One Health Pandemic Prevention and Mitigation: The Role of FDA

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"Biological threats—whether naturally occurring, accidental, or deliberate in origin—are among the most serious threats facing the United States and the international community."[1]

ABSTRACT

Ten years ago, world leaders gathered in Stone Mountain, Georgia to operationalize the One Health concept. One Health was born of the notion that animal health, human health, and ecosystem health are all interconnected. By developing capacities to work within that global network, proponents of One Health hoped that they could forestall the next great pandemic. As we now know, they could not. This paper, however, argues that the fundamentals of One Health are sound and the paradigm should be more fully embraced. In particular, the paper examines how FDA uses One Health and how it could expand its use to better prepare to avoid another pandemic.

I. INTRODUCTION

Scientists believe that SARS-CoV-2 originated from a virus circulating within a population of horseshoe bats.[2] Wuhan, China, where it apparently first appeared, is actually far from any bat colonies.[3] But continued environmental pressures and human-animal interactions, and possibly an intermediate animal vector, created a situation where the virus jumped to infect humans.[4] That sounds dramatic, but it is in fact the pathway taken by more than 75% of emerging or re-emerging human infectious diseases.[5] As just one example, researchers estimate that at least 3,200

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1 THE PRESIDENT OF THE UNITED STATES, NATIONAL BIODEFENSE STRATEGY i (2018), https://trumpwhitehouse.archives.gov/wp-content/uploads/2018/09/National-Biodefense-Strategy.pdf [https://perma.cc/BL8Q-EKDN].

2 Talha Burki, *The Origin of SARS-CoV-2*, 20 THE LANCET 1018 (2020).

3 *Id.* at 1018–19.

4 *See id.*

5 *Zoonotic Diseases*, CTRS. FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/onehealth/basics/zoonotic-diseases.html (last updated July 1, 2021) [https://perma.cc/6Z6H-DLBH].

different coronaviruses affect bats.[6] Most of those will not end up posing a threat to humans,[7] but there is no reason to assume that some will not. And bats may not even be the most common reservoir for zoonotic disease.[8]

Coronaviruses (SARS-CoV-1, SARS-CoV-2, and MERS-CoV) are only the most recent zoonotic[9] pathogens causing epidemic effects.[10] Most zoonotic disease in the United States is bacterial in nature, and therefore less likely to be airborne and more likely constrained to physical contacts.[11] But viral disease transmitted through respiratory droplets or carried by a common insect vector (mosquitoes, for example) can reach epidemic proportions, as we learned from Zika, MERS-CoV, and SARS-CoV-1. SARS-CoV-2 confirmed our worst fears: human-to-human respiratory transmission could cause a pandemic. Moreover, the dangers that Ebola, Zika, Lyme, many influenzas, and West Nile virus pose have not gone away, although they have fortunately not yet approached pandemic proportions. In fact, the likelihood of more emerging zoonotic disease is increasing.[12]

None of these trends have surprised researchers and public health officials working in infectious disease. In the early 2000s, scientists and public health experts observed a significant increase in the global circulation of infectious agents and the growing risk that zoonotic disease posed not just for epidemics, but for a full-scale global pandemic. For many people, SARS (Severe Acute Respiratory Syndrome or SARS-CoV-1) was a wake-up call. SARS surfaced in Guangdong Province, China in November 2002,

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[6] Burki, *supra* note 2, at 1018. These viruses persist in the animal host because they are not lethal to the host—or even necessarily deleterious. But in jumping species, the virus may prove harmful or lethal to the new host. It has been estimated that coronaviruses have been with us for over 300 million years. Joel O. Wertheim, Daniel K. W. Chu, Joseph S. M. Peiris, Sergei L. Kosakovsky Pond & Leo L. M. Poon, *A Case for the Ancient Origin of Coronaviruses*, 87 J. VIROLOGY 7039, 7043 (2013). But it is only in the last couple of decades that they have been causing us major trouble.

[7] Most coronaviruses are not transmissible human to human, although recent evolutionary changes in the virus may enhance such transmissibility, which poses a greater threat to humans. Sara Platto, Jinfeng Zhou, Yanqing Wang, Huo Wang & Ernesto Carafoli, *Biodiversity Loss and COVID-19 Pandemic: The Role of Bats in the Origin and the Spreading of the Disease*, 538 BIOCHEMICAL & BIOPHYSICAL RSCH. COMMC'NS 2 (2020).

[8] *See* Benjamin T. Plourde, Tristan L. Burgess, Evan A. Eskew, Tara M. Roth, Nicole Stephenson & Janet E. Foley, *Are Disease Reservoirs Special? Taxonomic and Life History Characteristics*, 12 PLOS ONE 1 (2017).

[9] Defined as pathogens that cause disease spreading between animals and people. *Zoonotic Diseases*, *supra* note 5.

[10] *Epidemic* is defined as "an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area." U.S. DEP'T OF HEALTH & HUM. SERVS., PRINCIPLES OF EPIDEMIOLOGY IN PUBLIC HEALTH PRACTICE: AN INTRODUCTION TO APPLIED EPIDEMIOLOGY AND BIOSTATISTICS 1–72 (3d ed., 2012), https://www.cdc.gov/csels/dsepd/ss1978/SS1978.pdf [https://perma.cc/V82F-ZWPM]. A *pandemic* is "an epidemic that has spread over several countries or continents, usually affecting a large number of people." *Id.*

[11] *See US Outbreaks of Zoonotic Diseases Spread Between Animals & People*, CTRS. FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/healthypets/outbreaks.html (last visited Apr. 2, 2021) [https://perma.cc/FRF9-Y5ZT]. There are exceptions of course; tuberculosis is carried in airborne particles.

[12] This increase is driven by an 1) increasing global desire for animal protein which leads to the 2) intensification and industrialization of animal production, 3) increased exploitation of wildlife, 4) unsustainable utilization of natural resources exacerbated by 5) faster travel and trade, 6) changes in food supply chains and 7) effects of climate change. U.N. ENV'T PROGRAMME & INT'L LIVESTOCK RSCH. INST., PREVENTING THE NEXT PANDEMIC: ZOONOTIC DISEASES AND HOW TO BREAK THE CHAIN OF TRANSMISSION 15–19 (2020).

probably also originating in a virus carried by horseshoe bats, and rapidly spread beyond China.[13] More lethal than the SARS-CoV-2, the virus causing our current pandemic, SARS-CoV-1 was fortunately less infectious and eventually faded after killing fewer than 1,000 people worldwide. But at the time, the public health community understood that it could have been much worse—and, of course, with SARS-CoV-2, it is.

One response to the growing perception of a global threat from zoonotic disease is the emergence of the concept of "One World, One Health." One Health is an extension of "One Medicine," the notion that the boundaries between human health and animal health are both artificial and counterproductive.[14] One Health takes the notion several steps further, incorporating data and expertise from human health, animal health, and ecosystem health. At its most ambitious, the idea is that only by understanding the combined system effects of industrialization, population growth, geopolitical issues, migratory movements of both humans and animals, and resulting ecosystem degradation can we really understand the emergence of new and re-emergent disease and toxicity. The idea would include understanding all health conditions, including those caused by chronic conditions, infectious disease, and environmental pollutions.

One Health, as a paradigm, is more than ten years old. Nonetheless, it did not prove to be a truly effective preventive measure in forestalling the current pandemic. This paper will examine the One Health approach and consider its strengths and weaknesses in helping to prevent and mitigate the growing problem of zoonotic disease. We will examine the history of One Health, its difficulties in operationalizing its vision, and how it can be used to forestall or at least moderate the next pandemic. In particular, the paper will examine what role the Food and Drug Administration (FDA), together with other agencies, might have within a One Health paradigm. We will see what steps FDA is implementing to operationalize its own One Health Initiative and consider some specific examples of where One Health can help FDA be better prepared for the next pandemic.

Part II explores what One Health is designed to do and some of the history behind its development. It also explores some of the weaknesses that made One Health a less effective tool in forestalling the current pandemic. Part III examines FDA's particular role within a One Health paradigm in terms of pandemic preparedness. After reviewing FDA's current efforts to implement the paradigm throughout the agency, this paper explores three examples where a One Health paradigm could enrich FDA's pandemic preparedness: 1) pro-active vaccination, treatment, and diagnostic platforms; 2) antibiotic resistance; and 3) gene drives. Regulatory and practical difficulties exist in developing each of these, but each could make a real difference in pandemic preparedness. FDA and its fellow agencies, such as the Centers for Disease Control and Prevention (CDC), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA), often collaborate, but their different mandates and responsibilities have historically led to the agencies functioning independently. A One Health paradigm is necessary to deliver a better, more coordinated response.

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[13] Rui-Heng Xu, Jian-Feng He, Meirion R. Evans, Guo-Wen Peng, Hume E Field, De-Wen Yu, Chin-Kei Lee, Hui-Min Luo, Wei-Sheng Lin, Peng Lin, Ling-Hui Li, Wen-Jia Liang, Jin-Yan Lin & Alan Schnur, *Epidemiologic Clues to SARS Origin in China*, 10 EMERGING INFECTIOUS DISEASES 1030 (2004).

[14] See *infra* Section II.A for an overview of the history of One Health.

