



**NAVAL
POSTGRADUATE
SCHOOL**

MONTEREY, CALIFORNIA

THESIS

**FINDING THE PATH OF LEAST ANTIBIOTIC
RESISTANCE: AN EXAMINATION OF
AGRICULTURAL POLICIES**

by

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March 2019

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REPORT DOCUMENTATION PAGE			<i>Form Approved OMB No. 0704-0188</i>	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instruction, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188) Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE March 2019	3. REPORT TYPE AND DATES COVERED Master's thesis	
4. TITLE AND SUBTITLE FINDING THE PATH OF LEAST ANTIBIOTIC RESISTANCE: AN EXAMINATION OF AGRICULTURAL POLICIES			5. FUNDING NUMBERS	
6. AUTHOR(S) Stephanie L. Smiley				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Postgraduate School Monterey, CA 93943-5000			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) N/A			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES The views expressed in this thesis are those of the author and do not reflect the official policy or position of the Department of Defense or the U.S. Government.				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release. Distribution is unlimited.			12b. DISTRIBUTION CODE A	
13. ABSTRACT (maximum 200 words) Antibiotic-resistant bacterial infections will remain an extremely serious health-security and economic threat for the United States—and the world—unless steps are taken to curb them. This thesis focuses on antibiotic use in agriculture and potential methods to slow resistance. By examining existing U.S. policies at the national and state level as well as policies in Denmark and the Netherlands, this research finds that the European countries have reduced antibiotic use and decreased resistant organisms present in food animals. This thesis recommends implementing a multifaceted policy package beginning with the creation of an enhanced, more integrated surveillance system, then enacting antibiotic-use reduction targets, prohibiting the use of antibiotics in healthy animals and requiring veterinarians to examine animals before prescribing them antibiotics for disease prevention. The United States must implement more policies that respond to this global threat to preserve medically important antibiotics that protect the health and safety of people and animals. The homeland security enterprise should prioritize antibiotic resistance as a threat and work collaboratively to implement strategies to mitigate it.				
14. SUBJECT TERMS antibiotics, antibiotic, public health, agriculture, Denmark, Netherlands, California, Maryland, antimicrobial, antimicrobials, stewardship, health, veterinarian, one health, resistance			15. NUMBER OF PAGES 153	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT UU	

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**FINDING THE PATH OF LEAST ANTIBIOTIC RESISTANCE: AN
EXAMINATION OF AGRICULTURAL POLICIES**

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Submitted in partial fulfillment of the
requirements for the degree of

**MASTER OF ARTS IN SECURITY STUDIES
(HOMELAND SECURITY AND DEFENSE)**

from the

**NAVAL POSTGRADUATE SCHOOL
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ABSTRACT

Antibiotic-resistant bacterial infections will remain an extremely serious health-security and economic threat for the United States—and the world—unless steps are taken to curb them. This thesis focuses on antibiotic use in agriculture and potential methods to slow resistance. By examining existing U.S. policies at the national and state level as well as policies in Denmark and the Netherlands, this research finds that the European countries have reduced antibiotic use and decreased resistant organisms present in food animals. This thesis recommends implementing a multifaceted policy package beginning with the creation of an enhanced, more integrated surveillance system, then enacting antibiotic-use reduction targets, prohibiting the use of antibiotics in healthy animals and requiring veterinarians to examine animals before prescribing them antibiotics for disease prevention. The United States must implement more policies that respond to this global threat to preserve medically important antibiotics that protect the health and safety of people and animals. The homeland security enterprise should prioritize antibiotic resistance as a threat and work collaboratively to implement strategies to mitigate it.

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TABLE OF CONTENTS

I.	ANTIBIOTIC RESISTANCE AS A HOMELAND SECURITY ISSUE	1
A.	IMPORTANCE.....	3
B.	ANTIBIOTIC RESISTANCE AND AGRICULTURE.....	4
	1. <i>Salmonella Heidelberg</i> Outbreak.....	6
	2. Agricultural Impact and Food Security.....	7
C.	HOMELAND SECURITY RELEVANCE.....	8
	1. Characterization of Antibiotic Resistance as a Crisis	8
	2. Antibiotic Resistance in Food Animals	10
	3. Health and Economic Burden of Antibiotic Resistance	11
	4. Efforts in the Homeland Security Enterprise to Address the Threat	11
D.	RESEARCH QUESTION	13
E.	METHODOLOGY	14
F.	LIMITATIONS AND SCOPE	16
G.	THESIS OUTLINE.....	17
II.	CASE STUDY: DENMARK.....	19
A.	MONITORING RESISTANCE: INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING AND RESEARCH PROGRAMME (DANMAP)	21
B.	ASSESSMENT	23
	1. Impacts of the Ban on Industry	24
	2. The Yellow Card Initiative.....	26
	3. Current Status of Resistant Zoonotic Bacteria in Denmark	28
C.	IMPLEMENTATION STRATEGIES.....	29
D.	CONCLUSION	30
III.	CASE STUDY: THE NETHERLANDS.....	31
A.	THREATS AND CONCERNS EMERGE	31
B.	FURTHER ACTION TAKEN TO REDUCE ANTIBIOTIC USE IN FARM ANIMALS	34
	1. Dispensing Antibiotics	35
	2. Monitoring Antibiotic Use and Resistance	36
C.	ASSESSMENT	36
D.	IMPACTS OF POLICIES ON INDUSTRY	38
E.	IMPLEMENTATION STRATEGIES.....	39

F.	CONCLUSION	40
IV.	UNITED STATES: LEGISLATIVE EFFORTS AND CURRENT POLICY	41
A.	POTENTIAL LEGISLATION	41
1.	Historical Discussion.....	41
2.	Preservation of Antibiotics for Medical Treatment Act (PAMTA)	42
B.	ACTION PLANS AND GUIDANCE	45
1.	Food and Drug Administration: Guidance for Industry.....	45
2.	United States Department of Agriculture: Antimicrobial Resistance Action Plan	51
C.	SURVEILLANCE SYSTEMS AND DATA COLLECTION	54
1.	USDA National Animal Health Monitoring System (NAHMS): Antimicrobial Resistance Studies	54
2.	National Antimicrobial Resistance Monitoring System (NARMS)	56
D.	CONCLUSION	57
V.	CASE STUDY: UNITED STATES	61
A.	CALIFORNIA.....	61
1.	Legislative Ban	61
2.	Antimicrobial Dispensing.....	62
3.	Monitoring Antibiotic Use and Resistance	64
4.	Implementation	64
5.	Potential Impacts on Industry	66
6.	Assessment	67
B.	MARYLAND.....	67
1.	Legislative Ban	67
2.	Antimicrobial Dispensing.....	68
3.	Monitoring Antibiotic Use and Resistance	68
4.	Opposition.....	69
5.	Implementation	70
6.	Potential Impacts on Industry	71
7.	Assessment	71
C.	CONCLUSION	71
VI.	CASE STUDY POLICY COMPARISONS.....	73
A.	LEGISLATIVE BANS	73
B.	ANTIMICROBIAL DISPENSING	77

1.	Veterinary Oversight	78
2.	The Dutch Quality System	79
3.	Prescribing Limits.....	79
C.	MONITORING	79
D.	OUTCOMES	83
E.	IMPACTS ON INDUSTRY	84
F.	CONCLUSION	85
VII.	CONCLUSIONS AND RECOMMENDATION	87
A.	PROPOSED POLICY PACKAGE	88
1.	Creating an Integrated Surveillance System	90
2.	Enacting Antibiotic-Use Reduction Targets	92
3.	Prohibiting the Use of Medically Important Antibiotics in Healthy Animals.....	94
4.	Requiring Annual Veterinary Examinations for Disease Prevention and Control	95
B.	RECOMMENDATION	96
C.	FUTURE RESEARCH OPPORTUNITIES.....	98
D.	CONCLUSION	100
	APPENDIX. PROPOSED POLICY ANALYSIS	103
	LIST OF REFERENCES.....	115
	INITIAL DISTRIBUTION LIST	129

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LIST OF FIGURES

Figure 1.	Process of Antibiotic Resistance.....	3
Figure 2.	How Antibiotic Resistance Spreads.....	5

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LIST OF TABLES

Table 1.	Nontherapeutic Uses Banned.....	73
Table 2.	Drug Classes Banned or Limited for Use in Food Animals	75
Table 3.	Penalties	76
Table 4.	Veterinary Requirements	77
Table 5.	Monitoring Requirements	80
Table 6.	Sectors Required to Submit Data on Antibiotic Use	82
Table 7.	Reduction in Antibiotic Use.....	83
Table 8.	Policy Analysis Options.....	89
Table 9.	Policy Package—Integrated Surveillance System	103
Table 10.	Policy Package—Antibiotic-Use Reduction Targets.....	106
Table 11.	Policy Package—Prohibit the Use of Antibiotics in Healthy Animals....	108
TABLE 12.	Policy Package—Annual Veterinary Examination for Prophylaxis.....	111

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LIST OF ACRONYMS AND ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CRE	carbapenem-resistant <i>Enterobacteriaceae</i>
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DHS	Department of Homeland Security
DVFA	Danish Veterinary and Food Administration
EBSLs	extended spectrum beta-lactamase-producing bacteria
FDA	U.S. Food and Drug Administration
IDSA	Infectious Diseases Society of America
KNMvD	Royal Dutch Veterinary Association
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
PAMTA	Preservation of Antibiotics for Medical Treatment Act of 2017
PDMP	prescription drug monitoring program
ROI	return on investment
SDa	Netherlands Veterinary Medicines Institute
USDA	United States Department of Agriculture

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EXECUTIVE SUMMARY

Antibiotic resistance is an emerging biological threat that poses an increasing risk to the United States and to the world.¹ The Centers for Disease Control and Prevention estimates that two million people are infected with drug-resistant bacteria annually and 23,000 deaths each year can be blamed on these infections.² According to the World Health Organization, resistant illnesses across the world are becoming more numerous and extremely difficult, and in some cases impossible, to treat with antibiotics.³ Bacteria that cause illnesses such as pneumonia, salmonellosis, shigellosis, gonorrhea, and tuberculosis may soon be completely resistant to antibiotics, rendering these conditions untreatable.⁴ The increasing number of antibiotic-resistant bacterial infections will remain a serious health-security and economic threat for the United States—and the world—unless steps are taken to curb it.

Many factors have contributed to the acceleration of the antibiotic resistance threat; however, the focus of this thesis is on the use of antibiotics in agriculture. While data regarding the use of antibiotics in food animals are limited, some sources report that 80 percent of all antibiotics sold in the United States are used for livestock.⁵ There is consensus among researchers that antibiotic use in food animals may contribute to antibiotic resistance in humans; dozens of studies and trials suggest a causal relationship.⁶ Given the amount of antibiotics used in animal husbandry, there is a need

¹ “Written Testimony of OHA for a Senate Committee on Homeland Security and Governmental Affairs Hearing Titled ‘The Federal Perspective on the State of Our Nation’s Biodefense,’” Department of Homeland Security (DHS), April 14, 2016, <https://www.dhs.gov/news/2016/04/14/written-testimony-oha-senate-committee-homeland-security-and-governmental-affairs>.

² “Antibiotic/Antimicrobial Resistance,” Centers for Disease Control and Prevention, accessed August 23, 2017, <https://www.cdc.gov/drugresistance/index.html>.

³ World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance 2014* (Geneva, Switzerland: World Health Organization, 2014), XI.

⁴ World Health Organization.

⁵ Michael J. Martin, Sapna E. Thottathil, and Thomas B. Newman, “Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers,” *American Journal of Public Health* 105, no. 12 (December 2015): 2409–10, <https://doi.org/10.2105/AJPH.2015.302870>.

⁶ Timothy F. Landers et al., “A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential,” *Public Health Reports* 127, no. 1 (2012): 4–22.

to explore evidence-based agricultural practices that curb the threat of antibiotic resistance.

This thesis examines current national and state-level agricultural strategies undertaken in the United States to slow the pace of antibiotic resistance and reviews policies and practices implemented abroad in Denmark and the Netherlands. These policies are grouped into the following categories for comparison:

- Legislative bans: illegal nontherapeutic uses, prohibited drug classes or drug classes with limits for use in food animals, and comparisons of penalties for noncompliance with policies
- Antimicrobial dispensing: requirements for veterinarians such as educational outreach, the level of oversight required by veterinarians, and limits on duration of treatment
- Monitoring requirements: i.e., requirements to review and report antibiotic distribution and use data; resistance levels in food, animals, and people; and sectors required to report antibiotic use data
- Outcomes and results: whether the policies implemented resulted in an overall reduction in antibiotic use and resistance in animals, and resistant infections in people

Taken together, the studied European countries appear to be slowing the threat of antibiotic use as a result of their policies—policies that the United States has largely not implemented. These countries also have robust surveillance systems that allow stakeholders to monitor trends and change course if needed. The Netherlands, particularly, achieved an overall reduction in antibiotic use, as well as reductions in resistant organisms in food animals and resistant infections in people.

This analysis leads to this thesis's proposal of several potential strategies to slow the threat of antibiotic resistance in the United States: 1) creating an enhanced, more integrated surveillance system, 2) enacting antibiotic-use reduction targets, 3) prohibiting the use of antibiotics in healthy animals, and 4) requiring veterinarians to examine

animals before prescribing them antibiotics for disease prevention. Each strategy is assessed using the Centers for Disease Control and Prevention's policy analytical framework, which analyzes the impact or reach the policies may have, how feasible they are to implement, and the potential economic and budgetary impacts.

This thesis recommends implementing all four policies as a package, but acknowledges that policymaking related to antibiotic resistance and agriculture in the United States has historically not been successful and has faced much opposition. Therefore, this thesis proposes implementing the policies in a phased approach beginning with increasing data collection and building an integrated surveillance system to promote informed decision-making regarding antibiotic resistance.

Further research is needed to address areas outside the scope of this thesis, such as farmer and veterinarian knowledge and attitudes about antibiotic resistance, antimicrobial resistance related to companion animals, animal waste management and its effects on antibiotic resistance, organic farming, agriculture antimicrobial-stewardship technical assistance organizations, and European food production practices that could be adopted in the United States.

Congress and governmental agencies must examine the successes of other nations that have actively responded to this global threat and work with industry partners to gain buy-in and acceptance of responsibility and duty to preserve medically important antibiotics to protect the health and safety of people and animals. The homeland security enterprise should prioritize antibiotic resistance as a threat and work collaboratively to implement the strategies outlined in this thesis to mitigate it.

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ACKNOWLEDGMENTS

It is hard to know where to begin with these acknowledgements, as there are many people to thank for helping me through this journey, but I will start with the unwavering support I received from my colleagues and friends at the Wisconsin Department of Health Services. To Division leadership, Karen McKeown and Chuck Warzecha, I appreciate everything you have done to support me—from ensuring that I was able to take the time away from work and providing me with opportunities to work on this thesis uninterrupted to checking up on me on a personal level. Thank you.

To my colleagues and staff, I could not have completed this if you all weren't so good at what you do. Thank you for your genuine interest in seeing me succeed, for asking me how I'm doing, for offering advice and your time, and keeping me relatively sane while I was working on this. Your support has meant the world to me!

I would also like to specifically thank Dr. Jeff Davis. He was instrumental in guiding me down my research path by giving me sources and ideas of case studies to examine for this project. I relied on his encouragement and advice throughout this project. I believe he would be proud of this work (and that I finished)—he was always interested in my progress.

And I also want to acknowledge Donny (Badger) Neuert—for encouraging me to apply to this program and cheering me on during every phase. His friendship and humor (and HLB lunches) got me through some of the more challenging parts of this experience. I will be forever grateful to have had his support, and my success in this project is due in large part to his reassurance and backing. He would have been thrilled to see this in the NPS thesis library considering I never let him read anything I wrote.

Thank you to my advisor, Anke Richter, and to my second reader, Lynda Peters, for advising on a topic that others may not necessarily see as germane to the homeland security field, and for your support, wisdom, and guidance throughout this entire process. I appreciate your check-ins and encouragement when I needed it most. I also want to

acknowledge the NPS and CHDS faculty and staff, especially Greta Marlatt who provided a never-ending stash of M&Ms—essential for good thesis writing.

To “1611”—I am so grateful for your friendship and to have gone through this experience with you. The spirit and resilience that this cohort has shown through thick and thin is a bond that will last forever. I know that our paths will cross again, hopefully for beers on a patio somewhere.

To my mom, thank you for all of your help while I was away or writing. You made this experience much easier by offering up your time whenever you were needed. I know that you believed I could do this, and I appreciate that you’ve supported me every step of the way.

Thank you to my extended family, my brother, grandparents, aunts and uncles, nieces and nephews, and in-laws, for allowing me the time I needed to complete this. I promise you’ll be seeing more of me in the future!

And finally, to my girls and my husband, Josh—thank you. Kiddos, I know this was hard on you. All of my time was spent “writing my thesis.” But guess what? It’s done, and we can hang out anytime you want! Josh, I know that it has not been easy to accompany me on this journey. You have supported me wholeheartedly, and your reassurance and encouragement are what have kept me strong enough to stay the course even though there were many times when I wanted to give up. Thank you for your patience with me and for lending me your ear when I got stuck or discouraged thinking I was never going to finish. I am so appreciative of all you do and am lucky to have you as my husband and my rock.

I. ANTIBIOTIC RESISTANCE AS A HOMELAND SECURITY ISSUE

Antibiotic resistance is an emerging biological threat that poses an increasing risk to the United States and to the world.¹ The Centers for Disease Control and Prevention (CDC) estimates that two million people are infected with drug-resistant bacteria annually and 23,000 deaths each year can be blamed on these infections.² According to the World Health Organization, resistant illnesses across the world are becoming more numerous and are extremely difficult, in some cases impossible, to treat with antibiotics.³ Bacteria that cause illnesses such as pneumonia, salmonella, shigella, gonorrhea, and tuberculosis may soon be completely resistant to the antibiotics available today, rendering the conditions untreatable.⁴ The increasing number of antibiotic-resistant bacterial infections will remain a serious health-security and economic threat unless steps are taken to curb it.

Many factors contribute to the acceleration of the antibiotic resistance threat; however, the focus of this thesis is the use of antibiotics in agriculture. While data regarding the use of antibiotics in food animals are limited, some sources report that 80 percent of all antibiotics sold in the United States are used for livestock.⁵ The U.S. Food and Drug Administration (FDA) reports that, in 2015, more than 21 million pounds of all antimicrobial drugs considered medically important in human medicine were sold

¹ “Written Testimony of OHA for a Senate Committee on Homeland Security and Governmental Affairs Hearing Titled ‘The Federal Perspective on the State of Our Nation’s Biodefense,’” DHS, April 14, 2016, <https://www.dhs.gov/news/2016/04/14/written-testimony-oha-senate-committee-homeland-security-and-governmental-affairs>.

² “Antibiotic/Antimicrobial Resistance,” Centers for Disease Control and Prevention (CDC), accessed August 23, 2017, <https://www.cdc.gov/drugresistance/index.html>.

³ World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance 2014* (Geneva, Switzerland: World Health Organization, 2014), XI.

⁴ World Health Organization.

⁵ Michael J. Martin, Sapna E Thottathil, and Thomas B. Newman, “Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers,” *American Journal of Public Health* 105, no. 12 (December 2015): 2409–10, <https://doi.org/10.2105/AJPH.2015.302870>.

for use in food-producing animals—a 26-percent increase in sales from 2009.⁶ In fact, 97 percent of these medically important drugs were sold over the counter, meaning they were available without a prescription or directive from a veterinarian.⁷ There is consensus among researchers that antibiotic use in food animals may contribute to antibiotic resistance in humans; dozens of studies and trials suggest a causal relationship.⁸ Given the large amount of antibiotics used in animal husbandry, there is a need to explore evidence-based agricultural practices that curb the threat of antibiotic resistance.

Antibiotic resistance refers to a pathogen’s ability to continue growing or resist being killed by the drugs used to treat infections, through the process demonstrated in Figure 1. When a person takes an antibiotic for an infection, sometimes not all bacteria are killed. The resistant bacteria survive and will continue to multiply. Unfortunately, resistant bacteria can then spread to other people or animals.⁹ Patients with infections caused by drug-resistant bacteria consume more health-care resources than patients infected with strains of non-resistant pathogens and are at a higher risk of poor health outcomes or death.¹⁰

⁶ Food and Drug Administration (FDA), “2015 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals” (report, Department of Health and Human Services, 2016), 52, <https://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf>.

⁷ FDA, 54.

⁸ Timothy F. Landers et al., “A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential,” *Public Health Reports* 127, no. 1 (2012): 4–22.

⁹ CDC, “Antibiotic/Antimicrobial Resistance.”

¹⁰ Damien Roux et al., “Fitness Cost of Antibiotic Susceptibility during Bacterial Infection,” *Science Translational Medicine* 7, no. 297 (July 22, 2015), <https://doi.org/10.1126/scitranslmed.aab1621>; C. Lee Ventola, “The Antibiotic Resistance Crisis,” *Pharmacy and Therapeutics* 40, no. 4 (April 2015): 277–83; “Antimicrobial Resistance,” World Health Organization, accessed October 9, 2016, <http://www.who.int/mediacentre/factsheets/fs194/en/>.

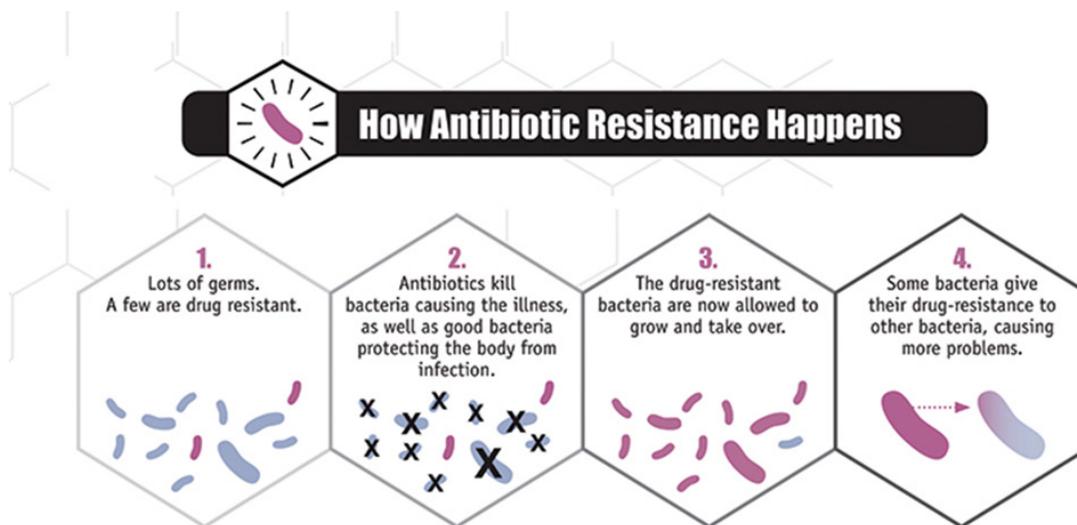


Figure 1. Process of Antibiotic Resistance¹¹

A. IMPORTANCE

The CDC’s “Antibiotic Resistance Threats in the United States, 2013” includes an assessment and prioritization of bacteria based on their threat level. The report, which was created with the help of experts from a workgroup serving the CDC Office of Infectious Diseases Board of Scientific Counselors, claims an estimated 610 deaths annually from carbapenem-resistant *Enterobacteriaceae* (CRE), bacterial infections typically acquired in health-care settings; 11,000 deaths attributable to methicillin-resistant *Staphylococcus aureus* (MRSA), which can be acquired in the community as well as in health-care settings; and 14,000 deaths annually from *Clostridium difficile* (*C.difficile*) infections, another health-care-associated infection.¹² Also included in the estimates are multidrug-resistant tuberculosis, drug-resistant *Salmonella*, drug-resistant *Campylobacter*, and drug-resistant *Neisseria gonorrhoeae*. Public health professionals have been focusing on surveillance of these drug-resistant organisms for the last several decades.

¹¹ Source: CDC, “Antibiotic Resistance Threats in the United States, 2013” (report, U.S. Department of Health and Human Services, 2013), <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>.

¹² CDC, 15–16.

The CDC classifies three drug-resistant bacteria as “urgent threats”: *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae* (CRE), and *Neisseria gonorrhoeae*.¹³ An “urgent” classification signifies a threat that may not be widespread yet, but could be. If an outbreak of any of these pathogens emerges, it would require significant and urgent public health response to perform surveillance and stop the spread. The CDC reports that “some CRE bacteria have become resistant to most available antibiotics”; of patients who are sick with blood stream infections due to CRE, nearly half do not survive.¹⁴ A more common bacteria is listed in the “serious threat” level—*Streptococcus pneumoniae*, which is responsible for meningitis and bacterial pneumonia. These bacteria cause 1.2 million drug-resistant infections and kill 7,000 people each year.¹⁵

B. ANTIBIOTIC RESISTANCE AND AGRICULTURE

In many parts of the world, low doses of antibiotics and other antimicrobials are given to livestock to accelerate growth and prevent disease among animals living in close quarters in less-than-sanitary conditions. As Figure 1 showed, bacteria that survive low doses of antibiotics become resistant to drugs. When resistant organisms are prevalent on farms, it becomes a serious issue for the public’s health since many of the drugs provided to animals are also used in human medicine. The infographic in Figure 2 describes how antibiotic resistance in animals can impact people.

¹³ “Antibiotic/Antimicrobial Resistance, Biggest Threats,” CDC, February 27, 2018, https://www.cdc.gov/drugresistance/biggest_threats.html.

¹⁴ “Carbapenem-Resistant Enterobacteriaceae in Healthcare Settings,” CDC, February 26, 2018, <https://www.cdc.gov/hai/organisms/cre/index.html>.

¹⁵ CDC, “Antibiotic/Antimicrobial Resistance, Biggest Threats.”

