or other sources, many developing countries will need financial and technical assistance to implement their treaty commitments. At a minimum and in the short run, developing countries will need assistance to begin collecting more and better data on antimicrobial use that will be needed to monitor the treaty. Beyond that, high-income countries should consider incentives to encourage low- and middle-income countries where antimicrobial use is currently limited to keep usage levels low, and provide support to developing countries to adjust to alternate approaches, as the Montreal Protocol's Multilateral Fund did. This support should be targeted to countries where livestock is a large proportion of GDP and where the impact of a ban on antibiotics for growth promotion will be larger if producers are moving to more intensive production systems without modern management practices. The nature of this support would be a matter for negotiation, but it might include:

- advance market commitments and/or subsidies for vaccines developed with the microbial disease burden of livestock in developing countries;
- transition support to pharmaceutical companies to move from antibiotic production to vaccine and other approaches of animal prophylaxis;
- transition support for monitoring antimicrobial use on farms; and
- support for agricultural extension programs designed to limit the impact of lower antimicrobial use at the farm level.

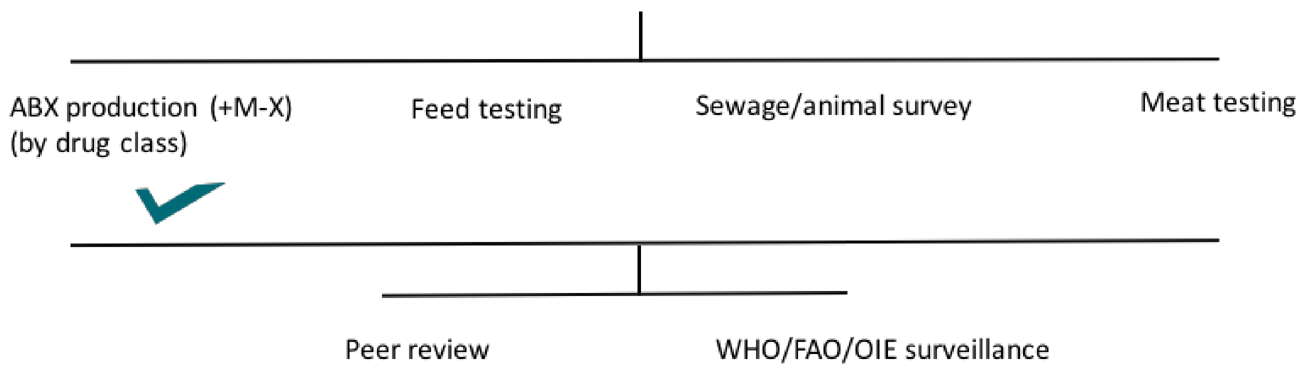
Mendelson et al. (2016) recommend a "Global Antimicrobial Conservation Fund for Low and Middle Income Countries" to complement the innovation funds recommended in the Review on AMR and elsewhere. The proposed fund, under the "One Health" approach, would promote conservation (responsible use) in human health and agriculture and would thus be broader than the Multilateral Fund set up under the Montreal Protocol. Among other things, the fund would help countries set up surveillance systems for consumption and resistance and provide support to build human resource capacity, both of which would be helpful in meeting commitments under the global treaty we are proposing.

Approaches to finance these transfers might include:

- a tax on all antimicrobials or those used for livestock (proposed by the Review on AMR because it would both produce revenue, create incentives for industry actors, and increase the cost competitiveness of alternatives);
- as part of a 'cap and trade' regime outlined above; and
- from general taxation.

3. Reporting, monitoring, and enforcement

Figure 3 (panel C): Options for reporting, monitoring, and enforcement



Source: Authors.

The ultimate goal of the global treaty we are proposing is to reduce consumption of antimicrobials in the livestock sector. Measuring that directly would require monitoring millions of, often geographically remote, farms around the world. Since that is not feasible, we propose following the Montreal Protocol model and monitoring "apparent consumption": production plus imports minus exports of antimicrobials for use in agriculture, disaggregated by drug class. These data should be relatively easy for even poor countries to collect and this information would then be combined with data on livestock populations from those governments, or estimates from the FAO, if necessary, to monitor progress against the targets.

The World Organization for Animal Health (OIE) has begun collecting this (highly aggregated) data on antibiotic use in animals and aquaculture by drug class and type of use (whether for growth promotion or therapeutic, including preventive). This database could serve as the platform to monitor compliance with the treaty. So far, however, it is only publishing data on reporting, not on use. Thus, the scope, transparency, and external validation of national-level data needs to be considerably improved. We also need better, more reliable data on livestock populations in developing countries. Over time, if better data becomes available, both the targets and the monitoring process could be adjusted to be more effective.

Finally, there is the question of enforcing the treaty. The initial steps toward compliance are, first, providing the data needed to establish baseline use and then reporting regularly on subsequent trends. Thus, after an initial period of providing support to build country-level capacity to collect data, all financial and technical assistance should be conditional on timely reporting. The treaty might also consider trade restrictions on countries failing to meet their obligations under the treaty, as well as on non-parties, but that may be neither politically acceptable nor particularly helpful. For example, attaching sanctions to compliance could undermine transparent reporting and the Montreal Protocol did not find such sanctions to be necessary.

Benedick (1998, p. 272) notes that many parties to the Montreal Protocol opposed a strong enforcement mechanism and that:

> In effect, the Montreal Protocol's non-compliance regime was based on assumptions that parties would act in good will, that peer pressure… would be an effective deterrent, and that when noncompliance did occur it would probably be the result of economic or technical problems rather than a willful act.

The AMR threat is large enough that one would hope a similar spirit would prevail in this case.

Conclusion

Antimicrobial resistance emerging from livestock is a significant threat to public health, it is global in nature and, therefore, it can only be contained by a global response. The good news is that the nature of the livestock AMR challenge suggests that it may be amenable to global treaty-making considering the high benefit-cost ratio of action and the limited number of antimicrobial producers. There are also a relatively small number of major livestock producers and exporters that use the majority of animal drugs and whose cooperation would be crucial to launch such an effort. However, due to a number of unknowns including acceptable usage levels and limited data availability on current use, the treaty will need to be designed from the outset to bring in new members, adjust targets as new information and alternatives become available, and provide appropriate incentive mechanisms. Due to the urgency of the threat, however, the first steps towards treaty-making should begin now.

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