II. WHAT IS ONE HEALTH?

One Health has been defined as "the collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals and our environment."[15] It focuses on transdisciplinary thinking, attempting to fully integrate human medical, veterinary, wildlife, and environmental sciences, to develop collaborative research and interventions. Its genesis came from concerns about infectious disease with pandemic potential originating in increasingly degraded wildlife habitats. One Health's proponents see these concerns as a matter of increasing urgency. Because the world population is projected to grow from 7 billion (measured in 2011) to 9 billion in 2050, human-animal interactions are expected to increase, and the expanding population will inevitably further encroach upon animal habitats.[16] Currently, approximately 55% of the world's population lives in urban environments.[17] Climate change is expected to cause the displacement of large populations of both humans and animals and will likely drive increasing urbanization.[18] Sixty-eight percent of the world population is likely to live in urban settings by 2050.[19] Without intervention, that urbanization may not occur in any planned fashion. It may strain infrastructure—housing capacity, sanitation, and food sources. Urban areas will encroach into previously uninhabited areas. Such urbanization provides more opportunities for zoonotic disease contacts.[20] One Health was designed to be a solution for these problems. It provides a full integration of human, animal, and environmental surveillance, research, and forecasting. This process was aptly described in 2005:

> [One Health] enhances the effectiveness of health systems by integrating contributions from new institutional economics, cultural epidemiology in a broader ecosystemic concept. The latter could have broader implications, because wildlife diversity could reduce risk of transmission of diseases (e.g., Lyme disease to human beings), and exposure to wildlife and bush meat represents a risk of newly emerging diseases in people

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15 AM. VETERINARY MED. ASS'N, ONE HEALTH—A NEW PROFESSIONAL IMPERATIVE: ONE HEALTH INITIATIVE TASK FORCE: FINAL REPORT 13 (2008).

16 *What is One Health?*, ONE HEALTH COMM'N, https://www.onehealthcommission.org/en/why_one_health/what_is_one_health (last visited Apr. 30, 2021) [https://perma.cc/BYE7-9GAQ]; *see also* Sarah Glazer, *Zoonotic Diseases: Can Future Pandemics Be Prevented?*, CQ RESEARCHER (June 26, 2020), https://library.cqpress.com/cqresearcher/document.php?id=cqresrre2020062600 [https://perma.cc/7D3R-J3M7].

17 *68% of the World Population Projected to Live in Urban Areas by 2050, says UN*, DEP'T OF ECON. & SOC. AFFS., UNITED NATIONS (May 16, 2018), https://www.un.org/development/desa/en/news/population/2018-revision-of-world-urbanization-prospects.html [https://perma.cc/M5QV-6NYP].

18 Kenneth L. Meyer, *Confronting the Pandemic Superthreat of Climate Change and Urbanization*, 63 ORBIS 565, 568 (2019).

19 *68% of the World Population Projected to Live in Urban Areas by 2050, says UN*, *supra* note 17.

20 Meyer, *supra* note 18. With SARS (CoV-2 and CoV-1) and much pandemic flu, the focus of surveillance has been on Asia. But we have a better idea of the extent of zoonotic disease in Asia than we do in other areas. For example, recent decimation of the Amazon rainforest will likely lead to new zoonotic reservoirs in Brazil. And those are not well understood or surveilled. Joel Henrique Ellwanger & José Artur Bogo Chies, *Zoonotic Spillover and Emerging Viral Diseases—Time to Intensify Zoonoses Surveillance in Brazil*, 22 BRAZ. J. INFECTIOUS DISEASES 76 (2018).

> (e.g., Ebola) and animals (e.g., Nipah virus). In turn, improved animal and human health contributes to wildlife conservation.[21]

More recently, One Health has been applied in chronic disease contexts as well.[22] Some One Health proponents urge the community to examine how physiologic changes due to shifting habitats and reduced biodiversity have effects that go beyond infectious zoonotic disease. They press for more attention to ecosystem health generally rather than merely on the zoonotic effects of environmental change.[23] FDA in particular has applied an expanded notion of One Health, also focusing on human-companion animal bond as a health factor and studying comparative factors in chronic diseases, like obesity and diabetes, as they affect both humans and the animals with whom they live.[24]

A. A History of One Health

The split between human medical science and animal veterinary science is so well engrained in most Western societies that we do not even notice it. For example, in eighteenth-century France, veterinary training was separated from medical training and over time, that division in academia and practice has become more solidified.[25] Now, legislative and administrative separation often exists between the agencies most concerned with human health and those concerned with animal health, the environment, and wildlife. However, since antiquity, animal, human, and environmental health have also been thought of as interdependent. Hippocrates noted the effects of climate on health.[26] For centuries, Hippocrates' paradigm of the balance of the four humors was believed to be equally applicable to animals and humans.[27] As modern notions of germ theory developed in the late nineteenth century, Rudolph Virchow, a German physician researching roundworms in swine, coined the term "zoonosis" and argued "Between animal and human medicine there are no dividing lines—nor should there be. The object is different but the experience obtained

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[21] Jakob Zinsstag, Esther Schelling, Kaspar Wyss & Mahamat Bechir Mahamat, *Potential of Cooperation Between Human and Animal Health to Strengthen Health Systems*, 366 THE LANCET 2142, 2144 (2005).

[22] Delphine Destoumieux-Garzón, Patrick Mavingui, Gilles Boetsch, Jérôme Boissier, Frédéric Darriet, Priscilla Duboz, Clémentine Fritsch, Patrick Giraudoux, Frédérique Le Roux, Serge Morand, Christine Paillard, Dominique Pontier, Cédric Sueur & Yann Voituron, *The One Health Concept: 10 Years Old and a Long Road Ahead*, 5 FRONTIERS IN VETERINARY SCI. 1 (2018).

[23] *Id.* at 3.

[24] ONE HEALTH: IT'S FOR ALL OF US, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/animal-veterinary/animal-health-literacy/one-health-its-all-us (last updated Jan. 14, 2021) [https://perma.cc/4SY2-GJX3].

[25] *See* Malinda Larkin, *Pioneering a Profession: The Birth of Veterinary Education in the Age of Enlightenment*, AM. VETERINARY MED. ASS'N (Dec. 19, 2010), https://www.avma.org/javma-news/2011-01-01/pioneering-profession [https://perma.cc/RM2Q-3NBK].

[26] JACQUES JOUANNA, GREEK MEDICINE FROM HIPPOCRATES TO GALEN: SELECTED PAPERS 168 (Philip van der Eijk ed., Neil Allies trans., 2012).

[27] In fact, Hippocrates' notions (as well as those of Galen of Pergamum who was likely responsible for the theory's dominance through the Middle Ages) were likely based more on animal dissections than human study. Anna Marie Eleanor Roos, *Biomedicine and Health: Galen and Humoral Theory*, ENCYCLOPEDIA.COM, https://www.encyclopedia.com/science/science-magazines/biomedicine-and-health-galen-and-humoral-theory (last visited May 1, 2021) [https://perma.cc/4BHH-UQ25].

constitutes the basis of all medicine."[28] His student, Canadian William Osler, brought the concept to North America.[29] In 1947, CDC, under the leadership of James H. Steele, DVM, MPH, established a Veterinary Public Health Division.[30] Calvin Schwabe, a professor at UC Davis School of Veterinary Medicine, coined the term "One Medicine."[31] He created a department to bridge the divide between animal and human health sciences; that department has evolved into an important One Health center today.[32]

In the early 2000s, as concerns increased about the potential for avian and other pandemic influenza, the interdependence of human and animal health and ecological change became more broadly salient. In 2004, spurred by indications of increasing spread of zoonotic disease, Rockefeller University hosted a global conference on current and potential development of disease among human, domestic animal, and wildlife populations.[33] Attendees took note of recent outbreaks of West Nile Virus, Ebola Hemorrhagic Fever, SARS, Monkeypox, Mad Cow Disease, and Avian Influenza and that human and animal health are connected. Further, they noted that environmental insults such as pollution, species loss, loss of native habitat, and global climate change were altering life on our planet and escalating the probability of zoonotic disease spreading.[34] They urged world leaders to adopt interdisciplinary and cross-sectoral approaches to disease prevention, surveillance, monitoring, control, and mitigation as well as environmental conservation.[35]At that conference, they developed the Manhattan Principles, which form the basis for the One Health/One World paradigm:

> 1) Recognize the essential link between human, domestic animal, and wildlife health and the threat disease poses to people, their food supplies and economies, and the biodiversity essential to maintaining the healthy environments and functioning ecosystems we all require.
>
> 2) Recognize that decisions regarding land and water use have real implications for health. Alterations in the resilience of ecosystems and shifts in patterns of disease emergence and spread manifest themselves when we fail to recognize this relationship.
>
> 3) Include wildlife health science as an essential component of global disease prevention, surveillance, monitoring, control, and mitigation.

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[28] *One Health: History*, CTRS. FOR DISEASE CONTROL AND PREVENTION (Oct. 25, 2016), https://www.cdc.gov/onehealth/basics/history/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fonehealth%2Fpeople-events.html (last updated Oct. 25, 2016) [https://perma.cc/BU5D-4FRU].

[29] *Id.*

[30] *Id.*

[31] *Id.*

[32] *Id.*

[33] Robert A. Cook, William B. Karesh & Steven A. Osofsky, *Conference Summary One World, One Health: Building Interdisciplinary Bridges to Health in a Globalized World*, ONE WORLD, ONE HEALTH (Sept. 29, 2004), http://www.oneworldonehealth.org/sept2004/owoh_sept04.html [https://perma.cc/8Y7Y-BNRS].

[34] *Id.*

[35] *Id.*

4) Recognize that human health programs can greatly contribute to conservation efforts.

5) Devise adaptive, holistic, and forward-looking approaches to the prevention, surveillance, monitoring, control and mitigation of emerging and resurging diseases that take the complex interconnections among species into full account.

6) Seek opportunities to fully integrate biodiversity conservation perspectives and human needs (including those related to domestic animal health) when developing solutions to infectious disease threats.

7) Reduce the demand for and better regulate the international live wildlife and bushmeat trade not only to protect wildlife populations but to lessen the risks of disease movement, cross-species transmission, and the development of novel pathogen-host relationships. The costs of this worldwide trade in terms of impacts on public health, agriculture, and conservation are enormous, and the global community must address this trade as the real threat it is to global socioeconomic security.

8) Restrict the mass culling of free-ranging wildlife species for disease control to situations where there is a multidisciplinary, international scientific consensus that a wildlife population poses an urgent, significant threat to human health, food security, or wildlife health more broadly.