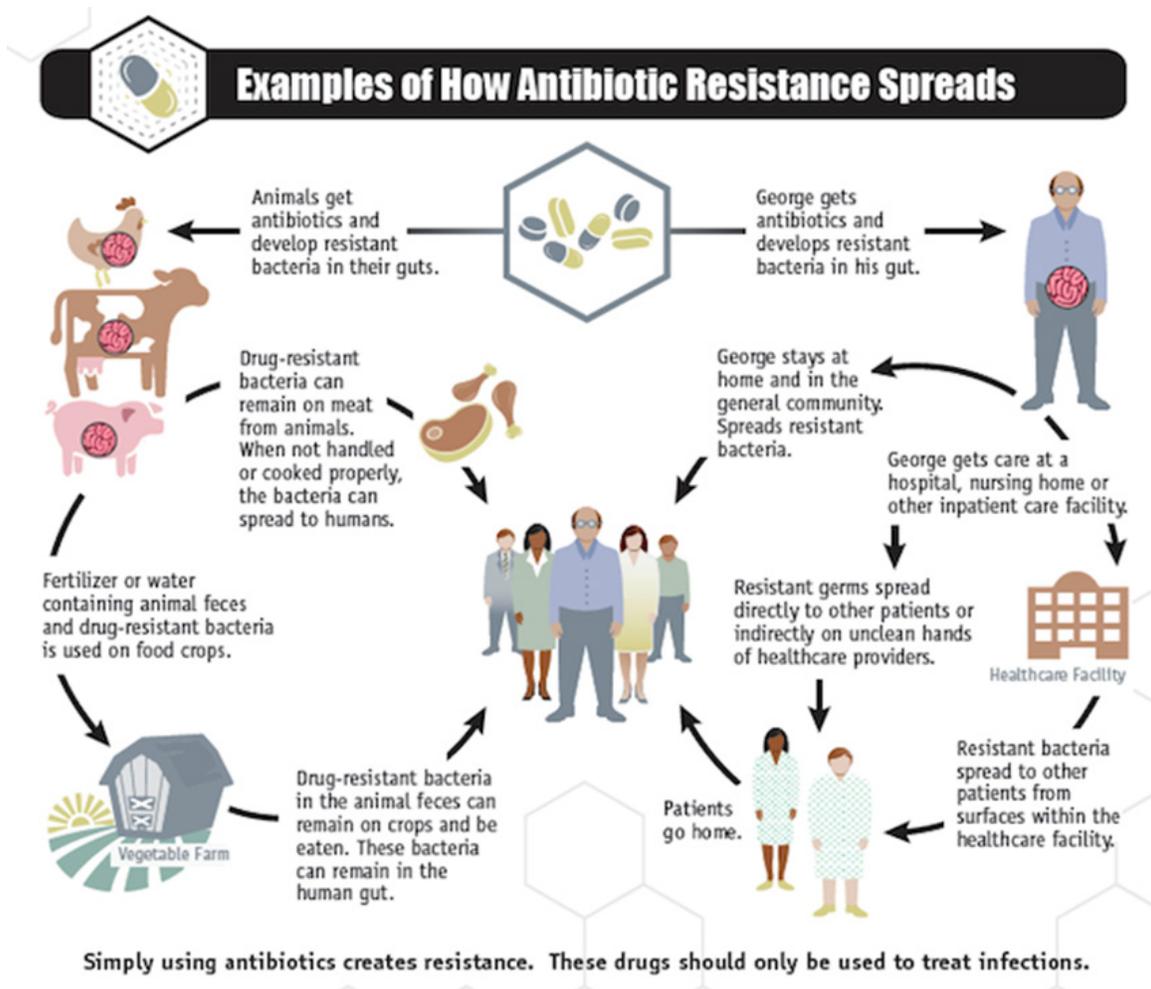


Figure 2. How Antibiotic Resistance Spreads¹⁶

There are two main ways that antibiotic-resistant bacteria develop—in the guts of animals and in the guts of humans. Antibiotic-resistant organisms can be transmitted in multiple ways. For example, drug-resistant bacteria can be present in animal meat; if the meat is not prepared properly, the resistant bacteria can spread to humans who consume the meat, where the resulting infections can be extremely difficult to treat. In fact, the CDC highlights several drug-resistant organisms in its aforementioned “Antibiotic Resistance Threats” report, three of which are foodborne organisms that are becoming drug-resistant: *Campylobacter*, *Salmonella*, and *Shigella*.¹⁷ To slow the emergence and

¹⁶ Source: CDC, “Antibiotic Resistant Threats in the United States.”

¹⁷ CDC.

spread of antibiotic-resistant bacteria, we must be sensible about using antibiotics in humans and animals. The sections that follow describe the effects antibiotic resistance has on humans, the agriculture industry, and food security.

1. *Salmonella Heidelberg* Outbreak

According to the CDC, an estimated 1,200,000 *Salmonella* infections occur each year, costing \$365 million in medical expenses.¹⁸ Of those infections, 100,000 are estimated to be resistant to antibiotics.¹⁹ In November 2016, the CDC worked with several states to investigate a multistate outbreak of multidrug-resistant *Salmonella Heidelberg* infections. The investigation identified dairy bull calves from Wisconsin as the likely source; an overwhelming majority of the patients interviewed, 63 percent, reported coming in contact with dairy calves or cattle.²⁰ Some farmers also reported that their dairy bull calves became sick or died. *Salmonella* bacteria are commonly found in the intestines of cattle and can be passed to humans through direct contact with animal feces and their environment. *Salmonella* bacteria can also be transmitted from one person to another.²¹

Fifty-six people from fifteen states were reported to be infected with the outbreak strain—more than one-third of them children under the age of five.²² Thirty percent of those sickened required hospitalization for their infections and fortunately no deaths were reported.²³ CDC tests concluded that this organism was resistant to multiple types of antibiotics, which meant there were limited treatment options and further testing was

¹⁸ CDC.

¹⁹ CDC.

²⁰ “Multistate Outbreak of Multidrug-Resistant *Salmonella Heidelberg* Infections Linked to Contact with Dairy Bull Calves,” CDC, February 16, 2018, <https://www.cdc.gov/salmonella/heidelberg-11-16/index.html>.

²¹ “*Salmonella Heidelberg* FAQ,” Wisconsin Department of Health Services, accessed December 3, 2016, <https://www.dhs.wisconsin.gov/salmonella/heidelberg/faq.htm>.

²² CDC, “Multistate Outbreak.”

²³ CDC.

needed for each individual's infection to determine which antibiotic would be successful.²⁴

Fortunately, this outbreak was limited in scope and severity; however, this example illustrates how multidrug-resistant organisms found within agricultural settings can transform into human infections and can cause a dangerous treatment situation for those who become ill.

2. Agricultural Impact and Food Security

Livestock is an important food source and a major contributor to the world economy. While antibiotics play a critical role in disease treatment in food animals, misuse of antibiotics for non-therapeutic means contributes to the spread of resistance, putting treatment options for livestock at risk as well. Treatment failure in animals due to drug-resistant infections would have a significant impact on food production as well as food security and the economy.

A recent economic impact study by the North American Meat Institute indicates that the livestock industry employs more than 1.8 million people in the United States, with an additional 3.6 million jobs in related industries.²⁵ The study also estimated that, nationwide in 2016, the meat and poultry industry created \$1.02 trillion in economic activity. In addition, the institute purports that the industry generates \$43.96 billion in state taxes. If superbugs emerge among livestock (bugs that cannot be treated due to antibiotic-resistant organisms), the financial losses would be catastrophic. Recall the 2015 avian influenza outbreak: the outbreak cost an estimated \$3.3 billion to the industry—considering all sectors that were effected—and an additional \$500 million in government spending to curtail the spread of the disease.²⁶ More than 10 percent of egg-

²⁴ CDC.

²⁵ North American Meat Institute, accessed November 5, 2017, <http://www.meatfuelsamerica.com/>.

²⁶ Maryn McKenna, "Bird Flu Cost the U.S. \$3.3 Billion and Worse Could Be Coming," *Phenomena* (blog), July 15, 2015, <http://phenomena.nationalgeographic.com/2015/07/15/bird-flu-2/>.

laying hens and 3 percent of turkeys in the United States were culled; the government subsidized those losses at the tune of \$190 million to farmers.²⁷

C. HOMELAND SECURITY RELEVANCE

Given the homeland security enterprise’s all-hazards approach, there is a case to be made that antibiotic resistance should be viewed as a homeland security priority. In 2003, the Department of Homeland Security designated the food and agriculture and the health-care and public health sectors as part of the nation’s critical infrastructure—“sectors whose assets, systems, and networks, whether physical or virtual, are considered so vital to the United States that their incapacitation or destruction would have a debilitating effect on security, national economic security, national public health or safety, or any combination thereof.”²⁸

The following literature review evaluates information from varied sources, including reports from government, public health and health-care experts, academia, and national and international health organizations.

1. Characterization of Antibiotic Resistance as a Crisis

Many public health organizations and health researchers refer to antibiotic resistance as a crisis, or a situation that is becoming dire. For example, the CDC asserts that health officials across the globe believe antibiotic-resistant organisms pose “a catastrophic threat” to the world.²⁹ The World Health Organization calls antimicrobial (including bacteria) resistance a “global health security threat that requires concerted cross-sectional action by governments and society as a whole.”³⁰ In fact, drug-resistant bacteria have been labeled as a threat to the public’s health by the Infectious Disease Society of America, the National Academy of Medicine, the American Medical

²⁷ McKenna.

²⁸ “Critical Infrastructure Sectors,” DHS, March 5, 2013, <https://www.dhs.gov/critical-infrastructure-sectors>.

²⁹ CDC, “Antibiotic Resistance Threats,” 11.

³⁰ World Health Organization, “Antimicrobial Resistance.”

Association, and the United Nations.³¹ Many scholarly works also take a doomsday tone when discussing antibiotic resistance: some call it a “looming public health crisis” while others say “it is a silent pandemic that is here to stay.”³²

In 2004, an article from the Infectious Disease Society of America described drug-resistant bacteria as a security issue; even more than a decade ago, all the antibiotic-resistant organisms that existed naturally could be bio-engineered through cloning or forced mutation.³³ The society goes on to say that research is needed to better respond to possible future bioterrorist attacks that could involve lab-created or engineered resistant organisms. The other security concern mentioned in this article is that the effectiveness of existing antibiotics during a future bioterrorism incident may be limited if the pathogens are resistant to today’s antibiotic options.³⁴

Within the U.S. homeland security enterprise, antibiotic resistance is listed as a priority in several strategy documents. For example, the *2015 National Security Strategy* refers to antibiotic resistance as a threat to global health security.³⁵ Antibiotic resistance was outlined as an emerging threat in the Department of Homeland Security’s May 2016 “Healthcare and Public Health Sector-Specific Plan.”³⁶ However, the *2014 Quadrennial Homeland Security Review* lists four priority biological threats and hazards: pathogens

³¹ “IDSA: Facts about Antibiotic Resistance,” Infectious Diseases Society of America (IDSA), accessed January 23, 2017, http://www.idsociety.org/AR_Facts/; Brad Spellberg et al., “Antibiotic Resistance in Humans and Animals” (discussion paper, National Academy of Medicine, 2016), <https://nam.edu/wp-content/uploads/2016/07/Antibiotic-Resistance-in-Humans-and-Animals.pdf>; “AMA Continues Efforts to Combat Antibiotic Resistance,” American Medical Association, November 16, 2015, <https://www.ama-assn.org/ama-continues-efforts-combat-antibiotic-resistance>.

³² Landers et al., “Review of Antibiotic Use”; Dušan Jasovský et al., “Antimicrobial Resistance—A Threat to the World’s Sustainable Development,” *Upsala Journal of Medical Sciences* 121, no. 3 (August 2016): 159–64, <https://doi.org/10.1080/03009734.2016.1195900>.

³³ IDSA, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews* (Alexandria, VA: Infectious Diseases Society of America, 2004), <http://mobile.cafescolorado.org/Bad%20Bugs%20No%20Drugs%20IDSA%20White%20Paper%20Jul%202004.pdf>.

³⁴ IDSA.

³⁵ The White House, *2015 National Security Strategy* (Washington, DC: The White House, 2015), 13–14, https://www.whitehouse.gov/sites/default/files/docs/2015_national_security_strategy.pdf.

³⁶ DHS, “Healthcare and Public Health Sector-Specific Plan” (planning document, Department of Homeland Security, May 2016), 15, <https://www.dhs.gov/sites/default/files/publications/nipp-ssp-healthcare-public-health-2015-508.pdf>.

that pose bioterrorism concerns, emerging infectious diseases, bioterrorist contamination of the food supply chain and/or water systems, and animal diseases and plant pathogens or pests that are highly disruptive.³⁷ Noticeably absent from this list is antibiotic resistance.

Most literature reviewed for this thesis characterizes antibiotic resistance as a threat to human health. It is widely recognized and could be classified as common knowledge. A wide and thorough search for material with a counter-argument—that antibiotic resistance does not pose a threat to human health—produced no results. There is, however, much debate on the causes of antibiotic resistance and whether certain uses exacerbate the problem or increase the risk to human health.

2. Antibiotic Resistance in Food Animals

The literature agrees that antibiotics are widely used as growth promoters for livestock. However, there is disagreement about the reliability of data on antibiotic dosage and frequency of use in agriculture. In addition, there is debate about the degree of risk this use poses to human health. Many studies indicate that there may be a significant risk, while others were inconclusive.³⁸ It is nearly impossible to make a scientific claim of risk in this regard; studies would need to be conducted for each type of bacteria and every possible transmission route. Several studies, however, have examined the prevalence of infections among livestock to look for epidemiological links between food animals and antibiotic-resistant infections in humans. For example, one study looked at the prevalence of drug-resistant *Campylobacter* in poultry, swine, and cattle and found that unpasteurized milk is a confirmed transmission mechanism for

³⁷ DHS, *The 2014 Quadrennial Homeland Security Review* (Washington, DC: Department of Homeland Security, 2014), 47, <https://www.dhs.gov/sites/default/files/publications/qhsr/a-homeland-security-strategy-for-countering-biological-threats-and-hazards.pdf>.

³⁸ Landers et al., “Review of Antibiotic Use.”

tetracycline-resistant *Campylobacter* infections.³⁹ Other example studies are provided in later chapters of this thesis.

3. Health and Economic Burden of Antibiotic Resistance

The current public health literature describes antibiotic-resistant infections as a substantial health and economic burden. Patients with infections caused by antibiotic-resistant bacteria tend to be hospitalized longer and have a higher risk of poor health outcomes or death.⁴⁰ There is less concrete information available, however, regarding the economic impacts of antibiotic resistance. The estimates vary, but there appears to be consensus that the cost of treating antibiotic-resistant infections places a significant burden on society. The CDC indicates the total economic burden placed on the U.S. economy due to antibiotic-resistant infections may be as high as \$20 billion a year in health-care costs, and \$35 billion in lost productivity.⁴¹ And, according to estimates, it costs \$19,000 to \$29,000 to treat each patient for an antibiotic-resistant infection.⁴² Still, the World Health Organization opines that there are limited studies on the matter and that the true impact has not adequately been measured.⁴³ The CDC also states that the economic burden of antibiotic-resistant infections has been difficult to gauge, but is an active area of research.⁴⁴

4. Efforts in the Homeland Security Enterprise to Address the Threat

The health-care and public health sectors are integral to cross-sector efforts to enhance the security and resilience of the homeland. In 1999, the Interagency Task Force

³⁹ M.A. McCrackin et al., “Effect of Antimicrobial Use in Agricultural Animals on Drug-Resistant Foodborne *Campylobacteriosis* in Humans: A Systematic Literature Review,” *Critical Reviews in Food Science and Nutrition* 56, no. 13 (October 2, 2016): 2115–32, <https://doi.org/10.1080/10408398.2015.1119798>.

⁴⁰ Interagency Task Force on Antimicrobial Resistance, “A Public Health Action Plan to Combat Antimicrobial Resistance” (planning document, Interagency Task Force on Antimicrobial Resistance, 2012), 8, <https://www.cdc.gov/drugresistance/pdf/action-plan-2012.pdf>; World Health Organization, “Antimicrobial Resistance.”

⁴¹ CDC, “Antibiotic Resistance Threats,” 11.

⁴² Ventola, “The Antibiotic Resistance Crisis.”

⁴³ World Health Organization, *Antimicrobial Resistance*, 12.

⁴⁴ CDC, “Antibiotic Resistance Threats,” 11.

on Antimicrobial Resistance was created to coordinate federal agency actions and accomplishments to address the public health threat of antimicrobial resistance.⁴⁵ This task force is made up of several federal agencies, including the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response, and the Department of Defense. The task force’s first action plan was developed in 2001 and has been revised several times to reflect goals to mitigate the problem. The latest report, “A Public Health Action Plan to Combat Antimicrobial Resistance,” published in 2012, outlines the goals and plans of the federal agencies that are taking steps to address antimicrobial resistance.⁴⁶ Goals focus on surveillance, prevention and control, research, and new product development.

In March 2015, the White House released the “National Action Plan for Combating Antibiotic-Resistant Bacteria,” which was developed in part to support the World Health Assembly Resolution 67.25.⁴⁷ Progress toward outcomes is to be monitored by the U.S. government task force charged with developing the plan. The task force, co-chaired by the Secretaries of Defense, Agriculture, and Health and Human Services, is to provide annual progress updates. At a high level, the goals of the plan are to:

- Slow the emergence of resistant bacteria and prevent the spread of resistant infections
- Strengthen national one-health surveillance efforts to combat resistance
- Advance the development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines

⁴⁵ “The Interagency Taskforce on Antimicrobial Resistance: 10 Years of Coordinated Federal Action,” Center for Disease Dynamics, Economics & Policy, accessed November 10, 2018, cddep.org/publications/interagency_taskforce_antimicrobial_resistance_10_years_coordinated_federal_action/.

⁴⁶ Interagency Task Force on Antimicrobial Resistance, “A Public Health Action.”

⁴⁷ The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria* (Washington, DC: The White House, March 2015), https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf; World Health Organization, “Antimicrobial Resistance Resolution” (committee report, Sixty-Seventh World Health Assembly, 2014), http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_73-en.pdf.

- Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development⁴⁸

It should be noted that since the change in presidential administration in January 2017, this plan has been removed from the White House’s website. It is unclear if the antibiotic resistance will continue to be a priority of the White House or the federal government.⁴⁹

There is agreement that antibiotic resistance is occurring, but there is also debate about whether or not the use of antibiotics in food animals threatens human health. Aside from the national and international reports on combating antibiotic resistance, this topic does not appear to be an area of study in homeland security academia. The homeland security enterprise should consider devoting more resources to addressing the threat of antibiotic resistance. The anthrax exposure after 9/11 accounted for a total of five deaths, while drug-resistant infections have accounted for tens of thousands of deaths; yet antibiotic resistance is considered an “emerging threat.”⁵⁰ The nation’s ability to respond to a bioterror or other widespread disease event depends heavily on the medical countermeasures available to us. The over-reliance on antibiotics for non-therapeutic uses puts this ability to respond at risk.

D. RESEARCH QUESTION

Have agriculture policies implemented abroad slowed the rate of antibiotic resistance and could they be implemented in the United States as a homeland security measure?

⁴⁸ White House, *National Action Plan*, 3.

⁴⁹ Search results for “Antibiotic Resistance,” The White House, accessed April 30, 2017, <https://search.usa.gov/search?query=antibiotic+resistance&op=Search&affiliate=wh>.

⁵⁰ “Amerithrax or Anthrax Investigation,” Federal Bureau of Investigation, accessed January 25, 2018, <https://www.fbi.gov/history/famous-cases/amerithrax-or-anthrax-investigation>; Zhabiz Golkar, Omar Bagasra, and Donald Gene Pace, “Bacteriophage Therapy: A Potential Solution for the Antibiotic Resistance Crisis,” *The Journal of Infection in Developing Countries* 8, no. 2 (February 13, 2014): 129–36, <https://doi.org/10.3855/jidc.3573>; DHS, “Healthcare and Public Health Plan,” 15.

E. METHODOLOGY

Because the goal of this thesis is to provide recommendations for policies and agricultural practices that will help the United States slow the threat of antibiotic resistance, analysis of various potential policy options was conducted using illustrative case studies. This hybrid model of policy options analysis and case study methodology is well suited for this research because current policies to address this problem in the United States are few and have not been implemented at a national level. Analysis included policies gleaned from abroad as well as local examples.

Using the CDC's policy analysis framework, polices were selected for this thesis using the following framing questions:

- What is the policy lever—is it legislative, administrative, regulatory, other?
- What level of government or institution has implemented the policy?
- How does the policy work/operate? (e.g., Is it mandatory? Is enforcement necessary? How is it funded? Who is responsible for administering the policy?)
- What is the legal landscape surrounding the policy? (e.g., court rulings)
- What is the historical context? (e.g., Has the policy been debated?)⁵¹

Polices were selected from abroad that were legislatively implemented at a national level and that had considerable information available to summarize the context and history leading up to the implementation—as well as information that provides sufficient assessment data. Denmark and the Netherlands met these criteria. The researcher also included two policies that have been implemented at the state level in the United States to contextualize the types of legislation that have been passed for this topic

⁵¹ “CDC’s Policy Analytical Framework,” CDC, accessed May 9, 2017, <https://www.cdc.gov/policy/analysis/process/analysis.html>.

domestically. This thesis also reviews current national efforts to curb the threat of antibiotic resistance.

Themes and patterns emerged from these case studies, which resulted in four proposed policy packages to implement in the United States. Again using the CDC's policy analytical framework, the proposed U.S. policy packages were analyzed based on the following criteria:

- Potential for the policy to impact risk factors:
 - How does the policy address the problem or issue?
 - What are the magnitude, reach, and distribution of benefit and burden?
 - What populations have benefitted? How much? When?
 - What populations have been negatively impacted? How much? When?
 - Has this policy impacted health disparities/health equity? How?
 - Are there gaps in the data/evidence-base?
- Likelihood that the policy can be successfully adopted and implemented
 - Political
 - What are the current political forces, including political history, environment, and policy debate?
 - Who are the stakeholders, including supporters and opponents? What are their interests and values?
 - What are the potential social, educational, and cultural perspectives associated with the policy option (e.g., lack of knowledge, fear of change, force of habit)?
 - What are the potential impacts of the policy on other sectors and high-priority issues (e.g., sustainability, economic impact)?
 - Operational
 - What are the resource, capacity, and technical needs developing,

- enacting, and implementing the policy?
 - How much time is needed for the policy to be enacted, implemented, and enforced?
 - How scalable, flexible, and transferable is the policy?
 - Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits
 - Budget
 - What are the costs and benefits associated with the policy, from a budgetary perspective? For example, for public (federal, state, local) and private entities to enact, implement, and enforce the policy?
 - Economic
 - How do costs compare to benefits (e.g., cost savings, costs averted, return on investment [ROI], cost-effectiveness, cost-benefit analysis, etc.)?
 - How are costs and benefits distributed (e.g., for individuals, businesses, government)?
 - What is the timeline for costs and benefits? (e.g., Within a year? A decade?)
 - Where are there gaps in the data/evidence-base?⁵²

F. LIMITATIONS AND SCOPE

This thesis uses the terms *antibiotic resistance* and *antimicrobial resistance*. Antimicrobials are all agents that can eliminate microorganisms, including antibiotics, which are a class of drugs used that kill bacteria.⁵³ While this thesis is focused primarily

⁵² CDC.

⁵³ “What Is the Difference between Antibiotic and Antimicrobial Resistance,” World Health Organization, accessed November 10, 2018, <http://www.emro.who.int/health-topics/drug-resistance/what-is-the-difference-between-antibiotic-and-antimicrobial-resistance.html>.

on policies that aim to slow the threat of antibiotic resistance, many of the examples used have focused more broadly on slowing the threat of all antimicrobial resistance, not only bacteria.

This thesis is also focused primarily on antibiotics used for non-therapeutic purposes in food animals; however, this is a much larger problem that should be examined and solved holistically. This thesis does not review policies aimed at the use of antibiotics in companion animals (i.e., pets) or the environmental impacts of agriculture manure spreading where resistance genes persist, and where wildlife can spread resistant organisms. This thesis does not address the use of antibiotics for disease prevention in fish farms, nor does it discuss antibiotic resistance in humans and the use of antibiotics in clinical settings or for human health. Policymakers can use this thesis for ideas to slow the threat in one area where antibiotics are used.

G. THESIS OUTLINE

Chapters II through IV present case studies of policies enacted in Denmark and the Netherlands, along with national-level U.S. strategies, to slow the threat of antibiotic resistance. Chapter V discusses policies enacted domestically in California and Maryland. Next, Chapter VI compares aspects of the different policies in each of the case studies and identifies themes, differences, and potential gaps. Finally, Chapter VII discusses various policy options for the United States with an analysis of each policy package, and closes out the thesis with a recommendation, future research opportunities, and a conclusion.

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II. CASE STUDY: DENMARK

European countries have been banning antibiotics to promote growth in livestock since at least the 1960s, but those bans were aimed at specific drugs rather than classes of drugs.⁵⁴ In 1974, scientists in the United States discovered that after poultry were given feed that contained the antibiotic oxytetracycline, drug-resistant bacteria dominated within the chickens' intestinal flora.⁵⁵ Six months later, people exposed on the farm also carried the drug-resistant bacteria, and they overtook 80 percent of the humans' intestinal flora as well. Interestingly, the bacteria in both the humans and poultry were resistant to multiple antibiotics, not just the oxytetracycline. After the laced feed was withdrawn, the humans no longer carried the resistant bacteria. Shortly after this study, Europe banned the use of tetracyclines as growth promoters in livestock; however, the United States as a nation has not.⁵⁶ This chapter examines the measures taken in Denmark in addition to this ban to further decrease the use of antibiotics for agricultural purposes as a potential solution to curbing the threat of antibiotic resistance.

In 1990, Denmark passed legislation that limited veterinarians' capacity to dispense veterinary products, including antibiotics.⁵⁷ According to Denmark's Ministry of Environment and Food,

Antibiotics may only be used for production animals, if the veterinarian has diagnosed an infection which justifies its use. Veterinarians may only on certain conditions supply or prescribe antibiotics for use by the farmer, and the farmer must follow the advice and instructions given by the veterinarian. Instructions must be given in writing and must include identification of target animals, diagnosis, drug and dosage, clinical symptoms that must be observed before treatment, withdrawal period, and administration route. The veterinarian may only distribute or prescribe

⁵⁴ Sharon Levy, "Reduced Antibiotic Use in Livestock: How Denmark Tackled Resistance," *Environmental Health Perspectives* 122, no. 6 (June 2014): A160–65, <https://ehp.niehs.nih.gov/122-a160/>.

⁵⁵ Levy.

⁵⁶ Levy.

⁵⁷ "Distribution and Use of Veterinary Drugs in Denmark," Danish Veterinary and Food Administration (DVFA), last modified May 11, 2017, https://www.foedevarestyrelsen.dk:443/english/Animal/AnimalHealth/Veterinary_medicine/Pages/default.aspx.

antibiotics for the farmer's continued treatment of diseased animals, except for adult cattle, for a maximum of 5 days.⁵⁸

In the early 1990s, Denmark scientists discovered the link between the use of avoparcin as a growth-promoting antibiotic and emerging bacteria that were resistant to vancomycin—another type of antibiotic that is used to treat seriously ill people.⁵⁹ Because these findings illuminated a serious threat to public health, Denmark banned the use of avoparcin as a growth promoter in May 1995 and the Commission of the European Union followed suit in 1997. In response to concerns that the growth promoter vieriniamycin contributed to antibiotic resistance, it too was banned in 1998. Within months of this ban and in response to public concerns, the cattle and poultry industries volunteered to stop using all growth promoters; the pork industry followed suit about a year later.⁶⁰

Denmark banned the use of antibiotics for growth promotion in the late 1990s and currently all antibiotics used in animals produced for food must be dispensed under the prescribed orders of a veterinarian, through a pharmacy.⁶¹ In addition, veterinarians are not permitted to profit from antibiotic sales.⁶² Denmark also implemented an extensive monitoring system to keep track of the sale and use of antibiotics, along with a strong surveillance system that detects the occurrence of resistant bacteria in food animals.⁶³

⁵⁸ Danish Veterinary and Food Administration.

⁵⁹ Laura H. Kahn, *One Health and the Politics of Antimicrobial Resistance* (Baltimore: Johns Hopkins University Press, 2016), 34.

⁶⁰ Kahn, 35.

⁶¹ Danish Veterinary and Food Administration, "Distribution and Use of Veterinary Drugs."

⁶² Levy, "Reduced Antibiotic Use in Livestock."

⁶³ Gitte Inselmann Frandsen and Heidi Kornholt, eds., *Data for Action: The Danish Approach to Surveillance of the Use of Antimicrobial Agents and the Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*, 2nd ed. (Kongens Lyngby, Denmark: National Food Institute, June 2012), http://orbit.dtu.dk/fedora/objects/orbit:120836/datastreams/file_72652d27-b645-44a7-b798-ee0fd7cbf7f2/content.

A. MONITORING RESISTANCE: INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING AND RESEARCH PROGRAMME (DANMAP)

The Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was formed in 1995 by the Danish Ministry of Food Agriculture and Fisheries and the Danish Ministry of Health.⁶⁴ According to its website, the program was established with the following objectives:

- To monitor the consumption of antimicrobial agents for food animals and humans
- To monitor the occurrence of antimicrobial resistance in bacteria isolated from food animals, food of animal origin and humans
- To study associates between antimicrobial consumption and antimicrobial resistance
- To identify routes of transmission and areas for further research studies⁶⁵

The program seeks to monitor trends and identify potential contributing factors to antibiotic resistance and the spread of resistant organisms. Because animals and humans can spread resistant organisms to one another, DANMAP insists on an integrated monitoring approach.⁶⁶ Denmark was the first country to establish a surveillance system for the use of antimicrobials.⁶⁷ Agencies involved in the program are the National Veterinary Institute and the National Food Institute, both affiliated with the Technical University of Denmark, and Statens Serum Institut, which is the national governmental public health entity responsible for infectious disease preparedness under the Danish Ministry of Health.⁶⁸ The program is a jointly funded effort by the Danish Ministry of

⁶⁴ World Health Organization, “Impacts of Antimicrobial Growth Promoter Termination in Denmark: The WHO International Review Panel’s Evaluation of the Termination of the Use of Antimicrobial Growth Promoters in Denmark” (report, World Health Organization, 2003), 10, http://apps.who.int/iris/bitstream/10665/68357/1/WHO_CDS_CPE_ZFK_2003.1.pdf.

⁶⁵ “About DANMAP,” accessed August 20, 2017, <http://www.danmap.org/About%20Danmap.aspx>.

⁶⁶ Frandsen and Kornholt, *Data for Action*, 6.

⁶⁷ Frandsen and Kornholt, 9.

⁶⁸ DANMAP, “About DANMAP”; “About SSI,” Statens Serum Institut, accessed November 11, 2018, <https://www.ssi.dk/English/Service/AboutSSI.aspx>.

Health, the Ministry of Food Agriculture and Fisheries, and the Ministry of Science, Innovation and Higher Education.⁶⁹

The National Food Institute obtains isolates from food animals through veterinary practices, private labs, and slaughter plants and sends data to DANMAP.⁷⁰ The institute also receives data from the Danish Veterinary and Food Administration, which obtains isolates from regional food control labs to send to DANMAP. On the human side, the Statens Serum Institut receives isolates and data from regional hospital labs and samples from general practice. Human data are then compiled and sent to DANMAP.⁷¹ The program also receives data from the Danish Medicine Agency and a program called VetStat. VetStat began in 2000 and collects data on the prescribed medicine used in animals.⁷² Veterinarians, pharmacies, and feed mills are required to report all administration of drugs for animal use each month.⁷³ The data for this system are gathered automatically through billing mechanisms and the system then aggregates data by farm, including by animal species, age, disease, drugs used and amount, date of purchase, and the prescribing veterinarian.⁷⁴ All of the data are produced in DANMAP's annual report, and they allow scientists to evaluate the ban on growth promoters in the country as well as other policies implemented to reduce the use of antimicrobials.⁷⁵ The information also helps analysts to identify emerging health threats and therefore to persuade industry to use antimicrobials judiciously.

⁶⁹ Frandsen and Kornholt, *Data for Action*, 9.

⁷⁰ "Organization: Organization and Workflow of DANMAP," DANMAP, last updated October 8, 2018, <https://www.danmap.org/About%20Danmap/Organization%20chart.aspx>.

⁷¹ DANMAP.

⁷² DVFA, "Distribution and Use of Veterinary Drugs."

⁷³ H. Stege et al., "VETSTAT—The Danish System for Surveillance of the Veterinary Use of Drugs for Production Animals," *Preventive Veterinary Medicine* 57, no. 3 (March 2003): 105–15, [https://doi.org/10.1016/S0167-5877\(02\)00233-7](https://doi.org/10.1016/S0167-5877(02)00233-7).

⁷⁴ Peter R. Wielinga et al., "Evidence-Based Policy for Controlling Antimicrobial Resistance in the Food Chain in Denmark," *Food Control* 40, no. 2014 (November 2013): 189; Anette M. Hammerum et al., "Danish Integrated Antimicrobial Resistance Monitoring and Research Program," *Emerging Infectious Diseases* 13, no. 11 (November 2007): 1633–39, <https://doi.org/10.3201/eid1311.070421>.

⁷⁵ Wielinga et al., "Evidence-Based Policy," 189.

One of the unique aspects of DANMAP is that it separates risk assessment from risk management—meaning scientists assess risks while the government entities implement risk management.⁷⁶ This system ensures evidence-based decision-making, since the data are readily available and appear to be a trusted source of information in the country. Everyone has access to the data, which allows all stakeholders to have the same information when assessing interventions.

B. ASSESSMENT

The World Health Organization published an evaluation of Denmark’s progress in 2003, roughly five years after the country banned antimicrobial growth promoters. The review examined impacts of the policies on the use of antimicrobial growth promoters, the ban’s effect on antimicrobial resistance, and the impact of the ban on human health, animal health, the environment, animal production, and the economy.⁷⁷ As expected, the use of antimicrobials in food animals dropped significantly following the ban—a decrease of 54 percent from 1994 to 2001.⁷⁸ The study noted an increase in the use of therapeutic antimicrobials in pigs following the ban due to increased diarrhea in weaning pigs; however, no increase was recorded for therapeutic use in poultry. Denmark’s surveillance system showed that, with the ban, the country was able to significantly reduce antibiotic-resistant *Enterococci* in food animals (an organism that can cause surgical wound infections and urinary tract infections). Due to data limitations, however, the authors of the study could not completely determine the impact of the ban on human carriage of antimicrobial-resistant organisms.⁷⁹

The World Health Organization panel found that pork production in Denmark increased after the ban, even though there was some loss in weaning productivity.⁸⁰ No

⁷⁶ Wielinga et al., 189.

⁷⁷ World Health Organization, “Impacts of Antimicrobial Growth Promoter Termination,” 9.

⁷⁸ World Health Organization, 6.

⁷⁹ M. M. Huycke, D.F. Sahn, and M.S. Gilmore, “Multiple-Drug Resistant Enterococci: The Nature of the Problem and an Agenda for the Future,” *Emerging Infectious Disease Journal* 4, no. 2 (June 1998): 239–49, <https://doi.org/10.3201/eid0402.980211>; World Health Organization, “Impacts of Antimicrobial Growth Promoter Termination,” 9.

⁸⁰ World Health Organization, “Impacts of Antimicrobial Growth Promoter Termination,” 10.

major effect was found in the finishers. The study showed a small decrease in feed efficiency in poultry after the ban but noted that it was offset by the fact that producers no longer needed to purchase growth promoters. The report also outlined an increase in pork production costs of slightly more than 1 percent or 7.75 DKK; there was virtually no net increase for poultry production and the ban did not adversely impact the Danish economy overall.⁸¹

1. Impacts of the Ban on Industry

The World Health Organization concluded that the ban of antimicrobial growth promoters reduced resistance in food animals and “there have been no serious negative effects” on production, price, animal health, or food safety in Denmark as a result of the ban.⁸² The authors recommended that the issues with diarrhea in weaning pigs be addressed. They also suggested that more non-antimicrobial strategies would be needed to improve production efficiency.

Not all the news was perceived as good, however. An Iowa State University study published in 2003 (funded by the U.S. National Pork Board) confirmed that even though antibiotic growth promoters were no longer used, antibiotic use increased for therapeutic purposes for two reasons: weaning piglets were contracting more illnesses and “therapeutic medications were increasingly substituted for the now-banned AGPs.”⁸³ The study also reported that “the policy resulted in an increase in the use of the products about which humans are most concerned.”⁸⁴ They found that the growth-promotion products that were banned were not as harmful to human health as the antibiotics that producers were using as substitutes either for the banned products or for therapeutic use after the ban. The authors argue, “This is a classic example of how a policy prescription can have consequences that are exactly the opposite of those intended.”⁸⁵ The authors also

⁸¹ World Health Organization, 10.

⁸² World Health Organization, 11.

⁸³ Dermot J. Hayes and Helen H. Jensen, “Lessons from the Danish Ban on Feed-Grade Antibiotics,” *Choices* 18, no. 3 (2003): 2

⁸⁴ Hayes and Jensen, 3.

⁸⁵ Hayes and Jensen, 3.

concluded that the economic effects included a 4.5-percent increase in production costs during the first year of the ban. This study assumed that production would continue to decline years after the ban and that some producers may need to quit the business. They authors further opined:

In general, the Danes achieved 80 percent of the benefits for 20 percent of the costs when they imposed a partial ban, and they encountered 20 percent of the benefits and 80 percent of the costs when they extended the ban.⁸⁶

This study is used often by food animal producers to lobby against growth promoter bans in the United States.

There has been some rebuttal to the Iowa State University study, including from a former director of the National Food Institute at the Technical University of Denmark, Jørgen Schlundt. During an interview for an article in the June 2014 issue of *Environmental Health Perspectives*, Schlundt shared his experiences talking to people from the United States about antimicrobial resistance and the Danish policies.⁸⁷ Given that Denmark’s farming culture is largely based on co-ops, he feels compelled to begin conversations “by saying that the Danes aren’t communists,” and by reminding others that the policies are based in science and on well-supported evidence.⁸⁸ Interestingly, he noted that many of the Danish researchers were trained in the United States by the CDC.

Also important to note is a Danish study published in 2010 that evaluated the changes in antimicrobial consumption and productivity on Denmark’s swine farms by examining their use of antimicrobials from 1992 to 2008.⁸⁹ The researchers concluded that antimicrobial use per kilogram of pig in the country decreased by more than 50 percent during that time period and that there was an improvement in productivity—the number of swine in the Danish swine industry increased. In addition, the number of pigs

⁸⁶ Hayes and Jensen, 5.

⁸⁷ Levy, “Reduced Antibiotic Use in Livestock,” A163.

⁸⁸ Levy, A163.

⁸⁹ Frank M. Aarestrup et al., “Changes in the Use of Antimicrobials and the Effects on Productivity of Swine Farms in Denmark,” *American Journal of Veterinary Research* 71, no. 7 (July 2010): 726, <https://doi.org/10.2460/ajvr.71.7.726>.

per litter per sow also increased. The mortality rate for all pigs did not appear to be affected. These findings suggest that productivity was not negatively impacted by the ban on growth promoters.⁹⁰ Therefore, the long-term effects predicted by the Iowa State University study authors are inaccurate; counter to the study's predictions, the Danish pork industry is flourishing.

2. The Yellow Card Initiative

Surveillance data indicates that during the period after the ban, from 2001 to 2009, consumption of antibiotics in all animal sectors was up 45 percent, with 80 percent of those antibiotics used in swine production, which aligns with the findings of the Iowa State University study mentioned previously.⁹¹ The authorities recognized that there was an increase in therapeutic use of antibiotics after the removal of growth promoters among weaning pigs.⁹² There was also a concurrent *Lawsonia intercellularis* outbreak that may have contributed to the increase in therapeutic use.⁹³ Also over that time period, cases of post-weaning multisystemic wasting syndrome were increasing, which likely contributed to the use of antimicrobials. Antimicrobial use continued to increase even ten years after the ban; however, researchers concluded that it was highly unlikely the increase was caused by the removal of growth promoters.⁹⁴

In response to this trend of increasing antibiotic use, the Danish Veterinary and Food Administration (DVFA) created the yellow card initiative. Instituted in 2010, the initiative was aimed at reducing the consumption of antibiotics by 10 percent by 2013.⁹⁵ Under the initiative, farms with herds exceeding the threshold of antibiotics per 100 animals per day in a nine-month period will be inspected by veterinarians and the farmer

⁹⁰ Aarestrup et al., 732.

⁹¹ "The Yellow Card Initiative on Antibiotics," DVFA, last modified May 18, 2017, <https://www.foedevarestyrelsen.dk:443/english/Animal/AnimalHealth/Pages/The-Yellow-Card-Initiative-on-Antibiotics.aspx>.

⁹² Kahn, *One Health*, 36.

⁹³ Aarestrup et al., "Changes in the Use of Antimicrobials," 730.

⁹⁴ Aarestrup et al., 731.

⁹⁵ DVFA, "Yellow Card Initiative," 1.

will be issued a yellow card warning. The warning compels the owner to reduce the consumption below the threshold limits within nine months. The producer can also be forbidden to use any antibiotics they may have in their possession if a particular type has been prescribed several times and is given through feed or water.⁹⁶ Inspections by the DVFA are unannounced during the nine-month period.

If after nine months the antibiotic consumption has not been reduced below the threshold limits, or if it was reduced below the maximum limits and then again rose above the limits in the twelve months after the first yellow card period, the DVFA may issue another injunction calling for increased supervision.⁹⁷ This injunction compels the producer to receive guidance from another veterinarian who will advise on how to reduce antibiotic use, at the farmer's expense. This injunction lasts five months and the DVFA may inspect the farm unannounced. A red card is issued if the farm has not reduced consumption below the maximum limits within five months of the second injunction. For a red card injunction, the DVFA may force the farmer to reduce his or her stock to ensure antibiotic consumption is within the acceptable levels. This injunction cannot be lifted until the DVFA confirms through inspections that the consumption is below the threshold limits.⁹⁸ There are economic impacts to the farms for not complying with these thresholds: the producer must pay a fine for each injunction, and all inspection visits are at the expense of the farmer.

The yellow card initiative appears to be an effective method of reducing antibiotic consumption. By 2013, a 10.2-percent reduction was achieved.⁹⁹ The Danes have issued an action plan to combat livestock-associated MRSA by reducing consumption for swine by 15 percent between 2015 and 2018.¹⁰⁰

⁹⁶ DVFA, 3.

⁹⁷ DVFA, 3.

⁹⁸ DVFA, 4.

⁹⁹ DVFA, 1.

¹⁰⁰ DVFA, 2.

3. Current Status of Resistant Zoonotic Bacteria in Denmark

In its 2016 report, the Danish Surveillance system, DANMAP, highlighted findings related to resistance in zoonotic bacteria.¹⁰¹ Because of the restrictive use of “medically important” antibiotics in swine farming, the report states, the most prevalent *Salmonella* serotype among Danish pigs, *Salmonella typhimurium*, has not been found to be resistant to fluoroquinolone (ciprofloxacin), an antibiotic used to treat bacterial infections in humans.¹⁰² The reports also states that *S. typhimurium* was the most common *Salmonella* serotype among human isolates that were tested for susceptibility to antibiotic resistance. Interestingly, for those who acquired the infections domestically, the tetracycline resistance increased from 55 percent in 2015 to 68 percent in 2016; however, both ciprofloxacin and nalidixic acid resistance were higher in isolates from individuals who acquired their infections while traveling outside Denmark.¹⁰³

The report also noted that, among broiler chickens’ isolates, fluoroquinolone-resistant *Campylobacter jejuni* levels appear to be higher in imported meat.¹⁰⁴ However, the group reports an increase of the levels of fluoroquinolone resistance among cattle isolates even though these antimicrobials are very rarely used in cattle.¹⁰⁵ The human findings are similar to that of *S. typhimurium* in that more isolates in people who traveled were found to be resistant than in those whose infections were acquired locally.¹⁰⁶

Taken together, the DVFA and DANMAP studies show that with reduction in use there has been some reduction in antibiotic resistance in animals, but the rates of resistant

¹⁰¹ Zoonoses are diseases that can be transmitted between animals and humans, either through direct exposure to animals or indirectly by contaminated food, water, or the environment. “Zoonoses and the Human-Animal-Ecosystems Interface,” World Health Organization, accessed November 21, 2017, <http://www.who.int/zoonoses/en/>.

¹⁰² DANMAP, “DANMAP 2016: Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark” (report, DANMAP, October 2017), 65, https://www.danmap.org/~/_media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP_2016_web.ashx.

¹⁰³ DANMAP, 66.

¹⁰⁴ DANMAP, 67.

¹⁰⁵ DANMAP, 69.

¹⁰⁶ DANMAP, 69.

infections among people have continued to increase. However, rates of resistance remain higher in imported meat and for individuals who have acquired their resistant infections outside of Denmark. This surveillance highlights the need for standard global solutions to this problem.

C. IMPLEMENTATION STRATEGIES

Denmark's ability to implement such sweeping regulation can be attributed in large part to its commitment to involving stakeholders and keeping the discussions and data about the situation transparent to the public.¹⁰⁷ The country also achieved greater buy-in for the policy changes by having independent third parties conduct the research. The government employed media campaigns to help convince the public of the risks associated with antimicrobials as growth promoters and to promote the good that producers are doing for the country and the world by not using growth promoters.¹⁰⁸ Many sectors of Denmark's agricultural industry are organized into co-ops, and many farmers are co-owners of slaughterhouses, which means that the industry was poised to work together to respond to pressures from the public, which may have promoted acceptance of the country's regulatory measures.¹⁰⁹

In addition, because of the shift away from antibiotics in veterinary practices, enhanced biosecurity measures were needed. Specifically, all-in/all-out strategies were employed to reduce disease transmission.¹¹⁰ This management practice ensures that infection from other animals is eliminated by keeping swine isolated in groups while on the farm. The groups are not mixed and when they move through the various production stages, the sites on the farms are completely emptied out and cleaned. Farmers also report allowing pigs to nurse longer to allow natural immunity to build up before they are moved to the next production stage.¹¹¹

¹⁰⁷ Wielinga et al., "Evidence-Based Policy," 191.

¹⁰⁸ Wielinga et al., 191.

¹⁰⁹ Wielinga et al., 191.

¹¹⁰ Wielinga et al., 191.

¹¹¹ Barry Estabrook, "Denmark's Drug-Free Pigs," *New York Times*, April 3, 2015, <https://www.nytimes.com/2015/04/03/opinion/denmarks-drug-free-pigs.html>.

D. CONCLUSION

Key to the Danes' ability to inform its policy decisions was the creation of DANMAP. This monitoring program allows the Danish government to perform surveillance on antimicrobial distribution and use and to track resistance patterns in the country. Without it, the government would not know what policy decisions are needed or whether its interventions have affected antibiotic use or resistance.

Denmark's ban on antibiotic growth promoters did not appear to impact industry and did show some success. The rates of vancomycin-resistant *Enterococci* (VRE) in pigs and poultry were reduced, yet there is no evidence that the rates were reduced in humans; VRE in humans is genetically different from the same bacteria typically found in animals.¹¹² Resistance to avoparcin and erythromycin decreased after the ban.¹¹³

The ban also had some unintended consequences: for instance, there was an increase in therapeutic antibiotic use among weaning pigs shortly after the ban. It is unclear if this increase is simply because there were more animals present, or if more infections were occurring. There is no evidence that the industry is using the antibiotics illegally—such as for routine disease prevention. It is possible that other factors are accelerating antibiotic resistance outside of drug use, like the use of copper and zinc in feed.

The Danish government understands that the fight against antibiotic resistance is far from over. Because of increasing consumption, the country has instituted goals to reduce the overall use of antibiotics in agriculture.¹¹⁴ DANMAP's surveillance also indicates that global solutions are needed given that imported meat and isolates from humans show greater resistance to antimicrobials than those in Denmark.

¹¹² Kahn, *One Health*, 40.

¹¹³ Frandsen and Kornholt, *Data for Action*, 16–17.

¹¹⁴ DANMAP, "DANMAP 2016: Use of Antimicrobial Agents," 16.

III. CASE STUDY: THE NETHERLANDS

Livestock producers in the Netherlands have not been able to use growth promoters since 2006, when the European Union banned the use of most antibiotics for this purpose. Even after the ban, however, the Netherlands was the top-ranked country for antibiotic use in agriculture.¹¹⁵ This chapter describes the steps the Dutch have taken to curb antibiotic use and the effects of their more conservative approach.

A. THREATS AND CONCERNS EMERGE

Microbial resistance levels in the Netherlands have traditionally been low in health-care settings and the country's use of antibiotics in human medicine is among the lowest in Europe.¹¹⁶ But, as Europe's leading meat exporter, the Dutch have also used large amounts of antibiotics in animal production and resistance levels are high.¹¹⁷ The Dutch began to express concern in 2004, prior to the effective date of the European ban on growth promoters, when methicillin-resistant *Staphylococcus aureus* (MRSA)—a hard-to-treat, antibiotic-resistant organism—was detected in a young girl who lived on a swine farm.¹¹⁸ Finding this organism in the Netherlands at the time was extremely uncommon, and MRSA rates in the country were among the lowest in Europe.¹¹⁹ The patient's family members were found to be carriers of this organism, and so too were friends of the family. The same strain was confirmed in their pigs.¹²⁰

¹¹⁵ D. C. Speksnijder et al., "Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model," *Zoonoses and Public Health* 62, no. s1 (April 2015): 79–87, <https://doi.org/10.1111/zph.12167>.

¹¹⁶ Dik Mevius and Dick Heederik, "Reduction of Antibiotic Use in Animals 'Let's Go Dutch,'" *Journal Für Verbraucherschutz Und Lebensmittelsicherheit* 9, no. 2 (June 1, 2014): 180, <https://doi.org/10.1007/s00003-014-0874-z>.

¹¹⁷ Christina Maria Joseph Elisabeth Vandenbroucke-Grauls, "Antimicrobial Resistance in the Netherlands: A Natural Experiment?" *Frontiers in Public Health* 2 (January 24, 2014), <https://doi.org/10.3389/fpubh.2014.00005>; Mevius and Heederik, "Reduction of Antibiotic Use in Animals," 180.

¹¹⁸ Andreas Voss et al., "Methicillin-Resistant *Staphylococcus Aureus* in Pig Farming," *Emerging Infectious Diseases* 11, no. 12 (December 2005): 1965–66, <https://doi.org/10.3201/eid1112.050428>.

¹¹⁹ Voss et al.

¹²⁰ "The Abstinence Method," *Modern Farmer* (blog), June 17, 2014, <https://modernfarmer.com/2014/06/abstinence-method/>.

Scientists quickly went to work to investigate pig farming as a source of MRSA in the Netherlands. A 2005 study found that other pork producers and their families were also carrying the organism.¹²¹ In one instance, the organism was found in the son of a veterinarian whose primary patients were pigs; it was also transmitted to a nurse who cared for the veterinarian's son in the hospital.¹²² Ultimately, this research demonstrated that people in the study area who came in contact with pigs had MRSA at a frequency 760 times higher than the general Dutch population.¹²³ Fearing the spread of MRSA in hospitals, doctors treat individuals who are at higher risk to carry the organism in isolation rooms until test results indicate they are not colonized or infected.¹²⁴

Given the public health implications posed by the MRSA situation, Dutch authorities began discussing what could be done to reduce the use of antimicrobials in veterinary practice in the Netherlands, even after the European antibiotic growth promoter ban was enacted. In 2008, the country convened a task force aimed at tackling antibiotic resistance in animal husbandry.¹²⁵ The members of the task force included industry stakeholders as well as the Royal Dutch Veterinary Association (KNMvD), the Dutch Ministry of Agriculture, and the Dutch Ministry of Health.¹²⁶ The group put together action plans through memoranda of understanding, which described measures to reduce antibiotic use and monitor resistance, and outlined a separation of duties between farmers and veterinarians with regard to prescribing antibiotics.¹²⁷

While this work was being conducted, another threat emerged—extended spectrum beta-lactamase-producing bacteria (ESBLs) were discovered in Dutch poultry

¹²¹ Voss et al., “Methicillin-Resistant Staphylococcus Aureus.”

¹²² Voss et al.

¹²³ Voss et al.

¹²⁴ *Modern Farmer*, “The Abstinence Method.”

¹²⁵ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 80.

¹²⁶ Speksnijder et al., 80.

¹²⁷ Speksnijder et al., 81.

meat in 2009.¹²⁸ ESBLs produce an enzyme that makes antibiotics ineffective. Strains of *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* are the most common ESBLs.¹²⁹

As with pig production, antibiotic use was also heavy in the poultry industry in the Netherlands. Given the increase in infections caused by ESBLs among patients in Dutch hospitals, scientists began looking at the prevalence of these bacteria in livestock production. One study looked at twenty-six boiler chicken farms and found that all animals were shedding ESBL-producing *E. coli* in their feces.¹³⁰ That meant that virtually all broiler meat products studied during this research were positive for ESBL-producing organisms. After the study, poultry farms were considered a source of ESBL-producing gram-negative bacteria. Shortly after, an investigation from the University Medical Center Utrecht revealed that poultry meat was a likely route of bacteria transmission to humans.¹³¹ The findings were disseminated in the media, resulting in concern from Dutch citizens.¹³²

Agricultural antibiotic use in the country was still high, even though the Netherlands adopted the European growth promoter ban. Much like in Denmark, Dutch sales data indicated that the country resorted to using more antibiotics after the ban for what was cited as therapeutic reasons—meaning drugs were reportedly used to treat sick animals.¹³³ In fact, one study showed that the Netherlands consumed the most antibiotics out of ten European countries in 2007.¹³⁴ The cited therapeutic uses ranged from

¹²⁸ Speksnijder et al., 81.

¹²⁹ Ontario Agency for Health Protection and Promotion, *Annex A: Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs)* (Toronto, ON: Queen's Printer for Ontario, 2011).

¹³⁰ Ilse Overdeest et al., "Extended-Spectrum β -Lactamase Genes of *Escherichia Coli* in Chicken Meat and Humans, the Netherlands," *Emerging Infectious Diseases* 17, no. 7 (July 2011): 1216–22, <https://doi.org/10.3201/eid1707.110209>.

¹³¹ M. A. Leverstein-van Hall et al., "Dutch Patients, Retail Chicken Meat and Poultry Share the Same ESBL Genes, Plasmids and Strains," *Clinical Microbiology and Infection* 17, no. 6 (June 1, 2011): 873–80, <https://doi.org/10.1111/j.1469-0691.2011.03497.x>.

¹³² Speksnijder et al., "Reduction of Veterinary Antimicrobial Use," 83.

¹³³ Carol Coglian, Herman Goossens, and Christina Greko, "Restricting Antimicrobial Use in Food Animals: Lessons from Europe," *Microbe* 6, no. 6 (2011): 277.

¹³⁴ Speksnijder et al., "Reduction of Veterinary Antimicrobial Use," 80.

treatment of disease to feed quality; non-infectious disease and changes in farming practices also contributed to the increase in use.¹³⁵

B. FURTHER ACTION TAKEN TO REDUCE ANTIBIOTIC USE IN FARM ANIMALS

Because of added public pressure to address the problem, the Dutch government continued its debate on the high levels of antibiotic use in food animals.¹³⁶ Although the memos released previously did not specifically outline goals for reducing antibiotic use, in 2010 the government began instituting mandatory reduction targets.¹³⁷ The goal was, based on 2009 levels, to reduce the use of antibiotics by 20 percent by 2011, 50 percent by 2013, and 70 percent by 2015.¹³⁸

In August 2011, the Dutch Health Council, which describes itself as an “independent scientific advisory body for government and parliament,” advised the Dutch government to ban newly developed antibacterial drugs, along with third- and fourth-generation cephalosporins and fluoroquinolones, for animals.¹³⁹ The council also recommended banning the drug colistin and phasing out the use of β -lactam antibiotics and aminoglycosides in animals.¹⁴⁰ Ultimately, the Dutch government decided to adopt the recommendation of restricting the use of third- and fourth-generation cephalosporins and fluoroquinolones in animal husbandry.