9) Increase investment in the global human and animal health infrastructure commensurate with the serious nature of emerging and resurging disease threats to people, domestic animals, and wildlife. Enhanced capacity for global human and animal health surveillance and for clear, timely information-sharing (that takes language barriers into account) can only help improve coordination of responses among governmental and nongovernmental agencies, public and animal health institutions, vaccine/pharmaceutical manufacturers, and other stakeholders.

10) Form collaborative relationships among governments, local people, and the private and public (i.e., non-profit) sectors to meet the challenges of global health and biodiversity conservation.

11) Provide adequate resources and support for global wildlife health surveillance networks that exchange disease information with the public health and agricultural animal health communities as part of early warning systems for the emergence and resurgence of disease threats.

12) Invest in educating and raising awareness among the world's people and in influencing the policy process to increase recognition that we must better understand the relationships between health and ecosystem integrity to succeed in improving prospects for a healthier planet.[36]

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[36] *Id.* The conference included representatives from the World Health Organization, the UN Food and Agriculture Organization, the Centers for Disease Control and Prevention, the United States Geological Survey National Wildlife Health Center, the United States Department of Agriculture, the Canadian

The Manhattan Principles have provided the overall philosophy for all One Health applications since 2004.[37]

The outbreak of H5N1 "bird flu" in 2005 came close on the heels of the deadly but contained SARS outbreak in 2003. In the United States, H5N1 got the attention of the Bush Administration, which saw H5N1 as a real pandemic risk and treated it as both a public health and national security risk.[38] That November, the Bush Administration announced the creation of the National Strategy for Pandemic Influenza.[39] While the National Strategy's *Implementation Plan*, published in May 2006, does not explicitly reference One Health, the plan itself notes the potential of wild animals as reservoirs for potential disease, the need to protect domestic livestock, and how those threats could impact human health.[40] The following year, the American Veterinary Medical Association and the American Medical Association adopted the concept of One Health and formed the One Health Initiative task force in 2007.[41] Its report was published in 2008[42] and sought to bring together U.S. human and animal health agencies, medical doctors, and veterinarians to collaborate on health issues that affect human and animal populations. The One Health Initiative continues as a non-profit organization that promotes collaboration among individual scientists, physicians, and veterinarians world-wide.[43]

An international conference on Avian and Pandemic Influenza in New Delhi in late 2007 recommended further development of a One Health concept.[44] In response to the recommendations from the New Delhi conference, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO) formed a collaboration with the

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Cooperative Wildlife Health Centre, the Laboratoire Nationale de Sante Publique of Brazzaville, Republic of Congo, the IUCN Commission on Environmental Law, and the Wildlife Conservation Society. *Id.*

[37] The Manhattan Principles were "updated" in 2019 by the "Berlin Principles." While adhering to the overall principles laid out in 2004, the latter attempted to reintegrate ecosystem health and integrity into One Health and refocus on climate change and antimicrobial resistance. They were published prior to the pandemic. *The Berlin Principles on One Health, 2019*, ONE WORLD, ONE HEALTH, https://oneworldonehealth.wcs.org/About-Us/Mission/The-2019-Berlin-Principles-on-One-Health.aspx (last visited May 1, 2021) [https://perma.cc/5B5Z-465Z].

[38] *Pandemic Flu: Preparing and Protecting Against Avian Influenza*, THE WHITE HOUSE, https://georgewbush-whitehouse.archives.gov/infocus/pandemicflu/ (last visited May 1, 2021) [https://perma.cc/VBU4-PHWA]; U.S. DEP'T OF HOMELAND SEC., NATIONAL STRATEGY FOR PANDEMIC INFLUENZA: IMPLEMENTATION PLAN VII (2006), https://www.cdc.gov/flu/pandemic-resources/pdf/pandemic-influenza-implementation.pdf?fbclid=IwAR0L2Mdh6pwWYpDQ_pcvSRWRM6T772WNTqGfIp2pk9G2nm6ahP2d-2VsOc [https://perma.cc/FYD9-WKFL].

[39] U.S. DEP'T OF HOMELAND SEC., *supra* note 38.

[40] *Id.*

[41] *See* AM. VETERINARY MED. ASS'N, ONE HEALTH: A NEW PROFESSIONAL IMPERATIVE 4 (2008), https://www.avma.org/sites/default/files/resources/onehealth_final.pdf [https://perma.cc/F2S9-NG4B].

[42] *Id. See also One Health*, AM. VETERINARY MED. ASS'N, http://www.avma.org/onehealth (last visited June 23, 2021) [https://perma.cc/T2TV-3U28].

[43] *One Health Initiative Will Unite Human and Veterinary Medicine*, ONE HEALTH INITIATIVE, https://onehealthinitiative.com/ (last visited May 1, 2021) [https://perma.cc/2RE2-XFZ8].

[44] U.N. FOOD & AGRIC. ORG., WORLD ORG. FOR ANIMAL HEALTH, WORLD HEALTH ORG., U.N. SYS. INFLUENZA COORDINATION, U.N. CHILD. FUND, & THE WORLD BANK, CONTRIBUTING TO ONE WORLD, ONE HEALTH: A STRATEGIC FRAMEWORK FOR REDUCING RISKS OF INFECTIOUS DISEASES AT THE ANIMAL-HUMAN-ECOSYSTEMS INTERFACE 5 (2008), http://www.fao.org/3/aj137e/aj137e00.pdf [https://perma.cc/5FC3-MMHA].

United Nations Children's Fund (UNICEF), the United Nations System for Influenza Coordinator, and the World Bank to develop a joint strategic framework to deal with the evolving risk of emerging and re-emerging infectious diseases. *Contributing to One World, One Health: A Strategic Framework for Reducing Risks of Infectious Diseases at the Animal–Human–Ecosystems Interface*[45] set out six objectives for countries hoping to develop infectious disease control at the animal-human-ecosystem interface. Those included: 1) increased and standardized surveillance capacity at local, regional, and global levels; 2) communication strategies to detect and respond to animal and human disease outbreaks at national, regional, and global levels; 3) developing global rapid response support capacity; 4) interagency and cross-sectoral collaboration and partnerships; 5) control endemic zoonotic disease in developing countries; and 6) increase collaborative research capacities. This work was further amplified at a conference hosted by the Public Health Agency of Canada "One World, One Health: from ideas to action" held in Winnipeg, Manitoba in 2009 which recommended supra-country, multi and trans-disciplinary methods to integrate efforts.[46]

With the vision well-defined, the next step was to try to operationalize the One Health Concept. In 2010, participants at a meeting hosted by the CDC in Stone Mountain, Georgia tried to do just that.[47] The Stone Mountain meeting featured all the major players: it was co-hosted by WHO, FAO, and OIE and included the United Nations, the World Bank, and the European Commission and representatives from numerous countries' ministries of health and agriculture. The fifty-four international leaders present identified key policy positions, and even more important from an operationalizing standpoint, the amount of financial commitment required to bring the vision to fruition.[48] At the meeting, participants created seven essential workgroups: One Health Training, Proof of Concept, Business Plan, Country Level Needs Assessment, Capacity Building, Information Clearing House, and One Health Global Network.[49] These workgroups were designed to continue their work after the meeting and, in fact, they did.[50] An information clearinghouse, the One Health Global Network, was launched in 2012.[51] There has been some success in attracting donors. For example, the Gates Foundation Challenge included One Health concepts.[52] There has also been significant success in building expertise through a One Health curriculum

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[45] *Id.* at 6.

[46] NAT'L CTR. FOR EMERGING & ZOONOTIC INFECTIOUS DISEASES, OPERATIONALIZING "ONE HEALTH": A POLICY PERSPECTIVE—TAKING STOCK AND SHAPING AN IMPLEMENTATION ROADMAP (2010), https://www.cdc.gov/onehealth/pdfs/atlanta/meeting-overview.pdf [https://perma.cc/P84K-WZJ7].

[47] *Id.* at 2.

[48] *Id.*

[49] *Id.* at 19.

[50] *See* Carol S. Rubin, *Operationalizing One Health: Stone Mountain and Beyond*, 366 CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY 173 (2013); *see also* John S. Mackenzie, Moira McKinnon & Martyn Jeggo, *One Health From Concept to Practice*, *in* CONFRONTING EMERGING ZOONOSES 171–86 (A. Yamada et al. eds., 2014).

[51] ONE HEALTH GLOBAL NETWORK WEBPORTAL, www.onehealthglobal.net (last visited May 1, 2021) [https://perma.cc/G3GE-UYCH].

[52] Mackenzie et al., *supra* note 50, at 175.

world-wide, and the One Health World Congress holds biennial meetings to achieve this goal.[53]

But there have also been gaps in implementation. The low-hanging fruit has been plucked, but the hard work remains with significant research and infrastructure needs unmet. The Proof of Concept working group recommended bigger and more controlled comparative studies of One Health disease prediction and control strategies, as well as the development of broader surveillance strategies that fully integrated human, animal, and environmental data.[54] In addition, it has noted difficulty in integrating environmental and ecosystem factors with the more standard disease/health activity.[55] While FAO and WHO have significant funding deficits, such deficits are an even greater problem for OIE. OIE struggles for resources for its One Health goals, and true One Health collaborations between WHO, FAO, and OIE are limited.[56] Significant gaps also exist in surveillance, especially at the human-animal interface.[57] Surveillance networks at the human-animal interface exist: FAO, OIE, and WHO created the Global Early Warning System for Major Animal Diseases (GLEWS), and FAO and OIE created the Expertise on Animal Influenza (OFFLU). Most surveillance currently is focused on livestock, and even that is fragmented. Wildlife surveillance is often non-existent, and that which does exist is often poorly funded. Perhaps the most promising network was the United States Agency for International Development (USAID) PREDICT program. This program was focused on detecting the transmission of novel infectious diseases from wildlife to humans.[58] But that program was eliminated in 2019.[59]

B. One Health Infrastructure in the United States

The CDC created a One Health office in 2009, and USDA soon followed suit.[60] Although FDA and EPA participate with USDA and CDC in One Health collaborations (and FDA has champions for One Health in the Center for Veterinary

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[53] The sixth One Health World Congress was held virtually in November 2020. ONE WORLD ONE HEALTH CONGRESS, https://worldonehealthcongress.org/ (last visited May 1, 2021) [https://perma.cc/C8JC-7Y9R].