An antibiotics policy working group of the Dutch Royal Veterinary Association also crafted guidance for the use of antimicrobials in terms of first, second, and third choices for veterinary treatment purposes.¹⁴¹ In 2013, requirements changed: farmers

¹³⁵ Cogliani, Goossens, and Greko, “Restricting Antimicrobial Use,” 277.

¹³⁶ Speksnijder et al., “Reduction of Veterinary Antimicrobial,” 81.

¹³⁷ Alejandro Dorado-Garcia et al., “Quantitative Assessment of Antimicrobial Resistance in Livestock during the Course of a Nationwide Antimicrobial Use Reduction in the Netherlands,” *Journal of Antimicrobial Chemotherapy* 71, no. 12 (December 2016): 3607.

¹³⁸ Mevius and Heederik, “Reduction of Antibiotic Use in Animals.”

¹³⁹ The Health Council of the Netherlands, accessed December 10, 2017, www.healthcouncil.nl; Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 81.

¹⁴⁰ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 81.

¹⁴¹ Mevius and Heederik, “Reduction of Antibiotic Use in Animals.”

could now only store first-choice drugs onsite for empiric treatment (i.e., before it is known which bacterium is infecting the animals).¹⁴² These drugs must be used in accordance with a mandatory treatment plan, which must be created with a veterinarian and based on guidelines from the Netherlands Veterinary Medicines Institute (SDa).

1. Dispensing Antibiotics

The Netherlands recognized that veterinary interests and the interests of farmers may be at odds with the goal of reducing antibiotic use.¹⁴³ In addition to the enacted regulatory bans, the Dutch government proposed changes to the way antibiotics were dispensed in the country. Antibiotics can only be obtained with a prescription from a veterinarian, and veterinarians are also responsible for dispensing the drugs.¹⁴⁴ To address continuity issues, in 2012 the government began requiring farmers to partner with only one veterinary practice.¹⁴⁵ Veterinarians are also required to inspect the farm before they can prescribe antibiotics to ill livestock—and only under strict conditions can second- and third-choice antimicrobials be used in animals.¹⁴⁶

To address conflict-of-interest issues with veterinarians, in 2011 the KNMvD—the professional veterinary association in the Netherlands—proposed a quality system for veterinarians that would include treatment guidelines, as well as a register where veterinarians could pursue accredited continuing education courses.¹⁴⁷ The system, referred to as the “approved veterinarian,” requires veterinarians to abide by the treatment guidelines and create farm-specific animal health and treatment plans, creating a one-on-

¹⁴² Mevius and Heederik.

¹⁴³ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 82.

¹⁴⁴ Speksnijder et al., 82.

¹⁴⁵ Speksnijder et al., 81.

¹⁴⁶ “Antibiotic Resistance in the Livestock Industry,” Government of the Netherlands, accessed January 14, 2014, <https://www.government.nl/topics/antibiotic-resistance/antibiotic-resistance-in-livestock-farming>.

¹⁴⁷ “History,” KNMvD, accessed January 24, 2018, <https://www.kwaliteitdiergeneeskunde.nl/kwaliteit/home/item/10836975/Geschiedenis>.

one relationship with farmers.¹⁴⁸ The KNMvD created a basic quality register for all veterinarians and has also compiled several specialty-specific, private quality registers. These registers list veterinarians who meet the criteria to be listed as approved veterinarians for that particular sector.¹⁴⁹

2. Monitoring Antibiotic Use and Resistance

Since 2012, veterinarians and livestock farmers have been required to report all antibiotics administered to farm animals to the SDa.¹⁵⁰ The SDa, the Netherlands Veterinary Medicines Institute, is a public-private entity that monitors the amount of antibiotics used by each Dutch livestock sector and examines the amount of antibiotics sold against the number of antibiotics used. The agency issues an annual report that displays trends in use and sales by livestock sector with a focus on critically important antibiotics. The report also includes the best information available on unmonitored sectors, such as some poultry-farming sectors, mink, sheep, goats, zoos, companion animals, and horses.

C. ASSESSMENT

In addition to its monitoring responsibility, the SDa is responsible for setting antibiotic-use reduction targets for each food-animal species. The organization includes an independent expert panel comprising veterinary scientists, epidemiologists, and human-medicine scientists. The panel reviews veterinary prescribing patterns as well as antibiotic use on farms and then uses the data to establish benchmarks for the types and quantities of antibiotics that should be used for each sector.¹⁵¹ The SDa's website states that it strives to meet multiple goals:

¹⁴⁸ "Veterinarians," Netherlands Veterinary Medicines Institute (SDa), accessed January 24, 2018, <http://www.autoriteitdiergeneesmiddelen.nl/en/veterinarians>.

¹⁴⁹ "Registers," KNMvD, accessed January 25, 2018, <https://www.kwaliteitdiergeneeskunde.nl/kwaliteit/sectorregisters>.

¹⁵⁰ Mevius and Heederik, "Reduction of Antibiotic Use in Animals."

¹⁵¹ "About SDa," accessed December 28, 2017, <http://www.autoriteitdiergeneesmiddelen.nl/en/about-sda>.

The SDa's final goal is not merely to realize a reduction in antibiotic use, but rather to restrict the usage of antibiotics in animals in such a way as to minimize the associated public health risks. To this end, the SDa defines specific target values for antibiotic use. To achieve the final goal, animal husbandries should increasingly focus on developing good practices for farm-oriented and chain-oriented animal health management and infection control, as this is the only way to become less dependent on antibiotics.¹⁵²

The SDa reports on the status of antimicrobial use in pigs, veal, cattle, broiler chickens, turkeys, and meat-rabbit farming sectors. In 2013, the SDa's goal was to cut antibiotic use in half compared to 2012 levels, which were already lower than previous years.¹⁵³ That said, it does not appear that the 2015 goal of an overall 70 percent reduction was met, nor was it met in any of the monitored livestock sectors. The SDa reported in 2015 that the veal farming sector had reduced its use of antibiotics by 35 percent since 2009; pig farmers were able to reduce their use by 56 percent, the broiler chicken sector by 60 percent, and dairy cattle farmers by 46 percent.¹⁵⁴ In its 2016 report, the SDa stated that the number of kilograms of antimicrobials sold declined by 64.4 percent between 2009 and 2016.¹⁵⁵ The use levels among most sectors continued to decline, though not as sharply as the declines noted in the previous five years, indicating that levels may be stabilizing.¹⁵⁶

A 2016 report issued by the Dutch Foundation of the Working Party on Antibiotic Policy, in collaboration with the National Institute for Public Health and the Environment of the Netherlands, stated that the lowest proportion of ESBL-producing *E. coli* was

¹⁵² SDa.

¹⁵³ SDa, "Usage of Antibiotics in Livestock in the Netherlands in 2012" (report, Netherlands Veterinary Medicines Institute, July 2013), 4, <http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/pdf/sda-report-usage-of-antibiotics-in-livestock-in-the-netherlands-in-2012-july-2013.pdf>.

¹⁵⁴ SDa, "Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2015: Trends, Benchmarking of Livestock Farms and Veterinarians, and a Revision of the Benchmarking Method" (report, Netherlands Veterinary Medicines Institute, December 2016), 7, <http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/Eng%20rapport%20AB%20gebruik%202015/engels-rapportage-2015---geheel-rapport-13122016.pdf>.

¹⁵⁵ SDa, "Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2016: Trends and Benchmarking of Livestock Farms and Veterinarians" (report, Netherlands Veterinary Medicines Institute, September 2017), 8, <http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/Eng%20rapport%20AB%202016/engels-def-rapportage-2016-deel-1-en-2-22-09-2017.pdf>.

¹⁵⁶ SDa, 3.

observed in random isolates of *E. coli* since 2007.¹⁵⁷ The report also found that ESBL/AmpC- prevalence in poultry meat had decreased substantially from the previous year. The decrease was attributed to the reduced use of antibiotics in this sector.¹⁵⁸ The authors of the report conclude that the Dutch policies aimed at reducing the total use of antibiotics have made a substantial impact on decreased resistance in the country.¹⁵⁹

D. IMPACTS OF POLICIES ON INDUSTRY

With no antibiotics available to them for use as prophylaxis, and with antibiotics only available after an inspection, one might conclude that farmers would have strong opposition to the Dutch antibiotic-use policies. Universally, however, this does not seem to be the case. A farmer interviewed for a National Geographic video story on the subject discusses how the transition was a natural one for him. After the MRSA scare, he and other pig farmers in his region formed a network of farmers who believed that healthy animals do not need antibiotics.¹⁶⁰ The group sought to find practices that helped them keep their animals healthy; they learned from each other what worked and shared their experiences with other farmers outside their immediate network. He believes it is important to stay the course: “You do it for yourself, for the next generation, but also to get more profit out of your farm.”¹⁶¹ The farmer sees better results now with healthy pigs, and notes that sick pigs do not result in any profit.

Not all farmers found it so easy to adapt to the policies, however. In the same National Geographic video series, a Dutch poultry farmer discusses his experience with the regulations and how he struggles when his animals are sick.¹⁶² He agrees that

¹⁵⁷ S. C. de Greeff, J. W. Mouton, and A. F. Hoeing, “NethMap 2016: Consumption of Antimicrobial Agents and Antimicrobial Resistance among Medically Important Bacteria in the Netherlands in 2015” (report, National Institute for Public Health and the Environment, June 2016), 14.

¹⁵⁸ de Greeff, Mouton, and Hoeing, 14.

¹⁵⁹ de Greeff, Mouton, and Hoeing, 15.

¹⁶⁰ Maryn McKenna, “Getting a Farm off Antibiotics,” vimeo video, posted by maryn, May 27, 2014, <https://vimeo.com/96639425>.

¹⁶¹ McKenna.

¹⁶² Maryn McKenna, “Questioning Farm Antibiotic Rules,” vimeo video, posted by maryn, May 27 2014, <https://vimeo.com/96640919>.

reducing antibiotic use is very good, but because the regulations mandate which antibiotics must be used first, he has been prohibited from using the third-choice group of antibiotics (i.e., those that are medically important to humans), even when he knows they are going to cure the animals. You can still develop resistance, he argues, by administering antibiotics that do not work first, and then using the ones you knew would work all along. He has a hard time with the stigma associated with poultry and swine farmers in the country.

As for overall impacts, in opening remarks during an international conference on antibiotic resistance in June 2014, the Dutch minister of agriculture reported that in three years the country was able to lower the rates of antibiotic use in agriculture while still remaining second in the world in agricultural exports.¹⁶³

E. IMPLEMENTATION STRATEGIES

Much of the Netherlands' success in reducing antibiotic use can be attributed to the government's role in setting targets or goals for the country. The memoranda that were established in 2008 did not significantly reduce the use of antibiotics as growth promoters.¹⁶⁴ This example demonstrates that bans on non-therapeutic use are likely not enough to slow resistance; only when governmental regulations with specific goals were enacted did the country see reductions in antibiotic use.¹⁶⁵

In addition, public opinion may have played a significant role in influencing changes in the Netherlands. The discovery of livestock as a reservoir for superbugs such as MRSA that are dangerous to humans—including farmers and their families—likely contributed to farmers' willingness to change their practices. Producers may have also felt pressure from public mass media campaigns regarding MRSA and other frightening resistant infectious diseases. The public began seeing the potential consequences of

¹⁶³ “Toespraak van minister Schippers bij de opening van de ministeriële conferentie antibioticaresistentie [Speech by Minister Schippers at the Opening of the Ministerial Conference on Antibiotic Resistance],” Rijksoverheid, June 25, 2014, <https://www.rijksoverheid.nl/documenten/toespraken/2014/06/25/minister-schippers-opent-ministeriele-conferentie-antibiotica-resistentie>.

¹⁶⁴ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 81.

¹⁶⁵ Speksnijder et al., 81.

antibiotic overuse in livestock and disapproved of the practice—thus the demand for judicious use of antibiotics in agriculture.¹⁶⁶ In addition, the Ministry of Economic Affairs notes that the policies were adopted due to the agriculture industry and veterinarians’ sense of urgency to respond.¹⁶⁷ Because of this public-private partnership, there was widespread support, which allowed for easy adoption.¹⁶⁸

F. CONCLUSION

After emergent health threats and political pressure, the Dutch implemented targets for reducing antibiotic use in livestock. Because of their monitoring systems, they understood that antibiotic use in the country remained high even after a ban on antibiotics as growth promotion for livestock. Industry had transitioned from growth-promotion use to therapeutic use—the bans were not enough to produce an overall reduction. The national targets and veterinary practices seem to be producing the reduction the country is seeking with limited impact on production.

¹⁶⁶ Speksnijder et al., 83.

¹⁶⁷ Rijksoverheid Ministry of Economic Affairs, “Reduced and Responsible: Policy on the Use of Antibiotics in Food-Producing Animals in the Netherlands” (report, Rijksoverheid, February 2014), <https://www.government.nl/binaries/government/documents/leaflets/2014/02/28/reduced-and-responsible-use-of-antibiotics-in-food-producing-animals-in-the-netherlands/use-of-antibiotics-in-food-producing-animals-in-the-netherlands.pdf>.

¹⁶⁸ Rijksoverheid Ministry of Economic Affairs.

IV. UNITED STATES: LEGISLATIVE EFFORTS AND CURRENT POLICY

At the national level, the United States, has implemented few regulations and only recently has issued limited guidance related to reducing the use of medically important antibiotics in food animals. This chapter discusses possible reasons behind the lack of action as well as current strategies that have been attempted or employed.

A. POTENTIAL LEGISLATION

Although legislation limiting the use of antibiotics in food animals has been introduced in the United States, none has been enacted. This section discusses potential bans discussed in the past as well as legislation that has been proposed to slow the threat of antibiotic resistance.

1. Historical Discussion

In 1969, the Swann Committee—a task force established in the United Kingdom to review the use of antimicrobials in food production for growth promotion—determined that multidrug-resistant *Salmonella* infections may be the result of growth promotion antibiotics in livestock and that action should be taken to limit their use.¹⁶⁹ Eight years after this report was published, the U.S. Food and Drug Administration (FDA) considered banning penicillins and tetracyclines for food animal use.¹⁷⁰ The FDA had planned to hold hearings on the issue, citing “studies relevant to transfer of drug resistance” and safety concerns related to the subtherapeutic use of antibiotics in animals.¹⁷¹ The discussion was intended to focus on the lack of evidence stating that penicillin-containing

¹⁶⁹ European Environment Agency, *Late Lessons from Early Warnings: The Precautionary Principle 1896–2000* (Copenhagen, Denmark: European Environment Agency, 2001), 94, http://www.rachel.org/lib/late_lessons_from_early_warnings.030201.pdf.

¹⁷⁰ “Penicillin-Containing Premixes; Opportunity for Hearing,” notice, *Federal Register* 42, no. 168 (August 30, 1977), 1, <https://www.scribd.com/document/76663776/FDA-Notion-of-Opportunity-for-Hearing-re-penicillin-1977>.

¹⁷¹ “Penicillin-Containing Premixes,” 3.

premises for feed are safe or effective for use.¹⁷² The effort, however, did not progress beyond a congressional committee; the farm lobby prevented the hearings from taking place.¹⁷³ According to a Frontline news report, a legislator with strong ties to the farm industry served on the subcommittee responsible for approving the agency's budget.¹⁷⁴ Given that farmers and drug manufacturers were opposed to these changes due to limited scientific evidence and economic concerns, the legislator threatened to cut the FDA's funding if they pushed forward. Ultimately, the secretary of the Department of Health and Human Services did not wish to gamble the department's funding on this proposal and asked that the proposed regulations be tabled for a later date.¹⁷⁵ That date never came.

There have been several legal attempts by advocacy organizations to resurrect the 1970s proposals, which have resulted in a continuous cycle of litigation and appeals; to date, the FDA has not been required to hold hearings regarding the safety of antibiotics used in animal feed. In 2011, the FDA formally withdrew the 1977 proposals and explained that the agency was committed to looking at other options to limit the use of growth promoters in food animals.¹⁷⁶ The agency issued guidance for the industry in 2012 and 2013, which is discussed later in this chapter.

2. Preservation of Antibiotics for Medical Treatment Act (PAMTA)

Beginning in 1999, the late Representative Louise Slaughter of New York cosponsored or introduced legislation several times to mitigate the risks of antibiotic resistance. Her last proposed legislation, the Preservation of Antibiotics for Medical Treatment Act of 2017 (PAMTA), would eliminate the non-therapeutic uses of medically

¹⁷² "Penicillin-Containing Premixes," 1.

¹⁷³ Levy, "Reduced Antibiotic Use in Livestock." A163.

¹⁷⁴ Emma Schwartz, "Inside an Early Attempt to Restrict Antibiotic Use on Farms," Frontline, October 14, 2014, <https://www.pbs.org/wgbh/frontline/article/inside-an-early-attempt-to-restrict-antibiotic-use-on-farms/>.

¹⁷⁵ Schwartz.

¹⁷⁶ "Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline Used in Animal Feed," notice, *Federal Register* 76, no. 246 (December 22, 2011), <https://www.gpo.gov/fdsys/pkg/FR-2011-12-22/html/2011-32775.htm>.

important antimicrobials in animals.¹⁷⁷ The proposed legislation is reminiscent of the hearing text from the 1977 proposal. The bill reads:

With respect to a medically important antimicrobial (as defined in subsection (q)), the applicant has failed to demonstrate that there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance that is attributable, in whole or in part to the nontherapeutic use (as defined in subsection (q)) of the medically important antimicrobial or drug.¹⁷⁸

The bill also includes a phased elimination of nontherapeutic use in animals, which directs the secretary of the Department of Health and Human Services to withdraw the approval of drugs for nontherapeutic use within two years. If the applicants, typically drug manufacturers, can prove that there would be no harm to human health due to antimicrobial resistance, the drugs could still be used for growth promotion or for prophylaxis.¹⁷⁹ If the bill were to pass, it would be illegal to use a medically important antimicrobial in food animals for anything other than treatment of disease or significant risk of disease (i.e., during an outbreak). The law would also require that the dosing would be as minimal as necessary to prevent or reduce the risk of transmission. During the 113th Congress, a previous version of this bill had seventy-eight cosponsors and was backed by more than 450 organizations.¹⁸⁰ Though the concept was first introduced nearly twenty years ago, the bill has yet to be taken up in committee.

As discussed earlier in this chapter, the 1977 FDA proposal sowed opposition to any legislation or regulation of antibiotics in agriculture. On its website, the Animal Health Institute has compiled testimony, reports, videos, and other documentation that

¹⁷⁷ “Text of H.R. 1587: Preservation of Antibiotics for Medical Treatment Act of 2017 (Introduced Version),” GovTrack.us, accessed October 2, 2017, <https://www.govtrack.us/congress/bills/115/hr1587/text>.

¹⁷⁸ GovTrack.us.

¹⁷⁹ GovTrack.us.

¹⁸⁰ Lydia Zuraw, “Rep. Slaughter Reintroduces Preservation of Antibiotics Legislation,” Food Safety News, March 25, 2015, <http://www.foodsafetynews.com/2015/03/rep-slaughter-reintroduces-preservation-of-antibiotics-legislation/>.

provide an opposing viewpoint.¹⁸¹ The institute also published a page titled “Fact or Fiction: Common Antibiotic Myths” to debunk estimates of the amount of antibiotics used in healthy animals, the threat levels of various organisms, and the claim that antibiotics in animals is what causes drug resistance.¹⁸²

According to the Center for Responsive Politics, sixty-one organizations reported lobbying against PAMTA since 2006.¹⁸³ When searching for “Preservation of Antibiotics for Medical Treatment Act” on the center’s website, at the top of the list of lobbyists are the Animal Health Institute, the National Chicken Council, the National Pork Producers Council, the National Milk Producers Federation, the National Turkey Federation, and Elanco Animal Health.¹⁸⁴ The vast majority of the lobbying organizations on the list represent the agricultural and pharmaceutical industries. Additionally, a Healthline news story reports that Pfizer has spent close to \$900,000 to oppose PAMTA.¹⁸⁵ And in 2017, the Animal Health Institute alone spent \$140,000 lobbying against PAMTA.¹⁸⁶

In June 2018, Senators Kirsten Gillibrand, Dianne Feinstein, Elizabeth Warren, and Richard Blumenthal announced a bill that would require the FDA to take additional steps to provide oversight of medically important antibiotics and their use in animals by requiring the secretary of the federal Health and Human Services Department to “review the durations of use.”¹⁸⁷ If the bill passes, a manufacturer would be required to justify approved indications for use in animals for durations greater than twenty-one days. If the

¹⁸¹ “What the Experts Are Saying,” Animal Health Institute, accessed March 13, 2018, <https://ahi.org/issues-advocacy/animal-antibiotics/what-the-experts-are-saying/>.

¹⁸² “Fact or Fiction: Common Antibiotic Myths,” Animal Health Institute, accessed March 13, 2018, <https://ahi.org/issues-advocacy/animal-antibiotics/fact-or-fiction-common-antibiotic-myths/>.

¹⁸³ “Lobbying Spending Database,” OpenSecrets, accessed March 13, 2018, <https://www.opensecrets.org/lobby/lookup.php>.

¹⁸⁴ OpenSecrets.

¹⁸⁵ Brian Krans, “Why Antibiotics Legislation Hasn’t Passed,” Healthline, June 22, 2014, <https://www.healthline.com/health/antibiotics/politics-pork-and-poultry-why-legislation-has-not-passed>.

¹⁸⁶ “Animal Health Institute, 2017,” OpenSecrets, accessed March 13, 2018, https://www.opensecrets.org/lobby/clientissues_spec.php?id=D000047156&year=2017&spec=ANI.

¹⁸⁷ Strengthening Antibiotic Oversight Act, 115th Cong. 2 (2018), <https://www.warren.senate.gov/imo/media/doc/Strengthening%20Antibiotic%20Oversight%20Act%20-%20final%20text.pdf>.

rationale is not considered to be “scientifically justified” or if it is found that the disease can be treated or prevented through other avenues after twenty-one days of treatment, the secretary must withdraw the approval that allows continued use.¹⁸⁸ The bill also instructs the FDA to examine antibiotics delivered to farms by reporting on data collected from veterinary feed directives and feed distribution reports. As of the writing of this thesis, the bill has only been introduced in the Senate and referred to the Committee on Health, Education, Labor, and Pensions.¹⁸⁹

B. ACTION PLANS AND GUIDANCE

While there has not yet been congressional action, the FDA and Department of Agriculture have joined the conversation with more urgency in recent years.

1. Food and Drug Administration: Guidance for Industry

In 2003, the FDA released guidance related to antimicrobial resistance. The document, titled “Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,” recommends an approach during the drug application process to evaluate new antimicrobial animal drugs against bacteria they are not intended to treat, referred to as “non-target bacteria.”¹⁹⁰ The guidance document’s scope is limited to new drugs that, when used, could potentially result in resistant foodborne pathogens. The agency recommends a pre-application risk assessment approach for all uses of new antimicrobial drugs to be administered with food animals. Drug manufacturers are not required to use this risk-assessment process, but those who wish to are advised to submit a hazard characterization based on information about the drug’s bacterial resistance.¹⁹¹

¹⁸⁸ Strengthening Antibiotic Oversight Act.

¹⁸⁹ “Strengthening Antibiotic Oversight Act,” S.3099, 115th Cong. (June 20, 2018), <https://www.congress.gov/bill/115th-congress/senate-bill/3099/committees>.

¹⁹⁰ Food and Drug Administration (FDA) Center for Veterinary Medicine, “Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern” (meeting minutes, Minor Use Animal Drug Program, 2010), 2, http://www.nrsp7.org/Minutes/2010/Fall2010_sm.pdf.

¹⁹¹ FDA Center for Veterinary Medicine, 8.

The sponsor also has the opportunity to identify emerging science or gaps in data that may be applicable to the hazard characterization, which allows a manufacturer to indicate that more research is needed to fully document potential food safety hazards.¹⁹² Once the FDA evaluates the hazard characterization, the agency works with the sponsor to determine if a risk assessment should be completed.¹⁹³ The final step in this process is the FDA’s determination of risk estimation, during which the agency alerts the sponsor to apply certain risk management principles when using the drug.¹⁹⁴

One year later, in 2004, the FDA released “Guidance for Industry #144: Pre-approval for Registration of new Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance.” The process detailed in the document is also not mandatory; it outlines recommended data types that should be used to characterize any potential resistance development when registering a product for use in food animals.¹⁹⁵ The FDA recommends providing basic information about the drug, such as the class of the drug, the type of action the drug takes on the antimicrobial spectrum of activity, the resistance mechanism, the molecular genetic basis of resistance to the antimicrobial drug, occurrence and rate of transfer of resistance genes, cross-resistance, co-resistance, and pharmacokinetic data.¹⁹⁶ The agency suggests that sponsors—during the product registration process—should focus on describing this information in relation to foodborne pathogens after the drug is administered to the animal.¹⁹⁷

¹⁹² FDA Center for Veterinary Medicine, 9.

¹⁹³ FDA Center for Veterinary Medicine, 152, 10.

¹⁹⁴ FDA Center for Veterinary Medicine.

¹⁹⁵ FDA Center for Veterinary Medicine, “Guidance for Industry #144: Pre-approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance” (guidance document, Food and Drug Administration, 2004), 4, <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052524.pdf>.

¹⁹⁶ FDA Center for Veterinary Medicine, 5–7.

¹⁹⁷ FDA Center for Veterinary Medicine, 10.

Several years later, in 2012, the FDA released guidance for industry aimed at addressing sensible antimicrobial use in food animals. The framework in “Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals” is intended to limit the use of antimicrobials in food animals for non-therapeutic means via voluntary measures:

In order to minimize the development of antibiotic resistance, FDA believes that it is important to ensure the judicious use of medically important antimicrobial drugs in animal agriculture. We recommend several steps to accomplish this including voluntary measures that would limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation. Such limitations would reduce overall medically important antimicrobial drug use levels, thereby reducing antimicrobial resistance selection pressure, while still maintaining the availability of these drugs for appropriate use.¹⁹⁸

Included in the guidance is a literature review as well as a summary of scientific studies examining the risks of using medically important antimicrobial drugs in livestock. The FDA concludes that all the strategies to slow antimicrobial resistance are necessary, and that the agency must take a more proactive approach toward the use of medically important antimicrobial drugs.¹⁹⁹

The “Guidance for Industry #209 document” also recommends two voluntary principles on the judicious use of antimicrobials in livestock. The first principle states, “The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.”²⁰⁰ The agency opines that antimicrobials for growth promotion and feed efficiency are not judicious uses and encourages uses that align with prevention and treatment of disease in food animals. As long as a veterinarian is involved with the use of medically important

¹⁹⁸ FDA Center for Veterinary Medicine, “Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals” (guidance document, Food and Drug Administration, 2012), 22, <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf>.

¹⁹⁹ FDA Center for Veterinary Medicine, 20.

²⁰⁰ FDA Center for Veterinary Medicine, 21.

antimicrobial drugs, the FDA believes that use for disease prevention is appropriate. The second principle is, “The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.”²⁰¹ The FDA believes that veterinarians should be involved in decision-making regarding the use of antimicrobials of medical importance, and encourages a phased increase in veterinary involvement, again on a voluntary basis.

A year later, the FDA issued “Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209.” This document explains how to submit new animal drug applications in accordance with the principles outlined in the #209 guidance. It defines what constitutes appropriate therapeutic use of antibiotics in food animals, states that veterinary oversight is needed to use antibiotics as prophylaxis, and specifies that any new drug uses should be accompanied by dosing duration and amount on the drug label.²⁰²

In the #213 guidance, the FDA also indicates that it will work with any drug sponsors interested in voluntarily revising their approved drug labeling to remove “production” uses of their medically important antimicrobial drugs.²⁰³ The FDA recommends that drug manufacturers revise the status of these drugs (when they are included in feed), which are currently available over the counter; instead, they recommend veterinary oversight through a veterinary feed directive, and a prescription if the drugs will be included in drinking water.²⁰⁴ The agency recognized that the veterinary feed directive regulations needed to be changed to facilitate easier

²⁰¹ FDA Center for Veterinary Medicine, 22.

²⁰² FDA Center for Veterinary Medicine, “Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209” (guidance document, Food and Drug Administration, 2013), 4–5, <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf>.

²⁰³ FDA Center for Veterinary Medicine, 5.

²⁰⁴ FDA Center for Veterinary Medicine, 6–7.

implementation of this voluntary change and minimize adverse impacts on the industry.²⁰⁵ The FDA published a final rule in June 2015 and also issued “Guidance for Industry #120: Veterinary Feed Directive Regulation Questions and Answers,” which provided guidance on the published rule that would help the industry make the voluntary changes.²⁰⁶

To measure if its strategy is working, the FDA reviews data, published in its annual summary report, on the sale and distribution of antimicrobials.²⁰⁷ The agency also largely funds the National Antimicrobial Resistance Monitoring System (NARMS), which collects data on antimicrobial resistance, which in turn allows the agency to review trends in antimicrobial resistance.²⁰⁸ This system is discussed later in the chapter.

While the FDA has made an effort to provide direction on how to reduce the use of medically important antibiotics in U.S. livestock, the effort is strictly voluntary. On the FDA’s website, a page titled “Strategy on Antimicrobial Resistance, Question and Answers” explains that the “FDA believes that the collaborative [voluntary] approach is the fastest way to implement the changes outlined in Guidance #213.”²⁰⁹ The FDA goes on to say that

initiating regulatory action would require the agency proceed on a product by product basis, would likely create significantly more disruption to animal health/agriculture industry, and would require significantly more resources and time to implement. This collaborative approach, as outlined in GFI #213, is the quickest way to achieve the greatest degree of public health protection.²¹⁰

²⁰⁵ FDA Center for Veterinary Medicine, 7.

²⁰⁶ FDA Center for Veterinary Medicine, “Guidance for Industry #233: Veterinary Feed Directive Common Format Questions and Answers” (guidance document, Food and Drug Administration, 2016), <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM474640.pdf>.

²⁰⁷ “FDA’s Strategy on Antimicrobial Resistance—Questions and Answers,” FDA, accessed August 20, 2017, <https://www.fda.gov/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216939.htm>.

²⁰⁸ Kahn, *One Health*.

²⁰⁹ FDA, “FDA’s Strategy on Antimicrobial Resistance.”

²¹⁰ FDA.

Although public health advocates were skeptical of a voluntary approach, if the FDA had reason to be confident about a voluntary strategy—it has successfully negotiated with all drug sponsors.²¹¹ This effort is discussed in greater detail later in this chapter.

The FDA addresses the idea that animal producers could use medically important antimicrobials for production purposes under the guise of preventing disease; once the labeling is voluntarily changed, the FDA therefore says, the products can no longer be used in an off-label manner, including for nontherapeutic use.²¹² The agency also indicates that with oversight of licensed veterinarians, these products would not be used for production purposes and it would be up to a veterinarian, based on his or her training and knowledge, to determine when to preventively treat animals against infection.²¹³

Even though many advocacy and public health organizations have applauded the FDA's efforts, they argue that these efforts might not go far enough. This guidance demonstrates only recommendations from the FDA and does not address routine use of antibiotics for prophylaxis without requiring evidence of a disease risk. The Pew Charitable Trusts have lauded the effort as an “important step in ensuring the judicious use of [antibiotics].”²¹⁴ However, the organization also asserts that there are problems with the approach; Pew found that nearly 30 percent of relevant drug labels do not have defined durations of use—most commonly Tylosin and tetracyclines.²¹⁵ The FDA solicited comments to establish durations of use for medically important antibiotics; the information was due at the end of December 2016, but it is unclear if the FDA has plans

²¹¹ “FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance,” FDA, January 3, 2017, <https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm>.

²¹² FDA, “FDA’s Strategy on Antimicrobial Resistance.”

²¹³ FDA.

²¹⁴ “Judicious Animal Antibiotic Use Requires Drug Label Refinements,” Pew, October 4, 2016, <http://pew.org/2dqrjCo>.

²¹⁵ Pew.

to require labeling changes to include duration of use for all medically important antibiotics.²¹⁶

2. United States Department of Agriculture: Antimicrobial Resistance Action Plan

The United States Department of Agriculture (USDA) does not have any regulatory authority regarding antimicrobial use in food animals; the FDA, not the USDA, is the governing agency responsible for the approval of new drugs and their uses as well as for setting the allowable levels of drugs in the tissues of food animals. However, the USDA recognizes that it must make coordinated efforts to address the issue given the urgency of antibiotic resistance.²¹⁷ With only prior “patchwork” efforts, the USDA saw a need to create a strategic vision for its part in the response to slowing antibiotic resistance.²¹⁸

In 2014, the USDA released an action plan for antimicrobial resistance.²¹⁹ In the plan, the agency argues that even though it has no regulatory authority, it has been at the table, partnering with other governmental agencies as well as industry to mitigate antimicrobial resistance. The agency released this action plan under the realization that its contribution has been limited.

For nearly two decades, USDA has been actively involved in surveillance, basic and applied research, and education and outreach to assess levels of AMR [Antimicrobial Resistance], to develop effective mitigation strategies. These activities have made important individual agency contributions to understanding the role of animal agriculture in AMR and to minimizing its selection and spread. However, these efforts lacked integration and prioritization at the departmental level. This has ultimately

²¹⁶ FDA, “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Establishing Appropriate Durations of Therapeutic Administration; Request for Comments,” *Federal Register*, September 14, 2016, <https://www.federalregister.gov/documents/2016/09/14/2016-21972/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing>.

²¹⁷ United States Department of Agriculture (USDA), “Antimicrobial Resistance Action Plan” (planning document, United States Department of Agriculture, June 2014), 1, <https://www.usda.gov/sites/default/files/documents/usda-antimicrobial-resistance-action-plan.pdf>.

²¹⁸ USDA, 2.

²¹⁹ USDA, 2.

limited their overall impact. USDA recognizes that considerable work remains, and there is a growing sense of urgency to address this problem. Through this action plan, USDA describes a roadmap for a comprehensive, integrated approach to develop effective, practical mitigation strategies for animal agriculture to help prolong the effectiveness of antibiotics used to treat people and animals.²²⁰

The action plan outlines three objectives that are foundational in the development of strategies to slow antimicrobial resistance:

- Determine and/or model patterns, purposes, and impacts of antibiotic use in food-producing animals.
- Monitor antibiotic drug susceptibilities of selected bacterial organisms in food-producing animals, production environments, and meat and poultry.
- Identify feasible management practices, alternatives to antibiotic use, and other mitigations to reduce [antimicrobial resistance] with food-producing animals and their production environments.²²¹

The USDA believes more work is needed to understand the agricultural role in antimicrobial resistance. The agency wishes to “address recognized knowledge gaps and develop effective, practical mitigation strategies that will help to prolong the effectiveness of antibiotics to treat both people and animals.”²²² The action plan outlines how the agency will gain better information on antibiotic resistance in food animals through surveillance, research and development, and education and outreach. The plan also outlines a proposal for surveillance and longitudinal studies of volunteer animal producers. The studies would collect data on antimicrobial drug use as well as information on farming practices through new surveys. The surveillance also requires biological sampling of the products at slaughter to test for antimicrobial resistant bacteria.²²³ In addition to the new studies, the plan outlines adding questions about antibiotic drug use and farm management practices to existing surveys. These are voluntary surveys and the data obtained from them will allow analysts to monitor trends

²²⁰ USDA, 4.

²²¹ USDA, 5.

²²² USDA, 5.

²²³ USDA, 10.

over time. This information could measure the impact of policy implementation and also help identify areas where mitigation measures are needed to slow antimicrobial resistance.²²⁴

An additional proposal in the USDA plan is to routinely perform antibiotic susceptibility testing on animal pathogens that are reported from veterinary diagnostic laboratories. The recommendation is to develop a voluntary system that would link all the gathered data to help veterinarians select appropriate treatment; it could also provide new information about emerging animal health threats and potentially new zoonotic or foodborne threats that could affect human health.²²⁵

Further, the USDA believes additional research is needed on microbial ecology in relation to several farm management practices, including feeding, administration of drugs, physical environment, and transporting animals.²²⁶ The agency argues that more research is needed to understand the causes behind antimicrobial resistance in food animals; however, the action plan is vague regarding how the research should be completed. Furthermore, the agency discusses the need to develop new antimicrobials and promote the use of alternatives to antibiotics to meet the challenges posed by antimicrobial resistance.

The USDA also recommends partnering with researchers in academia and government to advance new technologies and approaches to animal production that do not contribute to antimicrobial resistance. The USDA proposes working more closely with the CDC on education and outreach surrounding judicious use of antimicrobials. Specifically, the plan calls for a reinstatement of the “Get Smart: Know When Antibiotics Work on the Farm” campaign, which aimed to reach farmers and veterinarians and was recently discontinued.²²⁷ The plan also includes a proposal for an online presence that provides information about judicious antimicrobial use and summarizes the data gathered

²²⁴ USDA, 10.

²²⁵ USDA, 10–11.

²²⁶ USDA, 11.

²²⁷ USDA, 12.

from the other proposals. The tool would include best quality assurance practices gathered from various agriculture sectors.

Finally, the plan includes a proposal to make a maximum of \$6 million available through a competitive request-for-applications process to develop integrated projects to address antimicrobial resistance. A few examples provided in the plan are outreach and education materials, tools such as websites that meet various target audience needs, and new studies that examine the efficacy of research or education and outreach interventions related to antimicrobial resistance.²²⁸

It is unclear if the USDA has worked with partners or stakeholders to implement any of these strategies. A 2016 audit by its Office of Inspector General found that the USDA’s antibiotic resistance goals and objectives are ill-defined, which makes it difficult to measure progress or effectiveness of the agency’s efforts.²²⁹ The audit includes responses to all of the findings and timelines for completion; however, again, it is unclear if these activities have continued since the publication of the audit.

C. SURVEILLANCE SYSTEMS AND DATA COLLECTION

The United States does not have a comprehensive system—like those in Denmark and the Netherlands—to collect good data on antibiotic use or surveillance on resistance in animals or humans. This section discusses systems and projects that were initiated by federal agencies to measure antibiotic resistance but that are narrow in scope.

1. USDA National Animal Health Monitoring System (NAHMS): Antimicrobial Resistance Studies

According to the USDA’s webpage on the topic, the National Animals Health Monitoring System (NAHMS) was launched in 1983 to collect data on agricultural productivity, as well as animal health and management.²³⁰ Formal NAHMS studies on

²²⁸ USDA, 12.

²²⁹ USDA Office of Inspector General, “USDA’s Response to Antibiotic Resistance” (audit, United States Department of Agriculture, 2016), 2, <https://www.usda.gov/oig/webdocs/50601-0004-31.pdf>.

²³⁰ “About NAHMS,” USDA, accessed February 17, 2018, <https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms/about>.

the nation’s agricultural sectors did not begin until 1990, after several years of designing the program.²³¹ Today, NAHMS develops national data on disease exposure as well as incidence.²³²

One publication based on NAHMS data, released in July 2009, identifies the prevalence of *Salmonella* and *Campylobacter* on U.S. dairy farms and compares prevalence and resistance between 1996 and 2007, along with susceptibility.²³³ The authors found that the prevalence of *Salmonella* increased over the three study years—1996, 2002, and 2007. However, antimicrobial resistance was minimal and did not significantly increase over time among *Salmonella* isolates.²³⁴ In addition, *Campylobacter* was prevalent in most of the dairy farms observed in the study. Susceptibility testing was conducted on *Campylobacter jejuni* isolates in 2002 and in 2007 and showed that there was clear resistance to tetracycline; 47.4 percent of isolates were resistant in 2002 and 62.9 percent had become resistant by 2007.²³⁵

A more recent publication, released in April 2016, describes a 2012 NAHMS study on 2,119 randomly selected swine farms in thirteen states.²³⁶ The aim of the study was to identify the extent to which food animals, pigs in particular, carry resistant genes that could be transferred to humans. The researchers conducted two interviews on each site and collected biological specimens on some of the sites. *E. coli* was found on all of the sites, which is not surprising—*E. coli* is one of the many organisms that normally live in food animals. However, the researchers found that 92.8 percent of the *E. coli* from the specimens was resistant to at least one antimicrobial, with 91.2 percent resistant to

²³¹ “Collecting Vital Information on Animal Health,” USDA, April 2010, https://www.aphis.usda.gov/animal_health/nahms/downloads/NAHMS_brochure.pdf.

²³² USDA.

²³³ “Salmonella and Campylobacter on U.S. Dairy Operations 1996–2007,” USDA, July 2009, 1, https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_is_SalCampy.pdf.

²³⁴ USDA, 2.

²³⁵ USDA, 4.

²³⁶ “Escherichia Coli on U.S. Swine Sites: Prevalence and Antimicrobial Drug Susceptibility,” USDA, April 2016, 1, https://www.aphis.usda.gov/animal_health/nahms/swine/downloads/swine2012/Swine2012_is_Ecoli.pdf.

tetracycline alone. There was low resistance to ciprofloxacin, 0.4 percent of isolates, and 1.6 percent of isolates were resistant to amoxicillin.²³⁷

Two additional antimicrobial use studies are currently listed on the program's website: the "NAHMS Antimicrobial Use on U.S. Feedlots, 2017 Study" and the "NAHMS Antimicrobial Use on U.S. Swine Operations, 2017 Study." They were both scheduled to be conducted from May through August of 2017.²³⁸ The aim of the studies is to review the use of antimicrobials on feedlots containing at least fifty animals and to examine antimicrobial use on U.S. swine farms containing at least 1,000 animals.²³⁹ Both projects are new fields of study to be conducted every other year.²⁴⁰ These studies are outcomes of the USDA's Antimicrobial Resistance Action Plan and the projects will provide baseline data on antimicrobial use practices that existed prior to the feed changes the FDA implemented, as the information gathered is about antimicrobial use during 2016.²⁴¹ To conduct each study, USDA veterinarians were slated to interview feedlot operators who volunteered to participate in the study. The data collection phase for each project concluded in August 2017. As of the publication of this thesis, study results for both projects have not been published.

2. National Antimicrobial Resistance Monitoring System (NARMS)

Established in 1996 by the FDA, NARMS is a national surveillance system that tracks antibiotic susceptibility of enteric bacteria.²⁴² The program, which collects data on humans, animals, and retail meats, is a partnership between the FDA, USDA, and CDC to

²³⁷ USDA, 2.

²³⁸ "NAHMS Antimicrobial Use on U.S. Feedlots, 2017 Study," USDA, April 2017, https://www.aphis.usda.gov/animal_health/nahms/amr/downloads/FeedlotLaunchinfo.pdf; "NAHMS Antimicrobial Use on U.S. Swine Operations, 2017 Study," USDA, April 2017, https://www.aphis.usda.gov/animal_health/nahms/amr/downloads/SwineLaunchinfo.pdf.

²³⁹ USDA, "NAHMS Antimicrobial Use on U.S. Feedlots"; USDA, "NAHMS Antimicrobial Use on U.S. Swine Operations."

²⁴⁰ USDA, "NAHMS Antimicrobial Use on U.S. Feedlots"; USDA, "NAHMS Antimicrobial Use on U.S. Swine Operations."

²⁴¹ USDA, "NAHMS Antimicrobial Use on U.S. Feedlots."

²⁴² "The National Antimicrobial Resistance Monitoring System," FDA, accessed February 17, 2018, <https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm>.

monitor resistance among these specific foodborne bacteria: *Salmonella*, *Escherichia coli*, *Campylobacter*, and *Enterococcus*.²⁴³ The program performs whole-genome sequencing to analyze these bacteria by serotyping and speciation, which will contribute to the understanding of how resistant organisms can be distributed in the food chain.²⁴⁴

NARMS publishes annual data on its website. There are several dashboards on the site that allow users to view resistance by species and serotype or by sample source and place, resistance genes in *Salmonella*, multidrug resistance by antimicrobial agents, and multidrug resistance by the number of antimicrobial classes.²⁴⁵ In addition, visitors can download data on human clinical cases, retail meats, and animals. Another interactive online tool, *NARMS Now: Human Data*, which is hosted by the CDC, shows data on resistant bacteria that have been isolated from humans. On the site, the user can select the bacteria and serotype, the antibiotic, and a timeframe. Then, the user can select how the tool will display the resistance information by year and by state. It can be displayed as a map of the United States, with states shaded different colors depending on the percentage of isolates that are resistant, or it can be displayed in a table. Nationwide resistance can also be displayed by year in a graph or table.²⁴⁶

D. CONCLUSION

Reviewing the United States' efforts as a national package, the strategies certainly do not go as far as other countries' have. Perhaps the way policy decisions are discussed in European countries might explain the difference. On this issue in particular, the rationale for the European Union banning the use of antimicrobial growth promoters was based on the precautionary principle: "a precautionary measure to minimize the risk of

²⁴³ "About NARMS," FDA, accessed February 2, 2018, <https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059089.htm>.

²⁴⁴ FDA.

²⁴⁵ "NARMS Now: Integrated Data," FDA, last updated November 1, 2017, <https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm416741.htm>.

²⁴⁶ "NARMS Now: Human Data," CDC, accessed February 10, 2018, <https://wwwn.cdc.gov/narmsnow/>.

development of resistant bacteria and to preserve the efficacy of certain antibiotics used in human medicine.”²⁴⁷ This principle is not widely accepted in the United States for regulatory policymaking.²⁴⁸

Even though evidence links antibiotic use to antibiotic resistance, the industry purports that there is no proof linking the use of antibiotics in agriculture to drug-resistant infections in humans. Presumably because of industry pushback, U.S. strategies have not been implemented, and many of the regulations are voluntary. The ban of the off-label uses of cephalosporins is a positive step toward using fewer medically important drugs for humans in agriculture; however, this is likely not enough to make meaningful change. Another successful strategy appears to be the “Guidance for Industry #213” document. Again, however, this was a voluntary measure to transition medically important antimicrobials used in feed or water from over-the-counter status to prescription status, and to prohibit the use of medically important antimicrobials for growth promotion.²⁴⁹

The FDA issued a press release on January 3, 2017, with an update on the implementation.²⁵⁰ In the release, the agency commends the pharmaceutical industry for working with the FDA to align its products with the recommended guidance.²⁵¹ All thirty-one drug applications that indicated use of antimicrobial products for growth promotion were withdrawn or re-labeled without that particular use listed, meaning antimicrobials can no longer legally be used as growth promoters in the United States.²⁵² In addition, there were 292 drug applications that fell into the category of medically important antimicrobials fitting the criteria to transition to prescription or veterinary feed

²⁴⁷ Catherine J. Ball, “The Precautionary Principle: Policy Lates and Antimicrobial Resistance,” *Biochemical Society* (blog), March 17, 2014, <https://biochemicalsociety.wordpress.com/2014/03/17/the-precautionary-principle-policy-lates-and-antimicrobial-resistance/>.

²⁴⁸ John Graham, “The Perils of the Precautionary Principle: Lessons from the American and European Experience,” The Heritage Foundation, accessed March 14, 2018, </government-regulation/report/the-perils-the-precautionary-principle-lessons-the-american-and>.

²⁴⁹ FDA, “FDA Announces Implementation of GFI #213.”

²⁵⁰ FDA.

²⁵¹ FDA.

²⁵² FDA.

directive status.²⁵³ Of those applications, 93 were converted from over-the-counter to prescription, and 115 products were converted to veterinary feed directive status.²⁵⁴ This means all medically important antimicrobials being used in animal production have been modified to require veterinary oversight in some way.

What effect will this have on industry? It difficult to know—and it is unclear if the FDA has plans in place to evaluate these policies and their effects on the agriculture, veterinary, and pharmaceutical industries in the future. That said, in an interview with the *Wall Street Journal* in 2013, the chief executive of Zoetis, an animal health company formerly part of Pfizer, went on record saying that the FDA approach of eliminating growth-promotion indication from the label on feed “will not have a significant impact on our revenues.”²⁵⁵

What effect will this have on slowing the threat? The federal government may find it very difficult to measure. The United States has a limited set of data for comparison. The monitoring systems in place are specific to foodborne illness, sales data, or special studies conducted on an ad hoc basis. Based on the experiences of the other countries studied in this thesis, the United States may not see any declines in the use of antibiotics. There were no targets set for reducing overall use, nor were there regulations or strong guidance addressing the routine use of antimicrobials as disease prevention; will farmers continue to use medically important drugs as tools for disease prevention to achieve the same outcomes? Without a comprehensive data collection system, it will be impossible to monitor trends. The U.S. government will need to continue to rely on the antimicrobial sales data that it has used for decades.

²⁵³ FDA.

²⁵⁴ FDA.

²⁵⁵ Peter Loftus, “Zoetis Chief Leads Animal-Health Firm Following Split from Pfizer,” *Wall Street Journal*, November 19, 2013, <https://www.wsj.com/articles/zoetis-chief-leads-animalhealth-firm-following-split-from-pfizer-1384900462>.

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V. CASE STUDY: UNITED STATES

In the absence of national requirements, states are exploring legislation with the aim of preserving antimicrobials. California has enacted legislation that is based largely on antibiotic bans in Europe. It is interesting to note that California, the top agriculture-producing state in the nation in 2016, was able to pass such legislation.²⁵⁶ Only seven legislators voted against the bill, which suggests that producers were not opposed.²⁵⁷ While this bill may not be a true indicator of support for a national ban, it does offer evidence that such legislation may pass in other agriculture states. Maryland, however, a much smaller producer, proposed similar standards that were ultimately not adopted due to pressures from the farm lobby.

While this chapter only examines California's and Maryland's policies, a 2017 tracking project from the Association of State and Territorial Health Officials shows that several states have proposed legislation aimed at slowing antibiotic resistance. Only Maryland and Oregon proposed laws related to antimicrobials in the agriculture industry. Arkansas and Texas also proposed legislation, but the bills focus on the human health-care industry. While it is possible that other states may be exploring legislation, the position of most states is not known.

A. CALIFORNIA

In the absence of federal policy, California has sought state-level legislation to slow the threat of antibiotic resistance. California is the first state in the nation to implement a law limiting the use of antibiotics in livestock.

1. Legislative Ban

California Governor Jerry Brown signed legislation on October 10, 2015, banning the use of medically important antimicrobials as growth promoters or as a means to

²⁵⁶ "FAQs," USDA, accessed August 11, 2018, <https://www.ers.usda.gov/faqs/#Q1>.

²⁵⁷ "Could an Antibiotic Ban Come to the United States?," NYC Food Policy Center, October 19, 2016, <http://www.nycfoodpolicy.org/antibiotic-ban-come-united-states/>.

improve feed efficiency. According to a justification provided in a budget change request, the law was proposed to address the public health implications of use and overuse of antibiotics in livestock, which contributes to antibiotic resistance.²⁵⁸ Under this law, “medically important drugs” are considered those used by humans and that are necessary to treat or control the spread of disease, as well as those necessary for surgery and medical procedures.²⁵⁹ The bill prohibits the administration of medically important antimicrobial drugs “in a regular pattern” and states that the drugs can only be used under a prescription or veterinary feed directive through a veterinarian.²⁶⁰

The legislation also includes penalties for violations to the law, including \$250 per-day fines and \$500 per day for second violations. Violators are required to attend and complete an educational program on the judicious use of medically important antimicrobials within ninety days of the violation. Veterinarians who do not comply with the law as determined by the Veterinary Medical Board are subject to disciplinary sanctions under the Veterinary Medicine Practice Act.²⁶¹

2. Antimicrobial Dispensing

Under California’s legislative ban, farmers and veterinarians must establish a “veterinarian-client-patient relationship,” or VCPR. VCPRs are considered valid once a veterinarian examines the livestock or visits the farm when medically necessary.²⁶² The vet must be knowledgeable enough about the animals to diagnose medical conditions. When making medical judgements regarding the health of animals, the veterinarian must communicate with the farmer about the appropriate course of treatment and cannot prescribe drugs for a duration that is inconsistent with the medical or drug type. In

²⁵⁸ California Department of Food and Agriculture, “State of California Budget Change Proposal: 8570-007-BCP-2017-GB” (proposal, State of California, December 7, 2016), 2, http://web1a.esd.dof.ca.gov/Documents/bcp/1718/FY1718_ORG8570_BCP1186.pdf.

²⁵⁹ Livestock: Use of Antimicrobial Drugs, Pub. L. No. 27, Ch. 758 (2015), http://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201520160SB27.

²⁶⁰ Livestock: Use of Antimicrobial Drugs.

²⁶¹ Livestock: Use of Antimicrobial Drugs.

²⁶² Veterinarian-Client-Patient Relationship, 16 CCR § 2032.1, accessed January 27, 2018, [https://govt.westlaw.com/calregs/Document/I634D42502EDB11E39C87E838B6ADC7D8?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=\(sc.Default\)](https://govt.westlaw.com/calregs/Document/I634D42502EDB11E39C87E838B6ADC7D8?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=(sc.Default)).

addition, veterinarians can only prescribe drugs for use within twelve months of the last examination—meaning veterinarians cannot issue a script for potential future problems without an examination.²⁶³ To maintain a license, veterinarians must also “complete a minimum of one credit hour of continuing education on the judicious use of medically important antimicrobial drugs every four years as part of his or her continuing education requirements.”²⁶⁴ To meet this requirement, vets may complete the United States Department of Agriculture’s training program called Module 23: Use of Antibiotics in Animals.

Medically important antimicrobial drugs can only be sold by licensed retailers with a prescription or with a veterinary feed directive from a licensed vet. This restriction includes drugs that had previously been sold over the counter. As of January 1, 2018, additional regulations have been published that clarify which retail establishments are required to have a restricted livestock drug license in order to sell medically important antimicrobial drugs; the regulations also clarify requirements for record keeping, drug storage, and drug labeling.²⁶⁵

Furthermore, the law charges the California Department of Food and Agriculture to work with stakeholders to develop “antimicrobial stewardship guidelines and best management practices for veterinarians, as well as livestock owners and their employees who are involved with administering medically important antimicrobial drugs.”²⁶⁶ This guidance must include alternatives to the use of medically important antimicrobials such as vaccination, good hygiene, and farm management practices.²⁶⁷ The bill defines “antimicrobial stewardship” as a commitment to

use medically important antimicrobial drugs only when necessary to treat, control, and, in some cases, prevent disease, to select the appropriate

²⁶³ Veterinarian-Client-Patient Relationship.

²⁶⁴ “Animal Health,” California Department of Food and Agriculture, accessed January 15, 2018, <https://www.cdffa.ca.gov/ahfss/AUS/AnimalHealth.html>.

²⁶⁵ Sales of Restricted Livestock Drugs, 3 CCR, Div. 5, Ch. 1 (2018), www.cdffa.ca.gov/is/docs/AUS_AdoptedText.pdf.

²⁶⁶ Livestock: Use of Antimicrobial Drugs.