[54] Paul M. Rabinowitz, Richard Kock, Malika Kachani, Rebekah Kunkel, Jason Thomas, Jeffrey Gilbert, Robert Wallace, Carina Blackmore, David Wong, William Karesh, Barbara Natterson, Raymond Dugas & Carol Rubin, *Toward Proof of Concept of a One Health Approach to Disease Prediction and Control*, 19 EMERGING INFECTIOUS DISEASES J. (2013), https://wwwnc.cdc.gov/EID/ARTICLE/19/12/13-0265_ARTICLE [https://perma.cc/S9BA-7THB].

[55] *Id.*

[56] Mackenzie et al., *supra* note 50, at 172.

[57] NAT'L RSCH. COUNCIL, SUSTAINING GLOBAL SURVEILLANCE AND RESPONSE TO EMERGING ZOONOTIC DISEASES 56 (Gerald T. Keusch et al. eds., 2009); U.K. DEP'T FOR INT'L DEV., SURVEILLANCE AND MONITORING OF ZOONOSES ii (2011), https://assets.publishing.service.gov.uk/media/57a089ab40f0b652dd00034e/61303_zels_P3_surveillance-monitoring-zoonoses.pdf [https://perma.cc/HS4U-MCHR].

[58] Mackenzie et al., *supra* note 50, at 176–77.

[59] *U.S. Government Shutting Down USAID's Predict Program Investigating Disease Jumps From Animals To Humans*, KFF (Oct. 25, 2019), https://www.kff.org/news-summary/u-s-government-shutting-down-usaids-predict-program-investigating-disease-jumps-from-animals-to-humans/ [https://perma.cc/43KR-WFMR].

[60] U.S. DEP'T OF AGRIC., USDA "ONE HEALTH" APPROACH—FACT SHEET 2 (June 2016), https://www.usda.gov/sites/default/files/documents/fact-sheet-one-health-06-16-2016.pdf [https://perma.cc/87EL-UJR8].

Medicine (CVM)), neither agency has created a separate office focused on One Health. Fully integrating the environmental aspects into One Health Collaborations has been especially difficult. EPA's authority over animal issues is shared with the Department of the Interior Fish and Wildlife Services.[61] This shared authority creates ambiguous lines of regulatory authority. Causation of environmental effects is often less direct and more diffuse than health effects and therefore more difficult to identify and remedy. Moreover, the politicization of climate change makes any policy more complex. In addition, although the Department of Defense and the Department of Homeland Security (DHS) are very concerned with these issues as a matter of national security, the One Health endeavors of the health-focused agencies have never been fully integrated with those predominantly focused on national security.[62]

Despite significant interest in CDC and some substantial interest in parts of FDA and USDA, the One Health concept has failed to attract significant traction in Congress. Motivated by the Zika and Ebola outbreaks, Senator Al Franken introduced the One Health Act of 2016 (S.2634).[63] That bill, focusing on coordinated action by CDC, DHS, and USDA, called for the development of a national One Health plan to address potential zoonotic outbreaks.[64] It failed to get other co-sponsors. A bipartisan bill, the Advancing Emergency Preparedness Through One Health Act (S.2615),[65] was introduced in 2018 in the second session of the 115th Congress. That bill required DHHS and USDA to work together "to prevent, prepare for, and respond to zoonotic disease" and "advance scientific understanding of the connections among human, animal, and environmental health."[66] Although assigned to committee, that bill also failed to progress. Essentially the same legislation was once again introduced in the 116th Congress, this time in both the House and Senate. While H.R. 3771 and S. 1903 have attracted a few more co-sponsors, they have largely failed to progress.[67] Nonetheless, some aspects of One Health have made it into congressional requirements for pandemic preparedness without specifically mentioning One Health. The "Pandemic and All-Hazards Preparedness and Advancing Innovation Act of

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[61] For example, Fish and Wildlife Services is responsible for the Endangered Species Act, and EPA is responsible for implementation of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Where a pesticide may have an effect on an endangered species, both agencies must work together because both statutes are implicated. *About the Endangered Species Protection Program*, ENV'L PROT. AGENCY, https://www.epa.gov/endangered-species/about-endangered-species-protection-program (last visited July 25, 2021) [https://perma.cc/B8RJ-78KN].

[62] For an attempt to do so, see Gigi Gronvall, Crystal Boddie, Rickard Knutsson & Michelle Colby, *One Health Security: An Important Component of the Global Health Security Agenda*, 12 BIOSECURITY & BIOTERRORISM: BIODEFENSE STRATEGY, PRAC., & SCI. 221 (2014). Federal response to the pandemic and the need for extensive cooperation between DOD, FDA, and CDC have required enhanced collaboration. Some of this cooperation has included One Health aspects, but the environmental piece of One Health has not been a focus. FDA's Medical Countermeasures Initiative (MCMi), which is a major piece of FDA and DOD's collaboration, includes One Health concepts. *See infra* note 73 and accompanying text.

[63] One Health Act, S. 2634, 114th Cong. (2016).

[64] *Id.* § 2(b)(2).

[65] Advancing Emergency Preparedness Through One Health Act, S. 2615, 115th Cong. (2018).

[66] *Id.* § 3(b)(2)(B)(i), (viii).

[67] Advancing Emergency Preparedness Through One Health Act, H.R. 3771, 116th Cong. (2019); Advancing Emergency Preparedness Through One Health Act, S. 1903, 116th Cong. (2019).

2019" requires coordination between federal, state, and local agencies to respond to plant or animal disease that might pose a public health risk.[68]

C. Failure of One Health Efforts to Mitigate the Current Pandemic

Assuming that any one endeavor or framework could have caused or prevented the current pandemic is almost certainly irresponsible. Many of the likely failures are beyond the scope of this paper. For one, in the United States, public health has never attracted the kind of private or public funding that supports personal medical services. For example, federal funding for public health, mostly provided through CDC and FDA, has never exceeded 3.18% of total health expenditures, peaking soon after the 9/11 attacks.[69] Funding for pandemic preparedness mirrors that trend; it peaked in 2002 after 9/11, and despite a number of epidemic close-calls, it continued to steadily decline through the Bush, Obama, and Trump administrations.[70] We have heretofore been much more willing to imagine a public health crisis caused by an act of terrorism than to see it as the result of global population and climate change.

If the lack of funding is true at the national level, it is even clearer at the international level. Even WHO, far better funded than OIE, for example, has long struggled for funding. Member states' annual contributions support WHO, but many states have been reluctant to increase their share of the needed funds. This funding structure makes WHO even more reliant on earmarked voluntary contributions from states and non-

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[68] Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, Pub. L. No. 116-22, § 101, 133 Stat. 905, 907 (2019). Section 101 provides the following: "ZOONOTIC DISEASE, FOOD, AND AGRICULTURE.—Improving coordination among Federal, State, local, tribal, and territorial entities (including through consultation with the Secretary of Agriculture) to prevent, detect, and respond to outbreaks of plant or animal disease (including zoonotic disease) that could compromise national security resulting from a deliberate attack, a naturally occurring threat, the intentional adulteration of food, or other public health threats, taking into account interactions between animal health, human health, and animals' and humans' shared environment as directly related to public health emergency preparedness and response capabilities, as applicable."

[69] David U. Himmelstein & Steffie Woolhandler, *Public Health's Falling Share of US Health Spending*, 106 AM. J. PUB. HEALTH 56 (2016). By 2014, public health's share of federal health expenditures had fallen to 2.65%, a decline of 17% between 2002–2014. *Id.* Moreover, this decline is happening as health expenditures generally are increasing at rates that exceed current rates of inflation. *Id.*

[70] *See* NAT'L ACADEMIES OF SCIS., ENG'G & MED., GLOBAL HEALTH AND THE FUTURE ROLE OF THE UNITED STATES 68 (2017). The report notes that a 2016 report issued by the Trust for America's Health (TFAH) states that since 2002, one-third of funds for health security and one-half of funds for health care system preparedness were cut. *Id.*

In 2002, for example, health emergency preparedness funding was $940 million, and by FY2016 it had decreased to $660 million—this despite the constant emergence of threats that the U.S. health infrastructure has often just barely avoided. Similarly, annual funding for health care system preparedness has been reduced to just $255 million nationally, an amount intended to support every hospital in the country in being prepared for disasters. *Id.* (citation omitted).

These numbers have remained relatively steady over the last five years. Congress provided some additional funds for hospital preparedness after the Ebola scare in 2014 and largely ignored Trump Administration proposed cuts which would have brought the funding down more. Jon Greenberg, *Federal Pandemic Money Fell for Years. Trump's Budgets Didn't Help*, POLITIFACT (Mar. 30, 2020), https://www.politifact.com/article/2020/mar/30/federal-pandemic-money-fell-years-trumps-budgets-d/ [https://perma.cc/Z2PS-MJKU].

state actors.[71] Beyond funding, there is a stark failure of coordination among countries, agencies, regional actors, and global actors.[72]

Nonetheless, One Health has not seemed to effectively prevent something that fit so squarely within the paradigm that One Health was designed to offset. Many of the gaps in infrastructure and surveillance noted earlier may have played a role in that failure. The lack of binding international legal fixtures to require compliance likely exacerbated the impact of these gaps.[73] There is also, for example, evidence that global pandemic preparation put too much focus on containment at the expense of other preparedness.[74] Containment without adequate surveillance is bound to disappoint because the containment effort will inevitably come too late. We found ourselves without sufficient planning, equipment, and infrastructure once containment failed. Moreover, the world was far more focused, even after SARS-CoV-1, on potentials for pandemic flu than on the full reservoirs of coronaviruses. Availability bias[75] has affected funding and preparedness; we were simply unable to imagine the real risk of environmental pressures releasing a novel virus that could lead to a global pandemic.