²⁶⁷ Livestock: Use of Antimicrobial Drugs.

medically important antimicrobial drug and the appropriate dose, duration and route of administration; and to use medically important antimicrobial drugs for the shortest duration necessary and to administer them to the fewest animals necessary.²⁶⁸

3. Monitoring Antibiotic Use and Resistance

California's legislation also requires the state's Department of Food and Agriculture to begin a monitoring program that will gather information on the sale and use of antibiotics, along with information on antibiotic-resistant bacteria and livestock management practices. The department is required to work with the USDA, FDA, and CDC to enhance national surveillance efforts. The department must also collect regionally representative information from all of California's major livestock sectors and segments of the food production chain and ensure confidentiality within the monitoring system.

4. Implementation

The California Department of Food and Agriculture created a strategic plan for its two-year implementation period (2016–2017). In terms of the regulated-use component of this legislation, the implementation activities focused on administrative rule development and outreach activities to achieve compliance goals. The department has reviewed the statutory language to identify gaps in existing and new regulations. The goal was to finalize all regulations before 2018 and it appears all regulations have been published as of the writing of this thesis. The estimated total cost to implement the regulations is \$4 million, which includes \$1.393 million in California state tax dollars and an additional eight positions to be added to the California Department of Food and Agriculture.²⁶⁹

²⁶⁸ Livestock: Use of Antimicrobial Drugs.

²⁶⁹ Annette Jones, "California Senate Bill 27 Livestock: Use of Antimicrobial Drugs (An Interesting Journey)," National Institute for Animal Agriculture, accessed April 5, 2016, https://animalagriculture.org/resources/Documents/Conf%20-%20Symp/Conferences/2016%20Annual%20Conferene/Presentations/Jones_%20Annette_ABX.pdf.

In terms of outreach activities, the department has developed materials such as brochures, completed scores of presentations, and developed a web and social media presence.²⁷⁰ As of November 27, 2017, the department had visited approximately 340 retailers to further educate them on the upcoming law changes; this ensured that both licensed and unlicensed retailers were aware that medically important drugs are only to be sold under a veterinary feed directive or prescription.²⁷¹ Another objective of the strategic plan is to gather baseline compliance data from industry partners to develop a point of reference when evaluating future compliance. As of October 2018, the department had visited feed mills, distributors, and other facilities to provide outreach and education on the laws.²⁷² The department also provided technical assistance and advice regarding any changes feed mills needed to make with their veterinary feed directives to be in compliance with the new law.²⁷³

What is remarkable about this legislation is that California had a great window of opportunity to enact it. The environment evolved over many years, which allowed for discussion and collaboration. Interestingly, the majority of the opposition did not surround typical arguments that have been made at the national level; instead, the industry partners who provided comments or testified on early versions of the bill argued that the proposed legislation did not go far enough.²⁷⁴ Most of the industry partners remained neutral on the bill and only seven lawmakers did not vote in favor of it.²⁷⁵

²⁷⁰ “Antimicrobial Use and Stewardship Updates,” California Department of Food and Agriculture, November 27, 2017, https://www.cdfa.ca.gov/ahfss/AUS/docs/AUS_Update_Nov_2017.pdf.

²⁷¹ California Department of Food and Agriculture, “Antimicrobial Use and Stewardship Strategic Plan Calendar Year 2017” (planning document, California Department of Food and Agriculture, 2017), <https://www.cdfa.ca.gov/ahfss/AUS/docs/AUS-StrategicPlan2017.pdf>.

²⁷² “Antimicrobial Use and Stewardship,” California Department of Food and Agriculture, October 2, 2018, www.cdfa.ca.gov/ahfss/aus/docs/aus_update_Oct_2018.pdf.

²⁷³ California Department of Food and Agriculture, “Antimicrobial Use and Stewardship Updates.”

²⁷⁴ “Bill Analysis: SB 27,” State of California Legislative Council, June 1, 2015, http://www.leginfo.ca.gov/pub/15-16/bill/sen/sb_0001-0050/sb_27_cfa_20150601_193414_sen_floor.html.

²⁷⁵ John Tozzi, “California Enacts Strictest Animal Antibiotic Law in the U.S.,” Bloomberg, October 11, 2015, <https://www.bloomberg.com/news/articles/2015-10-11/california-enacts-strictest-animal-antibiotic-law-in-the-u-s->.

5. Potential Impacts on Industry

As stated previously, the majority of the industry partners remain neutral on the bill for varying reasons. In an interview with KQED News, a representative from the Farm Bureau commented, “We have members who are not able to use antibiotics that they used to, so we recognize the importance of being engaged in the discussion of having antibiotics available and effective in the future.”²⁷⁶ However, the Farm Bureau did not fully support the bill because it requires a veterinarian prescription for antibiotics, and rural producers may not have consistent access to veterinarians.²⁷⁷ Another article, published by Vox, suggests that farmers have been opposed to broad restrictions because of the nuances in determining therapeutic use versus nontherapeutic use.²⁷⁸ Pharmaceutical and agriculture lobbyists have argued that antimicrobial regulation could raise costs for farmers. The California Cattlemen’s Association voiced its concerns about prohibiting over-the-counter antibiotics as well as the potential burden created by requirements to report on farm antimicrobial use.²⁷⁹

Veterinarians who testified at an April 2015 hearing on the bill, and in a letter to the bill’s author, addressed the accessibility concerns from the food producers, stating, “The veterinarian-client relationship is very flexible in terms of how the veterinarian can best serve the client. In fact, a veterinarian may write a prescription for up to one year and develop a protocol for the client to administer the drug in his or her absence.”²⁸⁰ In the same letter, the California Veterinary Medical Association also shared concerns about the burden of reporting antibiotic use and uncertainty around whether reporting would be a breach of the veterinary medicine confidentiality statute. The Agriculture Council of

²⁷⁶ Lisa Aliferis, “Bill Making California Toughest in U.S. on Livestock Antibiotics Now Up to Governor,” KQED News, September 16, 2015, <https://www.kqed.org/stateofhealth/78255/bill-making-california-toughest-in-u-s-on-livestock-antibiotics-now-up-to-governor>.

²⁷⁷ Aliferis.

²⁷⁸ Julia Belluz, “California Enacted the Strictest Law yet on Antibiotic Use in Farms,” Vox, October 10, 2015, <https://www.vox.com/2015/10/10/9489849/california-antibiotic-resistance-sb27>.

²⁷⁹ “CCA Legislative Bulletin,” California Cattlemen’s Association, accessed February 18, 2018, http://www.calcattlemen.org/cca_news/cca_legislative_bulletin.aspx.

²⁸⁰ Valerie R. Fenstermaker, “SB 27 (Hill) - Livestock: Use of Antibiotics,” letter to Senator Jerry Hill, April 14, 2015, <https://cvma.net/wp-content/uploads/2015/04/SB-27-HILL-LTR.pdf>.

California also cited confidentiality concerns on its website when the bill was first introduced.²⁸¹ These issues are all examples of potential impacts that may make the industry hesitant to embrace this legislation and could potentially be examined when or if the California government performs an evaluation on its policy.

6. Assessment

By January 1, 2019, the Department of Food and Agriculture must submit a report to the state legislature outlining its monitoring efforts. The department must determine whether enough of the industry is on board to measure if the law is in fact moving the needle on non-therapeutic antimicrobial use and resistant organisms.²⁸² The complete assessment of this law can only be made after several years of data gathering and observation of trends. It therefore remains to be seen if the California legislation, as enacted, will have an impact on the rates of antibiotic resistance. However, through the monitoring and surveillance report, the Department of Food and Agriculture should have the information it will need to evaluate the effects of this law. The department should also look to evaluate the potential impacts on industry mentioned in the previous section.

B. MARYLAND

Maryland has also enacted legislation aimed at slowing the threat of antibiotic resistance. This section discusses the state's policy approach and the opposition it has encountered.

1. Legislative Ban

Maryland became the second state in the nation to pass legislation limiting routine antibiotic use in certain food animals.²⁸³ The law, effective January 1, 2018, only allows the use of medically important antimicrobial drugs in poultry, pigs, or cattle if a

²⁸¹ "Dairy," Agricultural Council of California," accessed February 18, 2018, <http://www.agcouncil.org/dairy>.

²⁸² Livestock: Use of Antimicrobial Drugs.

²⁸³ Keep Antibiotics Effective Act of 2017, Senate Bill 422, Ch. 788 (2017), http://mgaleg.maryland.gov/2017RS/chapters_noln/Ch_788_sb0422E.pdf.

veterinarian determines that it is necessary to treat or control disease or for a medical procedure. Medically important antimicrobial drugs cannot be used in a “regular pattern.”²⁸⁴ The regulations do not apply to cattle or swine farms selling less than 200 animals per year or poultry operations that sell less than 60,000 birds per year. Under the law, the secretary of the Maryland Department of Agriculture has the authority under the law to impose penalties up to \$2,000 for violations of the regulations. The law also prohibits medically important antimicrobial drugs used for growth promotion, feed efficiency, or weight gain purposes.²⁸⁵

2. Antimicrobial Dispensing

Under the passed legislation, prophylactic use of antibiotics is only allowed after a veterinarian determines that an event has caused a significant disease risk to the herd.²⁸⁶ However, earlier versions of the bill stated that the producer and veterinarian must have an established veterinarian-client-patient relationship as defined by federal code.²⁸⁷ In addition, earlier versions proposed requiring that these drugs are administered to the fewest number of animals possible for the shortest amount of time as stated by the prescription or veterinary feed directive, much like the California legislation. These provisions were struck from the final bill.

3. Monitoring Antibiotic Use and Resistance

The legislation requires the Maryland Department of Agriculture to report state-level data from the USDA, CDC, FDA, and any other appropriate national trade associations, organizations, and councils to the Maryland General Assembly. The reporting must happen each year on December 1, beginning in 2019.²⁸⁸ Earlier versions of the bill proposed that veterinarians and/or farm owners annually submit copies of medically important antimicrobial prescriptions as well as copies of veterinary feed

²⁸⁴ Keep Antibiotics Effective Act.

²⁸⁵ Keep Antibiotics Effective Act.

²⁸⁶ Keep Antibiotics Effective Act.

²⁸⁷ Keep Antibiotics Effective Act.

²⁸⁸ Keep Antibiotics Effective Act.

directives issued during the previous calendar year to the Maryland Department of Agriculture.²⁸⁹ The department would have been required to provide a report detailing all the information to the General Assembly each December.²⁹⁰

4. Opposition

According to news reports, the original version of the bill, which prohibited the use of antibiotics as prophylaxis without a prescription or veterinary feed directive, faced opposition. The bill had also required farmers to submit those prescriptions or directives to the Maryland Department of Agriculture—a measure that was deemed by some to be too onerous.²⁹¹ In addition, the Maryland Farm Bureau opposed the bill because it was considered duplicative to regulations at the federal level; however, the bureau president also stated that the policies would cause more outbreaks that would require antibiotics, which would cause resistance.²⁹² Industry representatives indicated that these measures were unnecessary because the public was already demanding antibiotic-free poultry and the industry is “pretty much headed in that direction, anyway.”²⁹³ Media accounts also report opposition to the bill—which took three years to pass—from the pharmaceutical industry.²⁹⁴

Not all industry members were opposed, however. An opinion piece in the *Frederick News-Post* written by a Maryland farmer challenged the industry’s opposition to the legislation.²⁹⁵ He acknowledged the use of medically important drugs by industry

²⁸⁹ Keep Antibiotics Effective Act.

²⁹⁰ Keep Antibiotics Effective Act.

²⁹¹ Lili Zheng, “UPDATE: Md. Bill to Keep Antibiotics Effective Clears Panel,” WMDT, March 16, 2017, <http://www.wmdt.com/news/maryland/maryland-bill-to-keep-antibiotics-effective-clears-panel/396914632>.

²⁹² Zheng.

²⁹³ Zheng.

²⁹⁴ David Collins, “Antibiotics Bill Would Ban Routine Use on Healthy Animals,” WBAL, March 15, 2017, <http://www.wbaltv.com/article/antibiotics-bill-would-ban-routine-use-on-healthy-animals/9137131>.

²⁹⁵ Alex Smith, “A Farmer’s Perspective on the Proposed ‘Keep Antibiotics Effective Act of 2017,’” *Frederick News-Post*, February 22, 2017, https://www.fredericknewspost.com/opinion/columns/a-farmer-s-perspective-on-the-proposed-keep-antibiotics-effective/article_906300ee-4e1f-5eaf-9f50-71f1d0bd5194.html.

as disease prevention—even if it is unwarranted—and urged fellow farmers to engage in conversations with one another about how best practices in farm management can be achieved.²⁹⁶

Furthermore, not all opposition came directly from industry. In fact, the Maryland Department of Agriculture registered written opposition to the act in February 2017.²⁹⁷ The department’s rationale was similar to industry; it was considered “duplicative and incomplete compared to the national effort by the FDA.”²⁹⁸ The department also submitted that the bill, as written, would “cause an unnecessary operational and fiscal impact on the Department.”²⁹⁹ The estimated costs to implement this legislation were between \$185,000 and \$262,000. The agency said additional resources would be needed to manage the regulatory components of the bill, and opposed the bill because it did not have the same authority that the federal government has to enforce its provisions. The department also opposed the provision prohibiting the use of medically important antibiotics for routine disease prevention. The agency considered it “confusing” and believed it should be “stricken from [the bill] as one of the conditions where medically important antimicrobials may not be administered.”³⁰⁰

5. Implementation

Under the law, the Maryland Department of Agriculture is allowed to adopt regulations to carry out the legislation.³⁰¹ It does not appear that much will need to be implemented by any entity, which is somewhat puzzling. According to a blog sponsored by the University of Maryland College of Agriculture and Natural Resources, the act is very similar to the FDA’s veterinary feed directive rule, thereby making it redundant to

²⁹⁶ Smith.

²⁹⁷ “Maryland Department of Agriculture Legislative Comment—Keep Antibiotics Effective Act of 2017,” Maryland Department of Agriculture, February 15, 2017, http://mda.maryland.gov/about_mda/Documents/2017-HB602-SB422-Antibiotics.pdf.

²⁹⁸ Maryland Department of Agriculture.

²⁹⁹ Maryland Department of Agriculture.

³⁰⁰ Maryland Department of Agriculture.

³⁰¹ Keep Antibiotics Effective Act.

the initiatives being undertaken at the federal level.³⁰² It is unclear what this legislation, as passed, will accomplish.

6. Potential Impacts on Industry

It is difficult to piece together precisely what led to the amendments that resulted in the passage of the final bill, but the legislation was significantly stripped down from its initial version, possibly due to the opposition. There will likely be limited effects to industry given that federal rules have already addressed the concerns this legislation targets. Perhaps the main impact to industry would be penalties for violators; however, the penalty does not exceed \$2,000. The law does not explain if multiple penalties can be accrued, or who—a veterinarian or a farmer, or some other individual—may violate the provisions. In addition, given that there is no state-level data collection effort, it remains to be seen how the effectiveness of this law will be evaluated.

7. Assessment

Because Maryland's law is redundant with FDA guidance and does not alter veterinarian involvement in food-animal production, nor does it require new data collection or surveillance, this legislation does not appear to contribute to knowledge or understanding of antibiotic use in animal husbandry in the state, nor does it set reduction goals for the use of medically important antimicrobials. It is unclear if the current law will have an impact on antibiotic use in Maryland—although it will be difficult to measure.

C. CONCLUSION

This chapter examined the two U.S. states that have, at the time of this writing, passed legislation to slow the threat of antibiotic resistance. California's law, the only law in the nation that requires a prescription by a veterinarian to use antibiotics in livestock, bans non-therapeutic uses and requires data to be collected on antibiotic use in food

³⁰² "Maryland's New Antibiotics in Livestock Law: What Does it Mean for Your Farm?" Maryland Risk Management Education, accessed February 19, 2018, <http://agrisk.umd.edu/blog/marylands-new-antibiotics-in-livestock-law-what-does-it-mean-for-your-farm>.

animals. Maryland's legislation essentially codifies FDA guidance by banning the use of medically important drugs for growth promotion or feed efficiency, but also assigns penalties for violations. Maryland, unlike California, received opposition from the farm lobby, possibly resulting in the stripped-down version of the legislation that was adopted. Even though these states' laws are different and were passed with varying levels of opposition, it is clear there is some commitment to regulation on antibiotic use.

The chapters that follow compare the policies that have been implemented in each of the case studies examined, provide an evaluation of various policy options that the United States could consider implementing, and recommend a way forward for the homeland security enterprise to help slow the threat of antibiotic resistance.

VI. CASE STUDY POLICY COMPARISONS

The case studies and current U.S. strategies presented in the previous chapters can be analyzed to determine if legal policies have led to a decline in antibiotic resistance in animals or people. This chapter compares three policy strategies among the case studies: legislative bans, antimicrobial dispensing, and monitoring. Each section includes tables that display different policy actions taken in the previously discussed countries. The Appendix contains a matrix summarizing the major policy actions for each case study.

A. LEGISLATIVE BANS

All the countries and states studied—with the exception of the United States at the national level—implemented a legislative or regulatory ban on the use of antibiotics as growth promoters. This section compares the types of uses that were banned and discusses whether there are penalties associated with violations. Table 1 displays the types of nontherapeutic uses banned—production and prevention—and if the ban was implemented for medically important antimicrobials only. Bans for production purposes include growth promotion and feed efficiency; banning routine disease prevention includes using antimicrobials without evidence of disease.

Table 1. Nontherapeutic Uses Banned

	Production		Prevention	
	Production purposes (e.g., growth promotion, feed efficiency)	Medically important antimicrobials only	Routine disease prevention—without evidence of disease	Medically important antimicrobials only
Denmark	Yes	No	Yes	No
Netherlands	Yes	No	No	N/A
California	Yes	Yes	No	N/A
Maryland	Yes	Yes	No	Yes
United States, national	No – however, all manufacturers have voluntarily complied with FDA guidance to ban the use	Yes	No	N/A

The United States' approach to antibiotic use as a growth promoter has been specific to the definition of medically important antimicrobials, or those drugs that are important for human medicine; the European countries studied, however, banned the use of all antimicrobials for growth promotion. The state-level regulations in the United States prohibit the administration of medically important antimicrobials "in a regular pattern," which means they should only be used to treat disease, to control the spread of disease, or for medical procedures.³⁰³ These regulations—along with national-level U.S. law—allow veterinarians to prescribe medically important antimicrobials if they are situationally needed to prevent disease. For example, the FDA describes the following scenario of acceptable use: "If a veterinarian determines, based on a client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use."³⁰⁴ However, the guidance indicates that use of medically important drugs in healthy animals without evidence of risk of disease is not judicious use.³⁰⁵ For purposes of this thesis, the United States allows use without evidence of disease; it therefore considers the United States to allow (rather than ban) antimicrobials for preventative purposes.

Even though it is voluntary for producers to stop using antibiotics for growth promotion in the United States, the pharmaceutical industry has responded by changing labels on medically important antibiotics to ensure that growth promotion use is discouraged. In addition, the FDA has restricted the use of some medically important antimicrobials in animals, as outlined in Table 2.

³⁰³ Keep Antibiotics Effective Act.

³⁰⁴ FDA Center for Veterinary Medicine, "Guidance for Industry #213," 213.

³⁰⁵ FDA Center for Veterinary Medicine, 213.

Table 2. Drug Classes Banned or Limited for Use in Food Animals

	Drug Class		
	Fluoroquinolones	Cephalosporins	Glycopeptides
Denmark	Yes – limited use	Yes – limited use	Yes – Avoparcin
Netherlands	Yes – 3rd and 4th generation	Yes – 3rd and 4th generation	Yes – Avoparcin
California	No additional limits	No additional limits	No additional limits
Maryland	No additional limits	No additional limits	No additional limits
United States, national	Yes – extra label use prohibited, and prohibited in poultry	Yes – extra label use of 3rd and 4th generation prohibited	Yes – none have been approved for use in food animals

Denmark banned the use of avoparcin for growth promotion in 1995 out of concerns that it was contributing to the resistance of vancomycin—a drug used to treat human infections.³⁰⁶ Avoparcin and vancomycin are chemically very similar antibiotics.³⁰⁷ Given that avoparcin was never approved for use in the United States, it is somewhat out of scope for this analysis; it is worth mentioning, however, because this was the first step in banning or limiting antibiotic use in agriculture settings.³⁰⁸ The United States, Denmark, and the Netherlands have all limited or restricted the use of fluoroquinolones in some manner, and the Netherlands and the United States have limited the use of third- and fourth-generation cephalosporins. Denmark has prohibited the use of cephalosporins in poultry.³⁰⁹ The Netherlands created a tiered system that outlines which drugs should be used first, second, or third for treatment in order to preserve the most important antibiotics for human consumption and limit the likelihood of resistance. No other countries studied in this thesis have this type of ranking system.

³⁰⁶ Kahn, *One Health*, 35.

³⁰⁷ Kahn, 34.

³⁰⁸ Alex Koppelman, “Is the Way We Raise Our Food Giving Us MRSA?” Salon, November 7, 2007, <https://www.salon.com/2007/11/07/staph/>.

³⁰⁹ Technical University of Denmark, “Decrease in Antimicrobial Use in Animals in Denmark,” ScienceDaily, October 8, 2015, <https://www.sciencedaily.com/releases/2015/10/151008083913.htm>.

Table 3 presents a comparison of penalties outlined in the countries' and states' policies. The California and Maryland laws impose monetary penalties for producers who violate their provisions. California's penalties are up to \$500 per day until the producer becomes compliant with the law while Maryland's penalties do not exceed \$2,000.³¹⁰ Denmark instituted its yellow card initiative, which set targets for antibiotic use; producers who exceed the threshold limits are given yellow cards and are fined. While the SDA in the Netherlands sets antibiotic-use reduction targets for each food-animal species, there is no penalty for failing to meet targets. Instead, producers who use too many antibiotics receive technical assistance on how to reduce their use.³¹¹

Table 3. Penalties

	Penalties imposed	Penalty type
Denmark	Yes	Fines if antibiotic use thresholds are not met; costs for inspection visit; for a third injunction, stock reduction is an option
Netherlands	No	Guidance provided to producers who use too many antibiotics ³¹²
California	Yes	Fines of up to \$500 per day until compliance
Maryland	Yes	Fines not to exceed \$2,000 imposed by the secretary of the Maryland Department of Agriculture
United States, national	Unknown	Unknown

Because the policies are voluntary in the United States, no specific penalties are outlined in the guidance for veterinarians and producers who use antibiotics in an off-label fashion. It appears that there are conditions where extra-label drug use is allowable and record keeping must be accurate and comprehensive. The guidance states that

³¹⁰ Andrew Amelinckx, "California Passes the Country's Strongest Regulations for Antibiotic Use in Livestock," Modern Farmer, October 15, 2015, <https://modernfarmer.com/2015/10/california-antibiotic-livestock-regulations/>; Keep Antibiotics Effective Act.

³¹¹ "Healthy Animals without Antibiotics," Wageningen University & Research, accessed July 19, 2017, <https://www.wur.nl/en/article/Healthy-animals-without-antibiotics.htm>.

³¹² Wageningen University & Research.

continued use of antimicrobials for production purposes is an “illegal extra-label use”; however, it is unclear what the penalties are, if there are any to begin with, for violating the law.³¹³

B. ANTIMICROBIAL DISPENSING

All the countries and states studied impose some limits on the use of antimicrobials and how they are dispensed. Table 4 presents requirements in each of the policies outlining whether or not a veterinary visit is required to use antibiotics, if a prescription is required to administer antibiotics, if a veterinarian-client relationship is required, and whether or not there are additional educational or certification requirements veterinarians must meet to provide antibiotics.

Table 4. Veterinary Requirements

	Veterinary visit required to prescribe antibiotics	Prescription required	Vet-client-relationship required	Continuing education for veterinarians related to antibiotics
Denmark	Yes – monthly visits for swine and cattle producers	Yes	No	No
Netherlands	Yes – prior to prescribing to sick animals, and periodic visits	Yes	Yes	Yes – in order to be listed in the veterinary quality register
California	Yes – yearly visit required	Yes – medically important drugs only	Yes	No
Maryland	No	Yes – medically important drugs only	Yes – for veterinary feed directives	No
United States, national	No	Yes – medically important drugs only	Yes – for veterinary feed directives	No

³¹³ “Resources for You—The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians,” FDA, accessed July 6, 2018, <https://www.fda.gov/animalveterinary/resourcesforyou/ucm380135.htm>.

1. Veterinary Oversight

A prescription is required for antibiotics in all the countries; however, in the United States this requirement is only for drugs that are deemed medically important to human medicine. The European countries require all antibiotics used in food animals to be dispensed through a veterinary prescription. Denmark additionally requires monthly visits from veterinarians to larger swine and cattle producers so the vets may advise on drug use and other animal health concerns.³¹⁴ The Netherlands mandates a vet visit before antibiotics can be prescribed to treat ill animals.³¹⁵ As far as dispensing policies, Denmark legislation does not allow veterinarians to profit from antibiotic sales and the government prohibited veterinary dispensing in 1990; all distribution is done through pharmacies.³¹⁶ However, Dutch officials do not believe that decoupling the prescription and sale of drugs will result in decreased antibiotic use.³¹⁷ The Dutch rely on their use targets to remove economic incentives from antimicrobial prescriptions and sales.³¹⁸

The California and Dutch policies are similar in that they both require a relationship with a veterinarian. The Netherlands policy specifies that producers can only contract with one veterinary practice whereas California only requires that veterinarian-client-patient relationships must be established for each farm. These two models also require veterinarians to visit farms before antibiotics can be prescribed to ill animals; however, the California model further requires a yearly visit to the farm from a veterinarian with an established relationship before antibiotics can be prescribed at all.

³¹⁴ Emese Kovács, “Lessons from the Danish Ban on Antimicrobial Growth Promoters,” Interfaith Center on Corporate Responsibility, September 7, 2011, <https://www.iccr.org/sites/default/files/090711LessonsFromTheDanishBan.pdf>.

³¹⁵ Government of the Netherlands, “Antibiotic Resistance in the Livestock.”

³¹⁶ DVFA, “Distribution and Use of Veterinary Drugs in Denmark.”

³¹⁷ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use.”

³¹⁸ Speksnijder et al.

2. The Dutch Quality System

Another aspect unique to the Netherlands model is the creation of a quality system for veterinarians. The system includes clinical treatment guidelines for veterinarians that can be enforced through private quality systems in place in the country.³¹⁹ Veterinarians who are abiding by these guidelines are listed in the country's registers as approved veterinarians, thereby pressuring veterinarians to follow the guidelines. Producers will know who the high-quality veterinarians are in the country and seek out their services. None of the other countries studied have this type of quality program for veterinarians. Also unlike the other countries, the Dutch quality system requires those who wish to be listed in the registry to pursue accredited continuing education courses aimed at reducing antibiotic use in agriculture.

3. Prescribing Limits

Denmark allows veterinarians to prescribe or distribute antibiotics for treatment to animals, with the exception of cattle, for a maximum of five days. No other policies examined had specific limits regarding the number of days antibiotics may be used for treatment. California's policy prohibits the prescription of drugs for a duration that is inconsistent with treatment guidelines for either the disease or the drug type.

C. MONITORING

This section compares the various monitoring requirements for each of the countries and states, including the individuals who are required to provide information. All the policies include some surveillance component to monitor the antibiotic resistance threat. The European countries' systems are integrated, nationwide systems that collect information on antibiotic use and resistance in human health and in agriculture, whereas the United States has disconnected monitoring systems that are limited in scope. In addition, the U.S. systems do not record antibiotic use. Table 5 outlines which countries and states measure antibiotic use, resistance levels in food, resistant infections in animals, and resistant infections in people.

³¹⁹ Speksnijder et al.

Table 5. Monitoring Requirements

	Monitoring exists	Antibiotic use, e.g., number of prescriptions	Resistance levels in food	Resistant infections in animals	Resistant infections in people
Denmark	Yes	Yes	Yes	Yes	Yes
Netherlands	Yes	Yes	Yes	Yes	Yes
California	Yes – enhances national-level monitoring	Yes – representative sample	Yes – representative sample	Yes – representative sample	Yes – representative sample
Maryland	Yes – same as national level	No	Limited	Sporadic	Yes
United States, national	Yes – limited to antibiotic sales data, ad hoc studies in animals, some foodborne resistant infections in people	No	Limited	Sporadic	Yes

Denmark’s DANMAP is an integrated system that monitors the use of antimicrobial drugs in food animals and in people, resistance levels in food, and whether or not resistant infections are increasing in animals and in people. Similarly, in the Netherlands, the SDa releases summaries on antimicrobial use in animals and people, as well as resistance levels in food and resistant infections in humans and animals. The Netherlands, unlike Denmark, sets benchmarks on the human side as well as the animal side for reducing antibiotic use.

The United States’ approach is somewhat fragmented compared to the European countries discussed. It has three disparate systems that serve specific purposes, some of which are not solely intended for monitoring antibiotic use or resistance. The FDA keeps data on the sale and distribution of antibiotics, which is published in an annual calendar year summary of sales and distribution data for drugs approved for use in food-producing

animals. These data do not include information on antibiotic use, which is an important distinction from the European policies. That said, the annual report is fairly detailed with regard to multi-year trends of sales and distribution information and provides data that indicate how many medically important antimicrobials are purchased with the intent to use—even though the FDA clearly states that “sales and distribution information does not represent actual use of the products” in its key points from the 2016 report.³²⁰

The USDA has sporadically conducted studies on antibiotic use in domestic livestock and poultry populations through NAHMS (the National Animal Health Monitoring System). The unit in charge of this system has also published info sheets on the sporadic antibiotic susceptibility studies performed. This system does provide some information about antibiotic resistance on the country’s farms. These studies, however, serve as snapshots of a point in time and are not set up with the frequency or continuity needed to monitor trends. Another U.S. system, one that is specific to antimicrobial resistance, is NARMS, the National Antimicrobial Resistance Monitoring System. This system collects data specifically on foodborne bacteria from humans, retail meat, slaughtering facilities, sick animals, and healthy animals on farms.³²¹ The intent of the system is to promote informed decision-making by providing the FDA, USDA, and CDC with data on antimicrobial resistance.

As for the state-level approaches, California’s policy requires the state’s Department of Agriculture to enhance surveillance efforts beyond those conducted at the national level. The department will be collecting additional data that are regionally representative of the state and will seek to create its own surveillance system, which will align and possibly feed into the national systems.³²² Maryland’s approach is to provide an annual summary of state-level data on medically important antibiotic use that is

³²⁰ “FDA Releases Annual Summary Report on Antimicrobials Sold or Distributed in 2016 for Use in Food-Producing Animals,” FDA, December 7, 2017, <https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm588086.htm>.

³²¹ Kahn, *One Health*, 57.

³²² California Department of Food and Agriculture, “Antimicrobial Use and Stewardship Updates.”

already compiled and made publicly available by the CDC, USDA, and FDA. The state is not planning to provide surveillance enhancements beyond the national level.

When it comes to who must submit data on antibiotic use to the government for antimicrobial surveillance systems, the countries and states differ, as shown in Table 6. The European countries require certain sectors to report antibiotic use data. In Denmark the onus is on the veterinarians, feed mills, and distributors to report any data they have regarding antibiotic use on farms; the producer is not required to report. Dutch policy requires farmers to report which drugs are administered and veterinarians to report what they have prescribed. As of the writing of this thesis, California’s surveillance system is not yet operational; it appears, however, that the state will take a voluntary approach to gather a representative sample of farmers and veterinarians who wish to participate and provide their antibiotic use information.³²³ Because Maryland relies on national data, there are no required reporters as part of its policies and the United States does not collect antibiotic use data.

Table 6. Sectors Required to Submit Data on Antibiotic Use

	Veterinarians	Farmers	Feed mills	Pharmacies/distributors
Denmark	Yes	No	Yes	Yes
Netherlands	Yes	Yes	No	No
California	No	No	No	No
Maryland	No	No	No	No
United States, national	N/A	N/A	N/A	N/A

³²³ “Surveys & Studies Get Involved to Help CA Agriculture!,” California Department of Food and Agriculture, accessed July 17, 2018, https://www.cdffa.ca.gov/ahfss/aus/docs/AUS_Surveys_&_Studies_Trifold.pdf.

D. OUTCOMES

This section compares the outcomes of the case studies. Because the U.S. policies are still being implemented, little is known about their eventual outcomes. For the European countries, Table 7 describes whether the policies have caused an overall reduction in antibiotic use, antimicrobial resistance in animals, and antimicrobial-resistant infections in people.

Table 7. Reduction in Antibiotic Use

	Overall reduction in antibiotic use	Overall reduction in antimicrobial resistance in animals	Overall reduction in antimicrobial-resistant infections in people
Denmark	Yes – use targets met after yellow card Initiative was introduced	Yes	No
Netherlands	Yes	Yes	Yes
California	Unknown	Unknown	Unknown
Maryland	Unknown	Unknown	Unknown
United States, national	Unknown	Unknown	Unknown

Both Denmark and the Netherlands saw reductions in antibiotic use as well as reduced resistance in animals. Denmark only achieved success after it instituted its yellow card initiative, which strengthened monitoring agencies’ ability to hold producers accountable to the regulations. In addition, studies from Denmark show reduced resistance in animals, yet resistant infections in people continue to increase. Their surveillance noted that resistance was higher among meat that was imported and for people who had acquired their infections outside the country. Similarly, setting benchmarks has allowed the Netherlands to witness declines in its antimicrobial sales and usage.³²⁴ The Netherlands has also seen declines in resistant organisms in livestock.³²⁵

³²⁴ de Greeff, Mouton, and Hoeing, “NethMap 2016.”

³²⁵ de Greeff, Mouton, and Hoeing.

The Dutch have observed stable rates, and in some cases reductions, of resistant infections in people as a result of their policies.³²⁶

Because the California legislation has only recently been implemented, there are not yet measurable outcomes. Similarly, the U.S. guidance and subsequent voluntary re-labeling by drug manufacturers has recently been implemented. It is also unclear how the FDA is measuring effectiveness; though the agency has made changes to its annual summary report on antibiotic sales, the 2017 report was not released until December 2018.³²⁷ This report was slated to include metrics that would indicate whether the guidance made an impact. Because Maryland's legislation is duplicative of national efforts, it is unlikely that these policies would have distinct outcomes; the FDA's summary report also does not include state-level information on antibiotic use.

E. IMPACTS ON INDUSTRY

The impacts on industry for the European countries appear to be minimal, and in some cases have increased productivity in certain livestock sectors. For example, after Denmark initially saw some negative effects for swine after their ban on antibiotics as growth promoters, the country was able to reduce its antibiotic use in swine while improving productivity, and without affecting mortality rate.³²⁸ The Dutch policies also appeared not to impact industry; according to the Dutch Minister of Agriculture in June 2014, the country had decreased use and remained second in agricultural exports.³²⁹

It remains to be seen what the impacts on industry will be for producers in the United States as a result of the drug labeling changes. If medically important drugs cannot be used for growth promotion but can still be used preventively, it is unclear how farmers and the pharmaceutical industry will be affected. Because California's policies are more restrictive, the state serves as a case study to observe as time passes. For example, will the veterinary-client relationship requirement put stress on the veterinary

³²⁶ de Greeff, Mouton, and Hoeing.

³²⁷ Research for this thesis concluded prior to the release of the report.

³²⁸ Aarestrup et al., "Changes in the Use of Antimicrobials."

³²⁹ Rijksoverheid, "Toespraak van minister Schippers [Speech by Minister Schippers]."

industry? Will producers suffer losses like Denmark's if they are not allowed to use a medically important antimicrobial drug in a regular pattern? Future research will be needed to assess the impacts of these policies in the United States.

F. CONCLUSION

This chapter summarized and compared various policy aspects and outcomes for the case studies examined in this thesis. The following broad themes from this emerged.

- Growth promotion bans: The European countries banned all antibiotics for growth promotion rather than just those antibiotics with medical importance to humans.
- Prevention bans: Only Denmark banned the use of antibiotics for routine disease prevention without evidence of disease.
- Drug class bans: All countries have banned flouroquinolones, cephalosporins, and glycopeptides at some level.
- Penalties: Denmark, California, and Maryland issue penalties to producers for failing to abide by the regulations set forth to slow antibiotic resistance.
- Veterinary oversight: The European and California laws require a veterinarian to visit the farm to prescribe antibiotics to food animals.
 - Denmark is the only country studied that does not require the establishment of a veterinarian-client-relationship.
 - The Netherlands is the only country that requires continuing education related to antibiotic use for veterinarians.
- Monitoring and surveillance: Antibiotic resistance monitoring exists, though differs, for all of the countries.
 - The European countries monitor antibiotic use and California will begin monitoring this for producers who wish to volunteer. The United

States does not monitor use but it does monitor antibiotic sales information.

- The European countries monitor resistance levels in food and resistant infections in animals and humans. At the national level in the United States, surveillance is limited for resistance levels in food and sporadic studies are conducted for resistant infections in animals; the country does monitor resistant infections in people both in the health-care setting and for certain enteric diseases.
- Unlike the European countries, the United States does not require anyone to submit data on antibiotic use.
- Required data submitters: Denmark and the Netherlands require veterinarians to report the antibiotics they administer. Producers in the Netherlands, but not in Denmark, are required to submit data.
 - Denmark also requires feed mills and pharmacies to report what antibiotics are sold to compare with the data for what vets administer.
- Outcomes: The European policies have had success in reducing antibiotic use and resistance in animals. Results vary when it comes to overall reduction in resistant infections in people; Denmark reported no reductions while the Netherlands has some indications that its policies are reducing infections acquired within the country.

Taken together, the studied European countries' policies appear to be slowing the threat of antibiotic use. These countries also have robust surveillance systems which allow for continued trend monitoring. California appears to be aligning many of its policies with these European countries and expanding surveillance to include more monitoring. California's policy may serve as a model that could be implemented at a national level.

The next chapter explores policy options aimed at enhancing current strategies the United States has already employed to slow the threat of antibiotic resistance.

VII. CONCLUSIONS AND RECOMMENDATION

The nation's ability to respond to a bioterror or widespread disease event depends heavily on its medical countermeasures. The non-judicious use of antibiotics inhibits our ability to respond. Antibiotic resistance poses a massive threat to the health security of the homeland and warrants attention from the homeland security enterprise.

The CDC lists several pathogens as “Category B” bioterrorism agents or diseases—“those that are moderately easy to disseminate; result in moderate morbidity rates and low mortality rates; and require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance.”³³⁰ Included in the Category B list are *Salmonella* and *Shigella*—organisms also named by the CDC as serious drug-resistant threats to the United States.³³¹ These organisms are present on farms, but there is little information about their prevalence and resistance. Because the United States has an uncoordinated approach to slowing the threat of antibiotic resistance, we are not well positioned to prevent outbreaks of resistant organisms or to preserve the medically necessary antibiotics currently available. We must look to interventions that will help mitigate the threat—and to do so, we must have better data that monitors use of antibiotics and tracks levels of resistance of drug-resistant organisms present on farms.

In the United States, no single entity is responsible for collecting antibiotic surveillance information. Several disparate sources publish separate reports on different aspects of the threat, such as resistance among foodborne pathogens, sales data, and special studies on use and resistance in animals. As mentioned previously, NARMS has the qualities of an integrated system in that it includes both human and animal resistance information; however, it monitors foodborne organisms only. No U.S. system reports on all antibiotic use to identify whether reduction targets are necessary.

³³⁰ “Bioterrorism Agents/Diseases,” CDC, accessed August 18, 2017, <https://emergency.cdc.gov/agent/agentlist-category.asp>.

³³¹ CDC, “Antibiotic/Antimicrobial Resistance, Biggest Threats,” 61, 71, 75.

Veterinarians and producers also have a role to play in how antibiotics are used and administered to food animals. They should be actively involved in antibiotic administration, especially to ensure that antibiotics are not being used for non-therapeutic reasons or being overused for disease prevention.

A. PROPOSED POLICY PACKAGE

The previous chapter compared policy aspects of the case studies and the current U.S. strategies. Based on that review, this chapter discusses proposed policies that could enhance existing U.S. strategies. The policy package includes four potential strategies: 1) creating an enhanced, more integrated surveillance system, 2) enacting antibiotic-use reduction targets, 3) prohibiting the use of antibiotics in healthy animals, and 4) requiring veterinarians to examine animals before they prescribe antibiotics for disease prevention.

Each strategy has been assessed with the CDC's policy analytical framework (see Table 1 and the Appendix) and is discussed in greater detail in the sections that follow. The Appendix assesses each policy option using framing questions to outline the scope and context of each policy; assesses the potential for the policy to impact risk factors, quality of life, disparities, morbidity, and mortality; examines the likelihood that the policy can be successfully adopted and implemented; and answers questions about the comparison of the costs to enact, implement, and enforce the policy with the value of benefits to the public.

Table 8 summarizes and grades each strategy according to its potential impact and feasibility, and gives ratings for economic and budgetary impact. It should be noted that this thesis does not include robust cost-benefit analyses for each policy option—limitations of doing so are outlined in the narrative for each option in the sections that follow.

Table 8. Policy Analysis Options³³²

Strategy	Impact	Feasibility	Economic and budgetary impact	
Integrated surveillance system	High Concerns about the amount or quality of data? No	Medium Concerns about the amount or quality of data? No	Favorable Concerns about the amount or quality of data? Yes	More favorable Concerns about the amount or quality of data? Yes
Antibiotic-use reduction targets	High Concerns about the amount or quality of data? No	Low Concerns about the amount or quality of data? No	More favorable Concerns about the amount or quality of data? No	More favorable Concerns about the amount or quality of data? No
Prohibit use of antibiotics in healthy animals	High Concerns about the amount or quality of data? Yes	Low Concerns about the amount or quality of data? No	Less favorable Concerns about the amount or quality of data? Yes	More favorable Concerns about the amount or quality of data? Yes
Annual veterinary examination for disease prevention and control	High Concerns about the amount or quality of data? No	Medium Concerns about the amount or quality of data? No	Favorable Concerns about the amount or quality of data? No	More favorable Concerns about the amount or quality of data? No
Scoring definitions	Low: Small reach, effect size, and impact on disparate populations Medium: Small reach with large effect size OR large reach with small effect size High: Large reach, effect size and impact on disparate populations	Low: No/small likelihood of being enacted Medium: Moderate likelihood of being enacted High: High likelihood of being enacted	Less favorable: High costs to implement Favorable: Moderate costs to implement More favorable: Low costs to implement	Less favorable: Costs are high relative to benefits Favorable: Costs are moderate relative to benefits (benefits justify costs) More favorable: Costs are low relative to benefits

³³² Criteria were developed from CDC, “CDC’s Policy Analytical Framework.”

1. Creating an Integrated Surveillance System

The first strategy proposed in this thesis is to create an integrated surveillance system to build upon the existing U.S. disease surveillance and antibiotic resistance data currently being collected. The integrated system would include information about resistant infections in people and animals and should be modeled after the Danish program, DANMAP, which was discussed in Chapter II. At a minimum, the system should monitor the consumption of antimicrobials in humans and animals and track antimicrobial-resistant bacteria found in animals, food, and people. Ideally, the system would allow analysts to identify the routes of transmission, whether from the farm, the environment, a health-care setting, or other means. In addition, the system should be robust enough to allow for the study of antimicrobial use and any links to emerging resistant organisms; additional research is needed in this area to plan for appropriate interventions to slow the threat of antimicrobial resistance. Given the small, sporadic studies about U.S. antimicrobial use as a contributor to antibiotic resistance, it is critical to put a national system in place that allows study on a larger scale.

Industry has not interpreted these small studies to indicate potential risks to public health. The Animal Health Institute, an association whose members are all pharmaceutical companies, continues to claim that “current science can’t really prove what causes all of the different types of antimicrobial resistance that create public health risks.”³³³ The institute also opines, “The assumption that simply giving antimicrobials to a larger number of animals creates a public health hazard due to resistance isn’t accurate, because it doesn’t account for the benefits of preventing disease and the need for higher doses and potentially stronger types of antimicrobials if an animal is sick.”³³⁴ Given the vocal and disparate opinions, the most important first step is to be able to factually resolve the issue. This requires data. Therefore, a national surveillance system that would contribute to the science of monitoring antibiotic resistance is essential to examine how

³³³ “Antibiotics in Livestock: Frequently Asked Questions,” Animal Health Institute, accessed September 23, 2018, <https://www.ahi.org/issues-advocacy/animal-antibiotics/antibiotics-in-livestock-frequently-asked-questions/>.

³³⁴ Animal Health Institute.

detrimental antibiotic use in agriculture is, and where to prioritize interventions to slow the threat if necessary. Although this thesis does not discuss human contributions to antibiotic resistance, an integrated system like Denmark's would create a holistic view of where to focus efforts and would allow us to better evaluate policy needs or effectiveness—whether in a farm or health-care setting.

Building the proposed surveillance system infrastructure would require collaboration between the FDA, USDA, and CDC, with support from the Department of Homeland Security. Legal policies would need to be enacted to compel veterinarians, producers, and health-care providers to submit information on antimicrobials prescribed and used, as well as information they obtain on antimicrobial resistance through testing of isolates from illness in animals and humans. The illness information could be facilitated through electronic laboratory reporting. The data collected in the system could then be linked with the FDA's antibiotic sales data to examine the full antibiotic supply chain, from manufacturer to user, and provide critical data for decision-making and trend monitoring. The information submitted on resistant pathogens in health-care through the National Healthcare Safety Network could be combined with the information already collected in NARMS to create a holistic picture of resistant organisms in the United States. To ensure compliance, penalties would likely need to be enacted for noncompliance.

As shown in the policy analysis table presented previously (Table 8), this policy would have a large reach but may face some opposition given the reporting burden required of veterinarians, human health-care providers, and farmers. Human health-care providers have been required to report resistant infections as part of national and local notifiable disease reporting requirements; however, antimicrobial use reporting has never been required. This could be challenging to implement, but the infrastructure could be based largely on what is required currently for opioid prescriptions to combat the opioid overdose epidemic. For example, states have enacted prescription drug monitoring programs (PDMPs), which create a “database that tracks controlled substance

prescriptions in a state.”³³⁵ Each time a pharmacist fills a prescription for a controlled substance, he or she must record it into a state’s PDMP.³³⁶ PDMPs provide surveillance on who may be heavy prescribers, as well as who may be heavy users.³³⁷ They give health officials the ability to apply targeted interventions to address the problem. Veterinarians and farmers, however, could see a PDMP-like surveillance system for antibiotic use in agriculture as overly burdensome; in the past, the Animal Health Institute has lobbied against more transparency regarding the use of antibiotics in animals.³³⁸

The potential costs for enacting this policy are unknown, and a robust cost-benefit analysis should be performed. It is also difficult to estimate the benefits of this system given that it is not an intervention, per se. This system would help create an accurate picture of agriculture’s contribution to the accelerating rate of antibiotic resistance. The desire to conduct robust cost-benefit analyses of the policy interventions recommended in this thesis depends on the scope of the problem, which cannot truly be defined until a more integrated surveillance system is implemented. That said, this thesis considers this policy option to have moderate costs based on implementation of the necessary technology. Costs are low, however, relative to the benefits to health security: the benefit of this particular system is that the United States would finally have proof of the problem and policymakers could implement interventions (those outlined in the subsequent sections) based on accurate information.

2. Enacting Antibiotic-Use Reduction Targets

The next strategy, enacting antibiotic-use reduction targets, is dependent on the implementation of the surveillance system discussed in the previous section. There is no feasible way to institute antibiotic use targets unless there is a more robust data system to determine if targets are being met. If an integrated surveillance system were in place, the

³³⁵ “Opioid Overdose—What States Need to Know about PDMPs,” CDC, last updated October 3, 2017, www.cdc.gov/drugoverdose/pdmp/states.html.

³³⁶ CDC.

³³⁷ CDC.

³³⁸ Open Secrets, “Lobbying Spending Database.”

USDA and FDA could collaborate to set antibiotic use targets for the farming industry. Legislation or administrative rule would need to be established to allow the USDA to set mandatory targets, and an administrative structure would need to be created. Penalties could be imposed for entities that do not meet established benchmarks.

This strategy could be adapted from the Dutch benchmarking model, the SDA. The Netherlands Veterinary Medicines Institute created what it calls an *expertpanel*, which includes scientists with expertise in epidemiology, veterinary medicine, and human health. The panel examines antibiotic use information and establishes benchmarks for the types of drugs that should be used as well as the amount for each food-animal sector, and has the ability to consult with another group of scientists for technical feedback. The SDA has a board that works with a supervisory commission and an advisory council of stakeholders. The expertpanel reports to this board. A similar structure could be created in the United States that works with the USDA and FDA.

It does not appear that a strategy like this one has been discussed previously in the United States, so there is no historical perspective of potential opposition. However, it is likely that the farming industry and pharmaceutical companies would oppose reduction targets due to their past objections to regulation in this context.

As shown in the policy analysis table (Table 8), this proposal would have a high impact; it would have a large reach in reducing the use of antibiotics. However, due to the likelihood of strong opposition, this policy option has a low feasibility score and has little to no likelihood of being enacted. In terms of the governmental impact, the costs may be relatively low to implement but there could be significant financial effects for the agriculture industry and pharmaceutical companies. Initially there may be animal losses as farmers find different methods that do not rely on antibiotics, and the pharmaceutical companies could face financial losses with fewer antibiotics being sold. That said, this thesis proposes that the costs to implement reduction targets would be relatively low compared with the overall benefit to humanity.

3. Prohibiting the Use of Medically Important Antibiotics in Healthy Animals

The third strategy would prohibit the use of antibiotics in healthy animals unless disease has been diagnosed in other animals in the same flock or herd. The policy would ensure that antibiotics are not provided to animals for non-therapeutic purposes, including routine disease prevention. This means that farmers would not be able to administer antibiotics to prevent disease solely because their animals are kept in close quarters or to use antibiotics in animals during transport—a practice that is allowed under the current FDA judicious use guidance.

This policy would require legislation or FDA guidance/rules and would likely require a phased implementation period to ascertain which drugs cannot be used for non-therapeutic purposes. As shown in Table 8 earlier in this chapter, this policy could have a high impact on antibiotic overuse in agriculture based on the European case study findings discussed in previous chapters. It also would have relatively low costs to implement in terms of the governmental role but could sustain significant costs in the agriculture industry, as producers would need to change their farming practices to achieve a highly bio-secure environment. The costs to implement are low relative to the overall benefits to human medicine.

This policy has low feasibility, with little to no likelihood of being enacted. The concept been introduced in legislation over the past two decades through the Preservation of Antibiotics for Medical Treatment Act, which would make it illegal to give medically important antimicrobials to food animals for non-routine disease control.³³⁹ The act has been introduced, in some form, since 1999 and has not passed. It is therefore unlikely that a policy measure like this one would pass. Such proposed legislation would meet resistance from the agriculture industry due to the necessary changes in farming practices.

³³⁹ “Preservation of Antibiotics for Medical Treatment Act of 2017, H.R. 1587, 115th Cong. 1 (2017), <https://www.congress.gov/bill/115th-congress/house-bill/1587/text>.

4. Requiring Annual Veterinary Examinations for Disease Prevention and Control

The final policy as part of this proposed package would require veterinarians, on an annual basis, to physically examine animals before they can prescribe antibiotics for prophylaxis. The veterinarian would, using professional judgment, decide if preventive treatment is needed to protect a herd against illness. This strategy is based on current policies in the Netherlands and California. The policy in the Netherlands requires veterinarians to administer all antimicrobials, and the country requires a veterinarian-client relationship that includes periodic inspections of the farm. However, farmers may be provided antibiotics without a vet visit if they have established their relationship with the veterinarian and inspections have been performed.³⁴⁰

It does not appear that this type of policy has been debated at the national level; however, similar requirements have been debated at the state level in California. The California laws do not require a visit or a physical examination for each potential disease incident before antibiotics can be prescribed, but they do require the establishment of a veterinarian-client relationship for animal patients (with the exception of wild animals). This relationship requires the veterinarian to be “personally acquainted with the animal(s) by virtue of an examination of the animal or by medically appropriate and timely visits to the premises where the animals are kept.”³⁴¹

The USDA has recorded at least one veterinarian shortage situation in most states in the United States, which means that there are not enough veterinarians to provide basic animal health services and/or services related to the food supply or public health.³⁴² Therefore, a visit for each instance of potential disease risk may not be practical. This thesis proposes an annual veterinary examination under a veterinary-client relationship.

³⁴⁰ Speksnijder et al., “Reduction of Veterinary Antimicrobial Use,” 82.

³⁴¹ Veterinarian-Client-Patient Relationship, 16 CCR § 2032.1

³⁴² “Veterinary Services Shortage Situations,” National Institute of Food and Agriculture, accessed September 9, 2018, https://nifa.usda.gov/vmlrp-map?state=433&field_status_value=All&field_vsgp_status_value=All&fy%5Bvalue%5D%5Byear%5D=2017; “VMLRP Veterinarian Shortage Situation Nomination Form (Form NIFA 2009–0001),” National Institute of Food and Agriculture, accessed October 6, 2018, <https://nifa.usda.gov/resource/vmlrp-veterinarian-shortage-situation-nomination-form-form-nifa-2009-0001#location>.

This policy would require legislation and would likely need to be implemented at the state level, given that veterinarians are licensed to practice by individual states. To track veterinary-client relationships, data would need to be collected at the state level. These data would then need to be aggregated at the national level to develop an overview of how well the system is functioning.

As shown previously in Table 8, this policy option has the potential to create a high impact given that drugs cannot be administered without the intervention of a veterinarian. This could be palatable to the industry since veterinary oversight is already required by the FDA in order to have a veterinary feed directive.³⁴³ In terms of the budgetary impact, this policy would have moderate costs to implement in government. This thesis proposes penalties for entities who violate the policy, which would require some level of enforcement from the USDA or state departments of agriculture. Many producers have already established relationships with veterinarians, who may already be visiting the farms annually; therefore, the costs to implement may not be significant to industry.

B. RECOMMENDATION

This thesis recommends that all four policies are implemented as a package; the policies on their own do not stand to make a large impact to slowing the threat of antibiotic resistance. However, given the history of policymaking related to antibiotic resistance and agriculture in the United States, it is unlikely that the full policy package would be adopted together.

Therefore, this thesis proposes that the U.S. government implement these policies in a phased approach beginning with the first policy—enhancing data collection and building an integrated surveillance system. This strategy should be prioritized over the other three simply because it is foundational and serves as necessary infrastructure to promote informed decision-making about antibiotic resistance. Even though there are numerous scientific studies about the link between antibiotic use and antibiotic resistance,

³⁴³ FDA Center for Veterinary Medicine, “Guidance for Industry #213,” 213.

the evidence leaves industry and policymakers unconvinced that more interventions are needed in the United States. An integrated system would be a first step to make the link between antibiotic use and resistant organisms among food animals more visible. Perhaps then, the general public, policymakers, and the agriculture and pharmaceutical industries would collectively engage to address this threat in the United States.