One Health also can seem utopian; by trying to solve so many global problems, it is at risk of solving none. One Health functions best when targeted goals are set up to reveal infrastructure and regulatory gaps and to create networked system responses. Future success will require more resources that truly operationalize the One Health Paradigm.[76] These include: 1) better surveillance and ecological modeling of zoonotic infection and transmission; 2) better food security to limit consumption of bush meat and limit environmental encroachment and exposure to zoonotic disease in the wild; 3) better systems surveilling pathogen transmission and antibiotic resistance in and between wild animals and domestic livestock populations; 4) better education about the ecological relationship with disease; 5) better systems for rapid dissemination of zoonotic outbreaks at the country, region, and global levels; 6) pro-active planning for containment, diagnostics, therapeutics, and vaccination with an understanding that the

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[71] Srikanth K. Reddy, Sumaira Mazhar & Raphael Lencucha, *The Financial Sustainability of the World Health Organization and the Political Economy of Global Health Governance: A Review of Funding Proposals*, 14 GLOBALIZATION & HEALTH 119 (2018).

[72] A blistering report, issued by the Independent Panel for Pandemic Preparedness and Response for the WHO Executive Board, notes that the WHO was unable to incentivize any reasonable cooperation between member states for pandemic response and that years of pandemic preparation failed to reveal actual gaps in national and international response. INDEP. PANEL FOR PANDEMIC PREPAREDNESS & RESPONSE, SECOND REPORT ON PROGRESS 7–8 (2021), https://theindependentpanel.org/wp-content/uploads/2021/01/Independent-Panel_Second-Report-on-Progress_Final-15-Jan-2021.pdf [https://perma.cc/B688-ZE6E].

[73] Alexandra L. Phelan & Lawrence O. Gostin, *Law as a Fixture Between the One Health Interfaces of Emerging Diseases*, 111 TRANSACTIONS ROYAL SOC'Y TROPICAL MED. & HYGIENE 241, 242–43 (2017).

[74] COUNCIL ON FOREIGN RELATIONS, IMPROVING PANDEMIC PREPAREDNESS: LESSONS FROM COVID-19 5–6 (2020), https://www.cfr.org/report/pandemic-preparedness-lessons-COVID-19/pdf/TFR_Pandemic_Preparedness.pdf [https://perma.cc/LZF4-F6DC].

[75] A cognitive heuristic, first identified by Amos Tversky and Daniel Kahneman, through which the frequency or probability of an event is judged by the number of instances of it that can readily be brought to mind. *Availability Heuristic*, OXFORD REFERENCE, https://www.oxfordreference.com/view/10.1093/oi/authority.20110803095436724 (last visited June 27, 2021) [https://perma.cc/DCP5-RSBJ]. This perception can lead to biased or incorrect judgments. Until SARS-CoV-2, flu was far more prevalent than any potentially lethal coronavirus.

[76] U.N. ENV'T PROGRAMME & INT'L LIVESTOCK RSCH. INST., PREVENTING THE NEXT PANDEMIC: ZOONOTIC DISEASES AND HOW TO BREAK THE CHAIN OF TRANSMISSION 7–8 (2020), https://reliefweb.int/sites/reliefweb.int/files/resources/ZP.pdf [https://perma.cc/73YH-796M].

developed world will depend on the capacity of the developing world to contain zoonotic disease; and 7) imagination and funds that support preparedness.[77] And we should probably not allow our current focus on coronaviruses to make us complacent about the potential for pandemic influenza. FDA can play a pivotal role leading a One Health guided response. As described below, FDA will need to manage pro-active planning for diagnostics, therapeutics, and vaccination and will need to provide the leadership for better surveillance and mitigation of antibiotic resistance. It will also play an important supporting role in assisting with general surveillance and containment possibilities.

III. FDA'S ROLE IN ONE HEALTH PANDEMIC PREPAREDNESS

CDC, not FDA, leads the United States efforts in One Health. But FDA plays a significant role, which the current pandemic has highlighted. In this section, I outline FDA's current efforts in implementing One Health and then provide three examples: 1) pro-active vaccination, treatment, and diagnostic platforms; 2) antibiotic resistance; and 3) gene drives where a robust One Health paradigm can help FDA prepare for the next pandemic. These examples will also illuminate some of the existing obstacles and gaps that need to be resolved to make that preparation effective.

A. FDA's One Health Initiative

FDA has adopted the principles that the One Health Initiative developed and is currently operationalizing One Health actions agency-wide. FDA established the One Health Steering Committee (OHSC) on September 9, 2019 to track the initiative within the agency.[78] The OHSC has two co-chairs, FDA Chief Scientist RADM Denise Hinton and CVM Center Director Steven Solomon, and has representatives from FDA Centers (the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Food Safety and Nutrition (CFSAN), the Center for Devices and Radiologic Health (CDRH), and the Center for Tobacco Products (CTP)) and some of the Offices (e.g., the Office for Regulatory Affairs (ORA)). The OHSC began by assessing the One Health needs and priorities within each Center at FDA, with the ultimate goal of "solving health problems by recognizing the interconnection between humans, animals, and their shared environment."[79] Although FDA's individual Centers have diverse goals, the OHSC seeks to break down silos through the One Health Initiative that limit collaborative efforts to improve the agency's public health mission. The OHSC has identified a

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[77] *See id.* at 53.

[78] *See Who's Who in One Health: FDA One Health Steering Committee*, ONE HEALTH COMM'N, https://www.onehealthcommission.org/documents/filelibrary/resources/whos_who/FDA_Whos_Who_Resources_page_templat_B5160EB6E8798.pdf (last visited June 23, 2021) [https://perma.cc/3RYA-ADBG].

[79] The detailed information concerning FDA's One Health Initiative presented here is gleaned from FDA's "Grand Rounds" on June 11, 2020, featuring Capt. Brianna Skinner from FDA's Office of Counterterrorism and Emerging Threats and former CVM director Bernadette Dunham under whose aegis the One Health Initiative at FDA was started. *See* U.S. FOOD & DRUG ADMIN., A PANDEMIC AND A CALL TO ACTION FOR ONE HEALTH: THE FDA ONE HEALTH INITIATIVE, https://www.fda.gov/science-research/fda-grand-rounds/pandemic-and-call-action-one-health-fda-one-health-initiative-06112020-06112020 (last updated June 17, 2020) [https://perma.cc/KSG3-M8GY] [hereinafter "Grand Rounds" Presentation].

number of ways in which FDA is, and will be, involved in One Health activities, including increased efforts in the development of new treatments, vaccines, and devices for the prevention and control of diseases across species, educational outreach, increased communication with the public about One Health principles, improvement of surveillance and control efforts, and interagency committees and councils. Many of these are directly related to efforts to mitigate the current pandemic and to forestall future pandemics.[80]

1. One Health Examples Within FDA

First, in direct response to the current pandemic, FDA has introduced One Health aspects into its Medical Countermeasures Initiative (MCMi) as part of FDA's programs in the Office of Counterterrorism and Emerging Threats (OCET).[81] OCET is collaborating with the Office of Minority Health and Health Equity (OMHHE) on a One Health project to prevent future pandemics by implementing a "One Health Stakeholder Collaboration."[82] OCET and OMHHE have proposed partnerships with the Global Virome Project, the One Health Institute at UC Davis, the One Health Commission, and the NIH. They have played an integral part in encouraging the use of One Health principles throughout FDA.[83]

FDA's Office of Regulatory Affairs (ORA) has also been involved in One Health activities, working with state, local, tribal, territorial, and foreign agencies, especially with regards to food safety.[84] ORA is enforcing regulations that protect the food supply chain, and in doing so is involved with all areas of One Health (humans, animals, and the environment).[85] The National Center for Toxicological Research (NCTR) has also embraced One Health principles, participating in interdisciplinary and interagency committees and councils, including the Global Coalition for Regulatory Science Research and FDA's Committee for the Advancement of Clinical and Scientific Education.[86]

CBER has been involved in numerous One Health activities, including efforts in the development of new diagnostic methods, medicines, devices, and vaccines for the prevention and control of diseases across species.[87] They have also been involved in

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[80] *Id.*

[81] *See Medical Countermeasures Initiative (MCMi)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/medical-countermeasures-initiative-mcmi (last updated May 21, 2021) [https://perma.cc/WKA5-L4E9].

[82] *See* "Grand Rounds" Presentation, *supra* note 79. The information appears in the second recording featuring Capt. Brianna Skinner, which is available at https://collaboration.fda.gov/pol0p8cifodw/. The information appears at about sixteen minutes and continues.

[83] *Id.* The information appears at about seventeen minutes and continues.

[84] *Id.* The information appears at about twenty-one minutes and continues.

[85] *Id.*

[86] *Id.* The information appears at about twenty-two minutes and continues.

[87] *Id.* The information appears at about twenty-three minutes and continues.

COVID-19[88] research, evaluating vaccines and diagnostic methods.[89] CDER also takes part in One Health activities through its project CURE ID. This project is an Internet-based database that lets clinicians report novel uses of existing drugs for difficult-to-treat infectious diseases.[90] This database aligns with the One Health approach because it encourages collaboration between agencies and disciplines, it is provided in part by a joint effort between FDA and the National Center for Advancing Translational Sciences (NCATS) (part of the NIH), and it includes efforts to identify treatments for diseases with zoonotic or environmental origins.[91]

CFSAN is involved in One Health through a program called One Water One Health, which addresses how to ensure availability of water for all, including water used for irrigation, water used in food production, and the protection of essential services by aquatic ecosystems.[92] This goal is partly accomplished through surveillance of foodborne pathogens in water for agricultural use and environmental sampling exercises.[93] Even CTP has participated in the One Health Initiative by including animals in their adverse event tracking system, capturing adverse events related to tobacco use not only in humans but in animals as well, through a partnership with the CVM.[94]

2. FDA's One Health Goals for the Future

The One Health Steering Committee (OHSC) has established four overarching goals for the agency.[95] The first goal is to "create a multidisciplinary mindset for the internal and external FDA stakeholders."[96] This goal is to be achieved through the development of new ways to share information between Centers, by engaging and communicating with stakeholders outside FDA, and the inclusion of diverse populations in One Health policies and decision-making by connecting people with similar interests and goals.[97] The second goal of the OHSC is to provide infrastructure and governance structure to coordinate One Health activities.[98] The third goal is to engage governmental partners, which OHSC suggests could be accomplished by determining how other governmental agencies already integrate One Health

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[88] COVID-19 is the human disease caused by SARS-CoV-2. *See Naming the Coronavirus Disease (COVID-19) and the Virus That Causes It*, WORLD HEALTH ORGANIZATION, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (last visited June 23, 2021) [https://perma.cc/DSU8-Y2JP].

[89] *See* "Grand Rounds" Presentation, *supra* note 79. The information appears in the second recording featuring Capt. Brianna Skinner, which is available at https://collaboration.fda.gov/pol0p8cifodw/. The information appears at about twenty-three minutes and continues. Other resources on CBER appear at about twenty-five minutes in.

[90] *Id.*

[91] *Id.*

[92] *Id.* The information appears at about twenty-eight minutes and continues.

[93] *Id.*

[94] *Id.* Information regarding CTP starts at about thirty-one minutes and continues in the recording.

[95] *Id.* This information starts at about one minute and continues.

[96] *Id.*

[97] *Id.*

[98] *Id.*

approaches into their activities.[99] Finally, the fourth goal is to use One Health to globally expand FDA's impact by creating an international presence and by ensuring that FDA's emergency plans incorporate One Health principles.[100]

B. Three Examples of Areas Where a One Health Paradigm Will Help FDA With Pandemic Preparedness

As noted above, much of FDA's current One Health Initiative is focused on future pandemic preparedness, and sustaining those efforts will be essential to FDA's ability to respond more quickly to future threats. Below, this paper describes in more detail three examples of areas where FDA could use the paradigm for that preparation. Some of these examples can be done using FDA's current existing authorities; some will require additional congressional action. During a declared public health emergency such as the one we are now living through with SARS-CoV-2, FDA can use the broad authority to regulate actions related to communicable disease contained in the Public Health Service Act.[101] Much of that power will be limited after the emergency has ebbed because the regulatory flexibility permitted by an active emergency will no longer be in place. For example, Emergency Use Authorizations can be issued only after and relating to a declared public health emergency.[102] When no such emergency continues to exist, the agency and sponsors will need to abide by heightened procedural and data requirements. Congressional funding will also likely be less available as the pandemic recedes. To be effective, preparation needs to occur before the next emergency occurs. One Health preparedness will also require more collaboration, both within the agency and especially with other agencies, than currently exists. Unfortunately, it will also likely require additional funding to operationalize.

1. Pro-Active Vaccine, Therapeutic, and Diagnostic Development

To respond to the next pandemic in ways that go beyond the standard methods of containment, FDA will need to adopt a proactive approach to the development of vaccines, treatments, and diagnostic tests. As our experience with SARS-CoV-2 shows, once the infection has fully penetrated a population, it will continue to spread at rates that greatly exceed our ability to provide treatments and preventive therapies in real time. Indeed, even diagnostic abilities were significantly retarded. We need to start developing preventive measures and therapies before a disease reaches epidemic status, ideally as a disease is identified as a potentially emerging zoonotic disease.[103]

Zoonotic disease pathogens include viruses (like SARS-CoV-2), parasites, fungi, bacteria, and prions, some of which persist in soil and may then transfer to animal

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[99] *Id.*

[100] *Id.*

[101] *See* Public Health Service Act, 42 U.S.C. § 247d *et seq.* (2019); *see also* 42 U.S.C. § 264 (2002).

[102] U.S. DEP'T OF HEALTH & HUMAN SERV., U.S. FOOD & DRUG ADMIN., OFF. OF THE COMM'R, OFF. OF THE CHIEF SCIENTIST, OFF. OF COUNTERTERRORISM & EMERGING THREATS, EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES: GUIDANCE FOR INDUSTRY AND OTHER STAKEHOLDERS (2017), https://www.fda.gov/media/97321/download [https://perma.cc/7A2N-EEPS].

[103] One difficulty in beginning development at this stage is that there are thousands of potential zoonotic threats, and FDA cannot reasonably prepare for all of them. This difficulty makes platform development for classes of diseases (e.g., coronaviruses) a necessary approach.

species which can then threaten humans.[104] Some exist endemically in animals, especially wildlife, and cause the animals no apparent harm.[105] Potential disease reservoirs exist both in wildlife and in domestic livestock. Currently, the most common ways to avoid zoonotic effects in humans are pasteurization (milk), improved animal husbandry practices,[106] and avoidance (banning pet shop turtles that carry salmonellosis), as well as culling and animal reservoir destruction (mink farm destruction pursuant to COVID-19 infection).[107] None of those methods are fully effective, and the latter has potential environmental consequences as well as being increasingly socially unacceptable just as more of human-animal contacts are mounting.[108]

Until recently, vaccination of wildlife was viewed as impracticable, but it is starting to be seen as a viable pathway to protect humans against zoonotic disease.[109] Livestock have been vaccinated for decades, but only recently in the context of avoiding epidemic zoonotic disease and still rarely in the United States.[110] Vaccination of animals may serve as an effective containment measure in some instances, but we also must prepare for the contexts, like SARS-CoV-2, where containment measures fail or are imperfect. This preparation would mean producing vaccines for animals and humans at the same time, or directly for humans where animal vaccination is impracticable. Such vaccine production requires monitoring existing disease in animal reservoirs, developing treatments for emerging pathogens proactively, and having diagnostic tests on hand to detect human outbreaks. As discussed above, the United States was better prepared for an influenza outbreak than it was for a coronavirus outbreak.[111] The United States not only had more global and national surveillance for such an outbreak, CDC also had more robust testing abilities, and there have been approved anti-virals applicable to influenza for some time.[112] CDC did have testing capabilities for MERS,[113] but the sheer number of potential coronaviruses, exacerbated by the fact that the common cold is a coronavirus, complicates the diagnostic puzzle. All of these factors dictate a much broader proactive approach to priority zoonotic disease.

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[104] Thomas Monath, *Vaccines Against Diseases Transmitted from Animals to Humans: A One-Health Paradigm*, 31 VACCINE 5321, 5322 (2013).

[105] *See id.* at 5322. This lack of symptoms seems to be the case with horseshoe bats carrying many strains of coronaviruses.

[106] Including antibiotics, as discussed *infra* Section III.B.2.ii, has negative downstream effects.

[107] Monath, *supra* note 104, at 5322.

[108] *Id.*

[109] *Id.* Unfortunately, coronaviruses in bat populations may be one of the more difficult applications to imagine for direct animal vaccination.

[110] Cassandra Willyard, *Flu on the Farm*, 573 NATURE S62, S63 (2019), https://media.nature.com/original/magazine-assets/d41586-019-02757-4/d41586-019-02757-4.pdf [https://perma.cc/TE4Y-JE42].

[111] U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. DEP'T OF AGRIC., U.S. DEP'T OF THE INTERIOR, ENV'T PROT. AGENCY, NAT'L OCEANIC & ATMOSPHERIC ASS'N, PRIORITIZING ZOONOTIC DISEASES FOR MULTISECTORAL, ONE HEALTH COLLABORATION IN THE UNITED STATES (2019), https://www.cdc.gov/onehealth/pdfs/us-ohzdp-report-508.pdf [https://perma.cc/ZYG4-9RHT] [hereinafter PRIORITIZING ZOONOTIC DISEASES].

[112] *Id.*

[113] *Id.* at 13.

In an article written in response to the Zika virus outbreak, David Bloom, Steven Black, and Rino Rappuoli described what a proactive approach might look like.[114] As they note, under standard methods, vaccines and treatments usually only become available after the crisis has passed.[115] Intermediate proactive methods, which already exist today in limited applications, use platform technologies that allow for the design of vaccine and therapeutic development before a specific disease has emerged based on characteristics of existing pathogens (e.g., coronaviruses, influenzas of various types, etc.).[116] If a therapeutic, vaccine, or diagnostic is approved or licensed for treatment or prevention of an existing pathogen, the existence of the platform allows for the substitution of a part (e.g., a synthetic gene), but the majority of the platform has already been validated.[117] This substitution can allow for a streamlined regulatory process that can develop a therapeutic or vaccine much more quickly.[118] As predicted by Bloom, Black, and Rappuoli, we have seen this model in action with SARS-CoV-2 in the context of monoclonal antibodies. This model also almost certainly allowed Moderna to have a head start on developing its SARS-CoV-2 vaccine since it had been working on developing a vaccine platform for the related coronavirus MERS.[119] Much of the approval for substitutions can be done with current FDA authorities, but FDA may need new authorities and guidance to make the model achieve platforms that are functionally proactive. To make the model work, FDA will also have to adopt a One Health approach because the likely reservoir for emerging pathogens is in animal species.[120] In fact, ideally FDA would help to develop treatments and vaccines for animals so that the pathogens never threaten human populations. That kind of involvement will require some significant changes. FDA would have to become more engaged in global surveillance. FDA might also need to become more engaged with preclinical drug development. FDA would also need some mechanism to encourage industry to engage in drug development for a market that is at best hypothetical.

One barrier is economic. Under a traditional drug development scheme, drugs are shepherded through the drug approval process by a patent holder that stands to recoup significant financial rewards if FDA approves its drug. That process has significant risks, but the rewards on average exceed those risks. For vaccines, the financial risks are much higher, and vaccine development is unlikely to be profitable.[121] And the

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[114] David E. Bloom, Steven Black & Rino Rappuoli, *Emerging Infectious Diseases: A Proactive Approach*, 114 PNAS 4055, 4055 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5402424/pdf/pnas.201701410.pdf [https://perma.cc/ZE3B-4SJY].