Once an integrated surveillance system is implemented, antibiotic-use reduction targets can be set. If the targets are not being met, more interventions could be deployed, such as prohibiting the use of antibiotics in healthy animals or requiring an annual veterinary exam, or perhaps requiring an exam before administering antibiotics for every instance of disease risk. Iterative steps can be taken to achieve a reduction in the use of antibiotics in food animals. While this approach would likely not see quick results, implementation would be easier and would likely allow industry to shape how the policies are enacted to ensure the least amount of disruption to businesses.

For any of these policies to be enacted, all stakeholders must be present and actively engaged; outreach should begin at the individual farm level. It is important to ensure that there are educational campaigns that reach farmers—not just industry associations. Individual producers must be informed about the threat of antibiotic resistance and be encouraged to be active participants in finding solutions.

There is limited information in the literature about the perceptions and attitudes regarding antibiotic resistance among U.S. livestock producers (as opposed to the industry associations). One study, conducted among rural South Carolina dairy farmers, indicated that while all farmers were utilizing some procedures to assess whether or not antibiotics were needed, only 32 percent of them had documented systematic procedures.³⁴⁴ In addition, 86 percent of those surveyed “were not concerned that overuse of antibiotics in animals could result in antibiotic resistance among farm workers.”³⁴⁵ The study also described perceived barriers to following proper antibiotic

³⁴⁴ D. B. Friedman et al., “Importance of Prudent Antibiotic Use on Dairy Farms in South Carolina: A Pilot Project on Farmers’ Knowledge, Attitudes and Practices,” *Zoonoses and Public Health* 54, no. 9–10 (December 1, 2007): 366–75, <https://doi.org/10.1111/j.1863-2378.2007.01077.x>.

³⁴⁵ Friedman et al.

administration procedures—namely, limited financial resources and time. The participants also discussed a need to have bilingual educational materials for farm workers to ensure all are educated on proper antibiotic administration. It should be noted, however, that the study was published in 2007, which means the knowledge base on risks of antibiotic resistance and proper administration of antibiotics may have since improved, as interventions have been implemented by the FDA and USDA. However, the key findings indicate that more education is needed on risks and judicious use of antibiotics, which is presumably still a need.

One way to reach farmers is through veterinarians. In the aforementioned study of South Carolina farmers, 100 percent of participants indicated that their preferred information sources about antibiotics were veterinarians.³⁴⁶ Veterinarians have an integral role in antibiotic stewardship practices in agriculture, as has been discussed in the policy recommendations in this thesis; however, they are also key to educating producers about the risks of overuse of antibiotics and judicious use. It is essential to hear first-hand input from livestock producers about how to implement policies in a way that is minimally intrusive and burdensome—and this can be done in collaboration with veterinarians. When governments make decisions for their people without the peoples’ feedback, the outcome is usually not positive: people resist and goals are not achieved. However, by working together on action steps and implementation plans, it is possible to achieve lofty goals. This type of approach was successful in Europe; in Denmark and the Netherlands, the producers were included in the discussions and most believed they were part of the solution.

C. FUTURE RESEARCH OPPORTUNITIES

This thesis described several case studies that focused on antibiotic use in agriculture, but many aspects of this issue were out of scope of this thesis. It is important that work continues to better understand this complex problem and examine emerging solutions that show promise in slowing the threat of antibiotic resistance.

³⁴⁶ Friedman et al.

First, policies that have been implemented should be evaluated. Much of the research published on the case studies does not evaluate the policies themselves, but is more statistical and epidemiological in nature. Better policy evaluation and assessment is needed to ensure that the policies are effective—Do they achieve what they intended to achieve and, if not, why?

In addition, several interventions other than legislative bans could be evaluated for their potential to curb the threat. This thesis touched briefly on production practices implemented in the European case study countries after their legislative bans, but more research should be conducted to determine if U.S. industrial operations could adopt some of the production practices in Denmark and the Netherlands to ensure that routine prophylaxis is not necessary. Some public health officials argue that the conditions in which food animals are raised in industrial operations in the United States may be partly to blame for the rise in the use of antibiotics and the acceleration of antibiotic resistance.³⁴⁷ Animals kept in close quarters in unsanitary conditions with weakened immune systems are more susceptible to infections, thus small doses of antibiotics are used as prophylaxis to ensure the animals do not become ill. Antibiotic use in this manner is likely to continue without regulation or widespread change to farming practices.

There are also other interventions that have not been explored in this thesis, such as evaluating the effectiveness of organizations in the United States that aim to educate interested veterinarians and farmers on antimicrobial stewardship and that work together to create plans that ensure proper drug use. In addition, this thesis did not investigate what role, if any, organic farming might play in addressing the threat of antibiotic resistance. These avenues could provide insights into other voluntary methods that individual producers could take if regulatory options are not sought.

This thesis focused solely on the administration of antibiotics to food animals; it did not discuss another important byproduct of farms and a source of antibiotic-resistant

³⁴⁷ Robert S. Lawrence, “The FDA Did Not Do Enough to Restrict Antibiotics Use in Animals,” *The Atlantic*, April 16, 2012, <https://www.theatlantic.com/health/archive/2012/04/the-fda-did-not-do-enough-to-restrict-antibiotics-use-in-animals/255878/>.

organisms: manure. There must be more research done on effective waste-management strategies on farms to eliminate modes of transmission between animals and people.

Furthermore, additional research should examine antibiotic resistance and pets. People live in close quarters with their animals, which increases the risk for sharing resistant organisms. There is limited information available regarding antibiotic use in pets and it is important to include this aspect of antibiotic administration as well as potential transmission modes in a surveillance system—especially considering the rising number of people who own backyard poultry that should be monitored.

Finally, this thesis did not explore farmer and veterinarian knowledge and attitudes about antibiotic resistance in great depth. It is possible that interventions not considered here would have a limited impact on the industries.

D. CONCLUSION

While the World Health Organization's study concluded that the Danish experience could be replicated in countries where the industry model operates similarly, the FDA and USDA have operated under the assumption that a ban on the use of antibiotics for growth promotion in livestock would not be adopted in the United States. This is unsurprising given that many industry groups do not widely accept that overuse of antibiotics in food animals contributes to antibiotic resistance. With the USDA's commitment to more surveillance, the FDA's guidance to industry on the judicious use of antimicrobials, and the voluntary changes that are being made by industry, the United States is at least acknowledging that it must engage in the conversation and pursue some solutions to this emerging threat. However, the current strategies are likely not enough to mitigate our country's contribution to this problem.

This thesis analyzed efforts in Europe and two U.S. states, and provided several strategies that could be employed at the national level that would bring the United States in line with other large agricultural industries in terms of its commitment to global health security. Antibiotic resistance will continue to be a global public health and homeland security threat if efforts to reduce reliance on antibiotics in animal husbandry are not strengthened. It is important to engage farmers and veterinarians and ensure they are

committed to finding solutions to this issue. Congress, the FDA, and the USDA should look to the successes of other nations that have actively responded to this global threat. The agencies should continue to work with industry partners to gain buy-in and acceptance of responsibility and duty to preserve medically important antibiotics to protect the health and safety of people and animals.

The research in this thesis has outlined several reasons why the United States has taken limited steps to implement strategies to curb the threat of antimicrobial resistance in the agriculture sector. This threat cannot continue to be ignored in the name of immediate expense or burdens to a sector—the costs to humanity are too great. Studying the response to this problem through a homeland security lens has illuminated a risk assessment issue for those who oppose restrictions on the use of antibiotics in an agricultural setting and science. This is a grave risk, regardless of the lack of evidence that every resistant organism can be traced to antibiotic use in livestock.

Science shows that people are being infected with multidrug resistant organisms through exposure to livestock that have developed drug-resistant bacteria because of the use of antibiotics. If the use is reduced, so is the resistance. This has been studied and proven yet, as a nation, this problem has been largely ignored. The homeland security enterprise should prioritize antibiotic resistance as a threat and work collaboratively to implement the strategies outlined in this thesis to mitigate it.

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APPENDIX. PROPOSED POLICY ANALYSIS

This appendix analyzes the four potential strategies that could enhance current approaches the United States has already employed to slow the threat of antibiotic resistance. The policies are:

- Creating an enhanced, more integrated surveillance system
- Enacting antibiotic-use reduction targets
- Prohibiting the use of antibiotics in healthy animals
- Requiring veterinarians to examine animals before they prescribe antibiotics for disease prevention

Using the CDC’s policy analytical framework, each of these strategies is analyzed in the following tables.

Table 9. Policy Package—Integrated Surveillance System

Framing questions	
<i>What is the policy lever—is it legislative, administrative, regulatory, other?</i>	Legislation.
<i>What level of government or institution will implement?</i>	Federal government.
<i>How does the policy work/operate? (e.g., Is it mandatory? Will enforcement be necessary? How is it funded? Who is responsible for administering the policy?)</i>	This would need to be a partnership between the FDA, USDA, and CDC with assistance from DHS. The policy would require veterinarians, producers, and health-care providers to report antimicrobial prescribing and use data. There may need to be consequences for entities who do not report.
<i>What are the objectives of the policy?</i>	This policy allows for a holistic view of where to focus efforts to slow the threat of antibiotic resistance and would assist in the evaluation of existing policy or demonstrate a need for new policy.

Framing questions	
<i>What is the legal landscape surrounding the policy (e.g., court rulings, constitutionality)?</i>	There would be concerns about confidentiality on the part of the data reporters, along with how the data would be used and disseminated.
<i>What is the historical context (e.g., Has the policy been debated previously)?</i>	Yes. Legislation has been introduced in the past for mandatory reporting of antimicrobial use in agriculture; however, larger integrated system has not been proposed. There has been limited discussion of implementing a system that integrates human antimicrobial use and animal use.
<i>What are the expected short-, intermediate-, and long-term outcomes?</i>	Short term, this policy would create baseline data. Intermediate would be to use the data to view trends. Long term it could be used for evaluating the effectiveness of various interventions.
<i>What might be the unintended positive and negative consequences of the policy?</i>	Unintended negative consequences would be a large reporting burden on farmers, human health-care providers, and veterinarians. Positive consequences include this system being leveraged for global use.
Potential for the policy to impact risk factors, quality of life, disparities, morbidity, and mortality	
<i>How does the policy address the problem or issue (e.g., increase access, protect from exposure)?</i>	This policy allows government to make informed decisions about interventions to slow antibiotic resistance.
<i>What are the magnitude, reach, and distribution of benefit and burden (including impact on risk factor, quality of life, morbidity, and mortality)?</i> <ul style="list-style-type: none"> • <i>What population(s) will benefit? How much? When?</i> • <i>What population(s) will be negatively impacted? How much? When?</i> 	This is a global problem. The United States would only be able to monitor the trends in the country. The surveillance system itself would benefit government agencies, scientists, researchers, farmers, veterinarians, health-care providers, animals, and people.
<i>Will the policy impact health disparities/health equity? How?</i>	This policy strategy does not impact health disparities.
<i>Are there gaps in the data/evidence base?</i>	It is not known what the impact of this particular strategy would be. However, the success of Denmark's system could provide some insights.

Likelihood that the policy can be successfully adopted and implemented	
<i>What are the current political forces, including political history, environment, and policy debate?</i>	Reporting requirements have not been welcomed by the farming industry. Veterinarians may be more accepting. Health-care providers typically do report resistant infections as part of nationally requirements, but none have been required to report antimicrobial use.
<i>Who are the stakeholders, including supporters and opponents? What are their interests and values?</i>	Veterinarians, human health-care providers, and farmers. This would be viewed as overly burdensome to report.
<i>What are the potential social, educational, and cultural perspectives associated with the policy option (e.g., lack of knowledge, fear of change, force of habit)?</i>	This would be viewed as additional regulation and a burden upon farmers.
<i>What are the potential impacts of the policy on other sectors and high-priority issues (e.g., sustainability, economic impact)?</i>	This would require a commitment from Congress to fund the data collection system at the federal level.
<i>What are the resource, capacity, and technical needs for developing, enacting, and implementing the policy?</i>	Unknown.
<i>How much time is needed for the policy to be enacted, implemented, and enforced?</i>	Unknown.
<i>How scalable, flexible, and transferable is the policy?</i>	This would be nationwide, so it is possible it could be leveraged to be used globally.
Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits	
<i>What are the costs and benefits associated with the policy from a budgetary perspective? (e.g., for public—federal, state, local—and private entities to enact, implement, and enforce the policy?)</i>	Unknown. There would be some costs for the producers and veterinarians to report information, and there would be costs to the government to set up the system.
<i>How do costs compare to benefits (e.g., cost savings, costs averted, ROI, cost-effectiveness, cost-benefit analysis, etc.)?</i> <ul style="list-style-type: none"> • <i>How are costs and benefits distributed (e.g., for individuals, businesses, government)?</i> • <i>What is the timeline for costs and benefits?</i> 	Unknown.
<i>Where are there gaps in the data/evidence base?</i>	Further research is needed to determine what it would cost to implement an integrated surveillance system in the United States.

Table 10. Policy Package—Antibiotic-Use Reduction Targets

Framing questions	
<i>What is the policy lever—is it legislative, administrative, regulatory, other?</i>	Administrative.
<i>What level of government or institution will implement?</i>	Federal government.
<i>How does the policy work/operate? (e.g., Is it mandatory? Will enforcement be necessary? How is it funded? Who is responsible for administering it?)</i>	The USDA will set mandatory antibiotic use targets for agriculture but can only do so if the previous policy strategy is implemented. There will be no way to know where to set targets unless a baseline is established through data collection.
<i>What are the objectives of the policy?</i>	The objective is to see a reduction in the use of antibiotics in general.
<i>What is the legal landscape surrounding the policy (e.g., court rulings, constitutionality)?</i>	None.
<i>What is the historical context (e.g., Has the policy been debated previously)?</i>	This does not appear to have been debated in the United States. However, the Netherlands and Denmark have both had targets implemented.
<i>What are the expected short-, intermediate-, and long-term outcomes?</i>	A long-term overall reduction in the use of antibiotics in livestock, thus reducing the prevalence of antibiotic resistance.
<i>What might be the unintended positive and negative consequences of the policy?</i>	There could be more sick animals if farmers are not relying on vets to help them meet antibiotic use targets, or if they are not employing different farming practices to promote better infection control/prevention.
Potential for the policy to impact risk factors, quality of life, disparities, morbidity and mortality	
<i>How does the policy address the (e.g., increase access, protect from exposure)?</i>	Setting mandatory goals will reduce antibiotic use and resistance on farms.
<i>What are the magnitude, reach, and distribution of benefit and burden (impact on risk, quality of life, morbidity, and mortality)?</i> <ul style="list-style-type: none"> • <i>What population(s) will benefit? How much? When?</i> • <i>What population(s) will be negatively impacted? How much? When?</i> 	Animals could potentially be negatively impacted. Farmers could be negatively impacted by financial losses. Farmers will be less likely to contract a drug-resistant infection if there are fewer resistant organisms on their farms due to reduced antibiotic use.
<i>Will the policy impact health disparities/health equity? How?</i>	No.
<i>Are there gaps in the data/evidence base?</i>	It is difficult to assess the impact in the United States, but European experiences could be examined.

Likelihood that the policy can be successfully adopted and implemented	
<i>What are the current political forces, including political history, environment, and policy debate?</i>	The farming industry would likely oppose this policy. It will be perceived as an overreach in regulation.
<i>Who are the stakeholders, including supporters and opponents? What are their interests and values?</i>	The farming industry and associations will be against this, as will pharmaceutical companies. Public health organizations and the medical and scientific community would be in favor.
<i>What are the potential social, educational, and cultural perspectives associated with the policy option (e.g., lack of knowledge, fear of change, force of habit)?</i>	Lack of knowledge about the issue of antibiotic resistance among farmers could contribute to a perception of overregulation.
<i>What are the potential impacts of the policy on other sectors and high-priority issues (e.g., sustainability, economic impact)?</i>	The pharmaceutical industry has argued market restrictions in antibiotic use may accelerate resistance. Introducing new drugs is key to addressing resistance; there are limited incentives for drug companies to develop new agents. The industry asserts that restrictions on antibiotics would result in lost earning potential. In addition, strict regulations increase development costs. Because of these factors, antibiotics are not an attractive economic choice for new drug development. ³⁴⁸ The world will continue to rely on existing antibiotics, resulting in accelerating resistance because of limited options. However, many of the antibiotics used in the animal industry are also off patent and companies that are selling these products may not be the same as those developing new products. The loss of sales in the animal sector may have no impact on the development of new antibiotics.
<i>What are the resource, capacity, and technical needs developing, enacting, and implementing the policy?</i>	This policy would require limited resources; however, an enforcement component would increase this substantially.
<i>How much time is needed for the policy to be enacted, implemented, and enforced?</i>	Likely two years.
<i>How scalable, flexible, and transferable is the policy?</i>	This would probably be very specific to the United States. Transferability would be limited.

³⁴⁸ E. Power, "Impact of Antibiotic Restrictions: The Pharmaceutical Perspective," *Clinical Microbiology and Infection* 12 (August 1, 2006): 25–34, <https://doi.org/10.1111/j.1469-0691.2006.01528.x>.

Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits	
<i>What are the costs and benefits associated with the policy, from a budgetary perspective? (e.g., for public—federal, state, local—and private entities to enact, implement, and enforce the policy?)</i>	The costs would be limited and the benefits to society as a whole would be large.
<i>How do costs compare to benefits (e.g., cost savings, costs averted, ROI, cost effectiveness, cost-benefit analysis, etc.)?</i> <ul style="list-style-type: none"> • <i>How are costs and benefits distributed (e.g., for individuals, businesses, government)?</i> • <i>What is the timeline for costs and benefits?</i> 	The costs would be limited and the benefits to society as a whole would be large.
<i>Where are there gaps in the data/evidence base?</i>	More research is needed to develop a fiscal analysis on what this would cost.

Table 11. Policy Package—Prohibit the Use of Antibiotics in Healthy Animals

Framing questions	
<i>What is the policy lever—is it legislative, administrative, regulatory, other?</i>	Legislative or administrative guidance issued to veterinarians.
<i>What level of government or institution will implement?</i>	Federal government.
<i>How does the policy work/operate? (e.g., Is it mandatory? Will enforcement be necessary? How is it funded? Who is responsible for administering the policy?)</i>	This policy would prohibit the use of antibiotics in healthy animals UNLESS disease has been diagnosed in other animals in the same flock or herd. This policy does not consider environmental factors or transport to be evidence of elevated bacterial disease risk.
<i>What are the objectives of the policy?</i>	This policy ensures that antibiotics are not provided to animals for non-therapeutic purposes, including routine disease prevention.
<i>What is the legal landscape surrounding the policy (e.g., court rulings, constitutionality)?</i>	None.
<i>What is the historical context (e.g., Has the policy been debated previously)?</i>	This policy has been introduced as part of the Preservation of Antibiotics for Medical Treatment Act, introduced by the late Louise Slaughter of New York.
Framing questions	

<i>What are the expected short-, intermediate-, and long-term outcomes?</i>	In the short term, it is possible that more animals would become ill because of production practices. Intermediate outcomes could include changes in farming practices and increased production, as seen in Denmark. Long term, the country should see less antibiotic-resistant organisms in meat and less resistant infections in animals and people.
<i>What might be the unintended positive and negative consequences of the policy?</i>	Unintended negative consequences include significant financial losses for farmers due to illness in animals.
Potential for the policy to impact risk factors, quality of life, disparities, morbidity, and mortality	
<i>How does the policy address the problem or issue (e.g., increase access, protect from exposure)?</i>	This policy ensures the judicious use of antibiotics to assist with reducing antibiotic resistance.
<i>What are the magnitude, reach, and distribution of benefit and burden (including impact on risk factor, quality of life, morbidity, and mortality)?</i> <ul style="list-style-type: none"> • <i>What population(s) will benefit? How much? When?</i> • <i>What population(s) will be negatively impacted? How much? When?</i> 	There will be less antibiotic-resistant infections in animals and people. If producers do not work to change production practices, there may be more infections and morbidity among animals in the short term, which will increase costs to the producers.
<i>Will the policy impact health disparities/ health equity? How?</i>	No.
<i>Are there gaps in the data/evidence base?</i>	Yes. It is unclear how much impact this policy would have in the United States without additional changes to farming operations.
Likelihood that the policy can be successfully adopted and implemented	
<i>What are the current political forces, including political history, environment, and policy debate?</i>	The agriculture industry would likely be opposed to this type of prohibition given historical opposition to similar bills. Pharmaceutical companies would also likely be opposed. Previous bills have never made it out of legislative committee.

Likelihood that the policy can be successfully adopted and implemented	
<i>Who are the stakeholders, including supporters and opponents? What are their interests and values?</i>	Agriculture industry, pharmaceutical companies, veterinarians, the general public. The agriculture industry would want to ensure animal health and a profitable industry. Pharmaceutical companies would want to ensure they do not lose money and veterinarians to ensure animal health. The general public wants to slow antibiotic resistance; however, they want to ensure that the food supply is not harmed and that prices do not go up due to the policy change.
<i>What are the potential social, educational, and cultural perspectives associated with the policy option (e.g., lack of knowledge, fear of change, force of habit)?</i>	This would likely require a phase-in approach to allow the industry the opportunity to adapt its practices (e.g., improve biosecurity to reduce risk of disease transmission).
<i>What are the potential impacts of the policy on other sectors and high-priority issues (e.g., sustainability, economic impact)?</i>	Unknown.
<i>What are the resource, capacity, and technical needs developing, enacting, and implementing the policy?</i>	The policy would not require capacity to implement at a governmental level, but capacity to provide outreach and technical assistance would be needed to ensure that producers and veterinarians know what is expected of them. This could be extensive. If producers need to change their practices, this may require advisement from experts.
<i>How much time is needed for the policy to be enacted, implemented, and enforced?</i>	Unknown. This would be a phased-in policy likely over several years, possibly 5 years after enacted, to allow producers to comply.
<i>How scalable, flexible, and transferable is the policy?</i>	This policy could potentially be leveraged in other countries.
Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits	
<i>What are the costs and benefits associated with the policy, from a budgetary perspective? (e.g., for public—federal, state, local—and private entities to enact, implement, and enforce the policy?)</i>	A fiscal note would be needed for government implementation. The possible costs to industry are unknown but likely sizeable given necessary changes to farming practices, the potential for illnesses in the short term, and potential animal loss.

Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits	
<p><i>How do costs compare to benefits (e.g., cost savings, costs averted, ROI, cost effectiveness, cost-benefit analysis, etc.)?</i></p> <ul style="list-style-type: none"> • <i>How are costs and benefits distributed (e.g., for individuals, businesses, government)?</i> • <i>What is the timeline for costs and benefits?</i> 	<p>Long-term benefits are immeasurable—the threat of antibiotic resistance will slow enough to allow pharmaceutical companies to research and develop new therapies. It could take decades to see the effects.</p>
<p><i>Where are there gaps in the data/evidence-base?</i></p>	<p>The industries will likely argue that there is insufficient evidence that reducing antibiotic use in agriculture reduces resistant infections in people.</p>

Table 12. Policy Package—Annual Veterinary Examination for Prophylaxis

Framing questions	
<p><i>What is the policy lever—is it legislative, administrative, regulatory, other?</i></p>	<p>Legislative.</p>
<p><i>What level of government or institution will implement?</i></p>	<p>Federal and state partnership.</p>
<p><i>How does the policy work/operate? (e.g., Is it mandatory? Will enforcement be necessary? How is it funded? Who is responsible for administering the policy?)</i></p>	<p>This policy would require the establishment of a veterinary-client relationship among producers and veterinarians and would require at least one physical examination of animals before they are prescribed antibiotics for prophylaxis. The veterinarian would, using professional judgment, decide if preventive treatment is needed to protect a herd when there is evidence of disease.</p>
<p><i>What are the objectives of the policy?</i></p>	<p>This policy aims to ensure judicious use of antibiotics in farm animals.</p>
<p><i>What is the legal landscape surrounding the policy (e.g., court rulings, constitutionality)?</i></p>	<p>None.</p>
<p><i>What is the historical context (e.g., Has the policy been debated previously)?</i></p>	<p>This does not appear to have been debated in the United States at a national level. It has been debated at the state level in California with the requirement of establishing veterinarian-client relationships.</p>
<p><i>What are the expected short-, intermediate-, and long-term outcomes?</i></p>	<p>Healthy animals with the lowest amount of antibiotics used.</p>

Framing questions	
<i>What might be the unintended positive and negative consequences of the policy?</i>	It may be difficult for herds to receive an annual visit/exam and would exacerbate an already taxed veterinary workforce.
Potential for the policy to impact risk factors, quality of life, disparities, morbidity, and mortality	
<i>How does the policy address the problem or issue (e.g., increase access, protect from exposure)?</i>	This policy ensures the judicious use of antibiotics to assist with reducing antibiotic resistance.
<i>What are the magnitude, reach, and distribution of benefit and burden (including impact on risk factor, quality of life, morbidity, and mortality)?</i> <ul style="list-style-type: none"> • <i>What population(s) will benefit? How much? When?</i> • <i>What population(s) will be negatively impacted? How much? When?</i> 	The animals will benefit by ensuring that they have been examined and given appropriate treatment or prevention. Farmers will likely need to pay more for more visits. Fewer resistant infections for people and animals.
<i>Will the policy impact health disparities/ health equity? How?</i>	No.
<i>Are there gaps in the data/evidence base?</i>	The total impact on these populations is unknown.
Likelihood that the policy can be successfully adopted and implemented	
<i>What are the current political forces, including political history, environment, and policy debate?</i>	This may be palatable given that every farm now must have a veterinary oversight per the FDA in order to have a veterinary feed directive. ³⁴⁹
<i>Who are the stakeholders, including supporters and opponents? What are their interests and values?</i>	Veterinarians could be for this, but they might be worried about having enough human capital in the field to keep up with the demand.
<i>What are the potential social, educational, and cultural perspectives associated with the policy option (e.g., lack of knowledge, fear of change, force of habit)?</i>	Unknown.
<i>What are the potential impacts of the policy on other sectors and high-priority issues (e.g., sustainability, economic impact)?</i>	If fewer antibiotics are being used, this will have an impact on the pharmaceutical companies.

³⁴⁹ FDA Center for Veterinary Medicine, “Guidance for Industry #213.”

Likelihood that the policy can be successfully adopted and implemented	
<i>What are the resource, capacity, and technical needs developing, enacting, and implementing the policy?</i>	The policy would not require a lot of capacity to implement at a governmental level, but technical assistance would be needed to ensure that veterinarians and farmers knew what was expected of them to comply.
<i>How much time is needed for the policy to be enacted, implemented and enforced?</i>	Unknown.
<i>How scalable, flexible, and transferable is the policy?</i>	This could be leveraged in other countries.
Comparison of the costs to enact, implement, and enforce the policy with the value of the benefits	
<i>What are the costs and benefits associated with the policy, from a budgetary perspective? (e.g., for public—federal, state, local—and private entities to enact, implement, and enforce the policy?)</i>	It is unknown what this will cost farmers; government cost will be limited.
<i>How do costs compare to benefits (e.g., cost savings, costs averted, ROI, cost effectiveness, cost-benefit analysis, etc.)?</i> <ul style="list-style-type: none"> • <i>How are costs and benefits distributed (e.g., for individuals, businesses, government)?</i> • <i>What is the timeline for costs and benefits?</i> 	Veterinarians will benefit; farmers will benefit but will end up spending more money on visits, and possibly less money on antibiotics. The benefits outweigh any potential costs. It could take decades to see the effects.
<i>Where are there gaps in the data/evidence-base?</i>	Unknown. More research is needed.

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