[115] *Id.* at 4056. An exception is the vaccine for Ebola that was developed in 2014. Of course, it is only still useful because Ebola remains endemic in the Democratic Republic of the Congo.

[116] *Id.*

[117] *Id.*

[118] *Id.*

[119] Victoria Rees, *CEPI Announces Three Programmes to Develop Coronavirus Vaccine*, DRUG TARGET REV. (Jan. 27, 2020), https://www.drugtargetreview.com/news/55371/cepi-announces-three-programmes-to-develop-coronavirus-vaccine/ [https://perma.cc/DWU7-NMEZ].

[120] Laura H. Kahn, Bruce Kaplan & Thomas P. Monath, *The Convergence of Human and Animal Medicine*, *in* HUMAN-ANIMAL MEDICINE, CLINICAL APPROACHES TO ZOONOSES, TOXICANTS, AND OTHER SHARED HEALTH RISKS 1–6 (Peter M. Rabinowitz & Lisa A. Conti, eds. 2010).

[121] The United States is the predominant purchaser of vaccines and uses its market power to drive lower prices for vaccines. *See, e.g.*, JONATHAN T. VU, BENJAMIN K. KAPLAN, SHOMESH CHAUDHURI, MONIQUE K. MANSOURA & ANDREW W. LO, NAT'L BUREAU OF ECON. RSCH., FINANCING VACCINES FOR GLOBAL HEALTH SECURITY (May 2020), https://www.nber.org/system/files/working_papers/w27212/

financial return for veterinary vaccines is even lower.[122] Encouraging broader vaccine development likely requires public sector financing and public-private partnerships for any hope of success.[123]

While traditional drug sponsors involved in Operation Warp Speed abound,[124] that involvement is likely because the government has offered billion-dollar contracts to the most promising contenders.[125] That kind of funding is unsustainable and politically impossible outside of an active pandemic. In fact, even modest congressional funding will likely be difficult to sustain. Some creative economic innovations are underway. For example, three vaccinologists have proposed the establishment of the Global Vaccine Development Fund, with an initial goal of $2 billion to support the development of vaccines that are economically unattractive to conventional developers.[126] Similarly, the Coalition for Epidemic Preparedness Innovations (CEPI), a collaboration between the governments of Norway and India, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum, was formed to develop vaccines for emerging infectious diseases and to assure equitable access to those vaccines.[127] Since the outbreak of COVID-19, CEPI has been leading, with WHO, the international consortium COVAX.[128] FDA has and will need to continue to be an active partner with such entities as new proactive models are developed.[129]

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w27212.pdf [https://perma.cc/J9QG-KF2Q]; Tracy A. Lieu, Thomas G. McGuire & Alan R. Hinman, *Overcoming Economic Barriers to the Optimal Use of Vaccines*, 24 HEALTH AFFS. 666, 666 (2005).

[122] Els N. T. Meeusen, John Walker, Andrew Peters, Paul-Pierre Pastoret & Gregers Jungersen, *Current Status of Veterinary Vaccines*, 20 CLINICAL MICROBIOLOGY REVS. 489, 490 (2007).

[123] VU ET AL., *supra* note 121, at 12.

[124] Operation Warp Speed is a collaboration involving the Department of Health and Human Services (DHHS), including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DOD). *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., FROM THE FACTORY TO THE FRONTLINES: THE OPERATION WARP SPEED STRATEGY FOR DISTRIBUTING A COVID-19 VACCINE 1, 6–7 (2020), https://www.hhs.gov/sites/default/files/strategy-for-distributing-covid-19-vaccine.pdf [https://perma.cc/YMU3-E2JU]. Its mission is to deliver vaccines, therapeutics, and diagnostics to fight SARS-CoV-2 in record time; the goal for the first vaccines is first quarter 2021. *See id.*

[125] As of this writing, the full contract amounts are not available. Sydney Lupkin, *How Operation Warp Speed's Big Vaccine Contracts Could Stay Secret*, NPR (Sept. 29, 2020), https://www.npr.org/sections/health-shots/2020/09/29/917899357/how-operation-warp-speeds-big-vaccine-contracts-could-stay-secret [https://perma.cc/A2TZ-BE5X].

[126] Bloom et al., *supra* note 114, at 4057; Stanley A. Plotkin, Adel A.F. Mahmoud & Jeremy Farrar, *Establishing a Global Vaccine Development Fund*, 373 NEW ENG. J. MED. 297 (2017).

[127] *About Us*, CEPI, https://cepi.net/about/whoweare/ (last visited August 8, 2021) [https://perma.cc/LNQ8-LNWG].

[128] *Id.* Since the outbreak of SARS-CoV-2, CEPI, together with WHO, has been leading COVAX, a collaboration of 150 countries engaged in developing vaccines for the virus. The United States is not a participant in COVAX, although FDA is actively engaged in issues surrounding the vaccine development.

[129] *See, e.g.*, U.S. FOOD & DRUG ADMIN., *Identification and Use of Biomarkers to Advance Development of Preventive Vaccines*, (Sept. 16, 2019), https://www.fda.gov/media/129175/download [https://perma.cc/P7P5-ESPZ] (where FDA, CEPI, and NIH hosted a workshop on identifying biomarkers for vaccine development). FDA (as well as its European counterpart, EMA) is a member of CEPI's Joint Coordination Group, which advises the organization in addressing challenges relating to all aspects of vaccine development and preparedness, including research and development, regulation, stockpiling, and equitable distribution and delivery. The Joint Coordination Group also advises the organization when a priority pathogen (e.g., SARS-CoV-2) is identified. *About Us*, *supra* note 127. FDA and CDC representatives also serve on the organization's Scientific Advisory Board. *Id.*

In addition, regulatory and structural barriers—or perhaps better stated, regulatory curves, gaps, and blind alleys—need to be negotiated. As an agency, FDA is significantly siloed. Each of the six Centers operate fairly autonomously.[130] Although the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) have so many overlapping authorities that they are used to working together closely,[131] that overlap is not necessarily true for the Center for Veterinary Medicine (CVM) and the other centers. CVM has the lowest overall budget[132] and significantly less political clout than the other Centers, and yet it is the logical lead for One Health endeavors. Moreover, the agency has become largely dependent on user fees; CBER, CDER, and CVM all use user fees to fund the drug review process.[133] But a proactive framework, separate from any specific product approval and without a typical drug sponsor, is likely to be outside of the user fee funding rubric.

A truly One Health approach may also require FDA to play a larger role in preclinical studies. Currently, FDA oversight of preclinical research is often limited to Good Laboratory Practices (GLPs),[134] and industry does not have major incentives to take advantage of opportunities for preclinical consultation with the agency.[135] FDA may suggest but does not require any specific animal models, and FDA has itself noted that better predictive animal and computer-based models are needed.[136] In addition, as noted below, while the agency could possibly oversee simultaneous approvals for human and animal drugs, overseeing simultaneous approvals is more complicated with biologics. A One Health approach would refocus some of that regulatory science on animal research and translation capabilities.[137] FDA could likely perform such oversight with current authorities if the process is structured as platforms that can

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[130] *See generally* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010).

[131] In 2003, FDA announced that CBER would be merged into CDER. *CDER and CBER Make it Official*, PINK SHEET (Oct. 6, 2003), https://pink.pharmaintelligence.informa.com/PS042559/CDER-and-CBER-make-it-official [https://perma.cc/JWF8-V7KA]. That did not happen, but the two Centers have an intercenter agreement that establishes jurisdiction and mechanisms for collaborative actions. Carl C Peck, Gerald V. Quinnan, Jr., & David A. Kessler, *Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research*, FOOD & DRUG ADMIN. (Feb. 16, 2018), https://www.fda.gov/combination-products/jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-biologics-evaluation [https://perma.cc/UAU9-6EXR]. Some products that are technically biologics, e.g., monoclonal antibodies, are regulated by CDER.

[132] U.S. FOOD & DRUG ADMIN., DEPARTMENT OF HEALTH AND HUMAN SERVICES: FISCAL YEAR 2021, 13, https://www.fda.gov/media/135078/download [https://perma.cc/63RE-8ZD8].

[133] *See, e.g.*, Erika Lietzan, *FDA's Reliance on User Fees*, YALE J. ON REGUL. (Sept. 4, 2017), https://www.yalejreg.com/nc/fdas-reliance-on-user-fees/ [https://perma.cc/Z4GB-U9SY]. FDA is now reliant on user fees to support product approvals and inspections.

[134] 21 C.F.R. § 58.1.

[135] While it is not unusual for a developer to meet with FDA for pre-development consultation, such meetings are not required.

[136] U.S. FOOD & DRUG ADMIN., INNOVATION STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL TECHNOLOGIES (Mar. 2004), https://www.who.int/intellectualproperty/documents/en/FDAproposals.pdf?ua=1 [https://perma.cc/A9GN-EPEW].

[137] In 2004, FDA announced the Critical Path Initiative to introduce more regulatory science methods into the drug approval process. *See, e.g.*, Janet Woodcock & Raymond Woosley, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 ANN. REV. MED. 1, 1 (2008). A new version of Critical Path that focused on preclinical platforms could be effective.

expedite approval on a voluntary basis, although FDA may not have authority to mandate preclinical pathways.

Finally, the overall jurisdiction for development and regulation of animal and human therapies relating to infectious zoonotic disease is unusually fragmented. FDA's CBER regulates human vaccines.[138] CDER regulates monoclonal antibodies.[139] FDA's CVM is responsible for animal drugs.[140] USDA, not FDA, has authority over animal biologics and therefore vaccines and biologic treatments and diagnostics.[141] This authority applies both for livestock and wildlife, although any systematic treatment or preventive applications in wildlife populations would require state and/or Fish and Wildlife Services' oversight.[142] Moreover, USDA's regulatory pathway is not the same as FDA's. Veterinary vaccine requirements are considered generally less rigorous than those that FDA applies to human vaccines.[143] However, any biologic that simultaneously makes human and animal health claims will be regulated as a drug by FDA.[144] In addition, any treatment that might be considered a pesticide (for example, something that targets parasites in an aquaculture) may be regulated primarily by FDA as an animal drug and secondarily as a pesticide by EPA; that FDA/EPA hierarchy may reverse outside of aquaculture.[145] In addition, if the product will be used in a vertebrate animal that may be used in food or animal feed, USDA's Food Safety and

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[138] *CBER Offices & Divisions*, U.S. FOOD & DRUG ADMIN. (Sept. 18, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-offices-divisions [https://perma.cc/QT8B-6NY3]. Such products are regulated under the Public Health Service Act and the Food, Drug, and Cosmetic Act (FDCA). 42 U.S.C. § 201 *et seq*; 21 U.S.C. § 301 *et seq*.

[139] *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER)*, U.S. FOOD & DRUG ADMIN. (Feb. 2, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/transfer-therapeutic-products-center-drug-evaluation-and-research-cder [https://perma.cc/6UYG-XHRF].

[140] *Center for Veterinary Medicine*, U.S. FOOD & DRUG ADMIN. (July 16, 2020), https://www.fda.gov/about-fda/fda-organization/center-veterinary-medicine [https://perma.cc/9SQN-XEMC]. FDA has authority over new animal drugs through the FDCA. Intentional genomic alterations in vertebrate animals are also considered animal drugs subject to FDCA review. *Id.*

[141] Veterinary biologics are primarily regulated under the Virus-Serum-Toxin Act, 21 U.S.C. §§ 151–159 (1985) and is therefore administered by USDA's APHIS Center for Veterinary Biologics (APHIS CVB).

[142] There is only one vaccine currently approved for free-ranging wildlife, the RABORAL V-RG® oral rabies recombinant vaccine (Merial, Lyon, France), which is approved to vaccinate raccoons and coyotes. Other vaccinations are used, but generally off-label. Availability of oral bait vaccines make these vaccinations more feasible. NEPA requires environmental assessments for vaccinations of wildlife populations. The plight of the black footed ferret is a classic One Health paradigm; plague in that species threatens its survival and in turn passes it to its main predator, prairie dogs, which in turn threaten zoonotic transfer to humans. *See, e.g.*, *U.S. Fish and Wildlife Service Seeks Public Comment on Proposed Use of Vaccine to Protect Prairie Dogs, Endangered Black-footed Ferrets*, U.S. FISH & WILDLIFE SERVICE (Apr. 12, 2016), https://www.fws.gov/mountain-prairie/pressrel/2016/04122016_US-Fish-and-Wildlife-Service-Seeks-Public-Comment-on-Proposed-Use-of-Vaccine-to-Protect-Prairie-Dogs-Endangered-Black-footed-Ferrets-.php [https://perma.cc/DUP6-RPDE].

[143] Meeusen et al., *supra* note 122, at 490. There are advantages for developers of veterinary vaccines in that they can conduct much of the preclinical and clinical work in the target species. This ability has obvious advantages for translatability.

[144] *See* Emily W. Ruell, Donna M. Gatewood, Jeanette R. O'Hare & John D. Eisemann, *A Decision Support Tool for Determining Federal Regulatory Authority Over Products for Vertebrate Animals*, 27 VERTEBRATE PEST CONTROL CONF. 422, 428 (2016) https://doi.org/10.5070/V427110620 [https://perma.cc/N2BF-34XW].

[145] *Id.* at 429.

Inspection Service (FSIS) and FDA are responsible for enforcing tolerances or food additive regulations.[146]

On one hand, these overlapping authorities exist to meet the different requirements that these products serve for animals, particularly animals used for food, which may be quite different than human requirements and also have different safety standards. FDA and USDA have a memorandum of understanding (MOU)[147] that is designed to cross and resolve jurisdictional boundaries created by USDA's authority for animals in an area that is otherwise FDA's jurisdiction. But that MOU was not developed to deal with this type of issue. Under a One Health paradigm, FDA and USDA will have to develop a more granular and focused collaboration specific to the prevention and mitigation of zoonotic disease.

2. A One Health Approach to Combatting Antibiotic Resistance

One area that fits squarely within a One Health paradigm for thwarting the next pandemic and where FDA's role is pivotal is in combatting antibiotic resistance. SARS-CoV-2 has us all focused on viral vectors, but bacterial vectors pose potentials for epidemic and possibly pandemic disease. One fortunately still rare, but clearly existing, threat is the rise of antibiotic-resistant tuberculosis.[148] Salmonellosis, plague, brucellosis, and Lyme disease are much more common in the United States and still carry a significant disease burden, though they do not create epidemic effects.[149] There is a global trend of serious outbreaks of antibiotic-resistant disease, including a worrisome increase in resistance to antibiotics that are critical for human medicine.[150] CDC estimates that such infections caused more than 2.8 million illnesses and 35,000 deaths in the United States in 2019, an increase of 25% since 2013.[151]

Antibiotics are unquestionably one of the greatest medical success stories of all time. Since their development in the 1940s, death and morbidity from infections has been reduced to the point that we take antibiotic availability for granted. With antibiotics, we are somewhat victims of our own success. First, antibiotics have developed such a mystique that people around the world seek them as a first line of

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146 *Id.* at 423.

147 U.S. FOOD & DRUG ADMIN. & U.S. DEP'T OF AGRIC., MEMORANDUM OF UNDERSTANDING BETWEEN THE ANIMAL AND PLANT HEALTH INSPECTION SERVICE, UNITED STATES DEPARTMENT OF AGRICULTURE AND THE FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (2019) https://www.aphis.usda.gov/animal_health/vet_biologics/publications/APHIS_FDA_biologics_MOU.pdf [https://perma.cc/TEJ4-XL6E].

148 Michael Gross, *Antibiotics in Crisis*, 23 CURRENT BIOLOGY R1063 (2013); *see also* CTRS. FOR DISEASE CONTROL, FACT SHEET: MULTIDRUG-RESISTANT TUBERCULOSIS (MDR TB) (May 4, 2016), https://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm [https://perma.cc/KEP5-96WF] [hereinafter CTRS. FOR DISEASE CONTROL, FACT SHEET].

149 PRIORITIZING ZOONOTIC DISEASES, *supra* note 111.

150 WORLD HEALTH ORG., WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE (2001), http://www.who.int/drug resistance/ [https://perma.cc/6ZHR-B7GJ]; PETER WIELENGA & JORGEN SCHLUNDT, CONFRONTING EMERGING ZOONOSES 213–32 (2014).

151 CTRS. FOR DISEASE CONTROL, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES (Dec. 2019), https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf [https://perma.cc/9RSM-E6SX]; Beth E. Karp, Heather Tate, Jodie R. Plumblee, Uday Dessai, Jean M. Whichard, Eileen L. Thacker, Kis Robertson Hale, Wanda Wilson, Cindy R. Friedman, Patricia M. Griffin & Patrick F. McDermott, *National Antimicrobial Resistance Monitoring System: Two Decades of Advancing Public Health Through Integrated Surveillance of Antimicrobial Resistance*, 14 FOODBORNE PATHOGENS & DISEASE 545, 545 (2017).

defense against any infection, including for viral infections that are impervious to their action. Antibiotics are therefore subject to misuse in human contexts.[152] Second, antibiotics proved so successful in livestock that they have allowed the development of concentrated animal feeding operations (CAFOs) that have exacerbated already rampant misuse.[153] Third, antibiotics have made medical treatment of infection so successful that the pharmaceutical industry is far more interested in pursuing more profitable drugs that treat chronic disease.[154] Ironically, that success and resulting focus on chronic disease has limited our global selection of available antibiotics.[155] Antibiotic resistance has all the hallmarks of a problem that should fit a One Health solution. Resistance can be attributed to misuse of antibiotics in human medicine and widespread use in livestock for not just medicinal use but as a growth enhancer. Runoff from human and animal waste caused by that misuse has increased reservoirs of resistance in the environment both in soil and among wildlife. Increasingly resistant pathogens then pose a risk to livestock and humans.

i. Medical Misuse

Medical misuse of antibiotics is a global problem. It is equally prevalent in China as in the United States and other high-income countries. It is increasingly a problem in developing countries as well.[156] Global use of antibiotics increased 30% between 2000 and 2010. Although most countries require some sort of prescription for antibiotics, those requirements are vastly under-enforced. In some countries, nonprescription use of antibiotics accounts for a majority of antibiotic use.[157] In the United States, FDA tried to address human medical misuse through labeling changes designed to better inform physicians to curb inappropriate prescribing.[158] Nonetheless, poor prescribing practices persist, as does consumer misuse.[159] Some people have suggested that to really address the misuse in humans, FDA needs to subject antibiotics to Risk Evaluation and Mitigation Strategy (REMS)-like oversight that would impose

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[152] *The Antibiotic Alarm*, 495 NATURE 141, 141 (2013). One researcher reports that in some states, antibiotics are prescribed at a rate of one prescription for every person in the population/year. C. Lee Ventola, *The Antibiotic Resistance Crisis Part 1: Causes and Threats*, 40 PHARMACY & THERAPEUTICS 277, 278 (2015).

[153] *See, e.g.*, Mary J. Gilchrist, Christina Greko, David B. Wallinga, George W. Beran, David G. Riley & Peter S. Thorne, *The Potential Role of Concentrated Animal Feeding Operations in Infectious Disease Epidemics and Antibiotic Resistance,* 115 ENV'T HEALTH PERSPS. 313 (2007).

[154] Dominique L. Monnet, *Antibiotic Development and the Changing Role of the Pharmaceutical Industry*, 17 INT'L J. RISK & SAFETY MED. 133 (2005).

[155] *Id.*

[156] Daniel J. Morgan, Iruka N. Okeke, Ramanan Laxminarayan, Eli N. Perencevich & Scott Weisenberg, *Non-Prescription Antimicrobial Use Worldwide: A Systematic Review*, 11 LANCET INFECTIOUS DISEASES, 692 (2011).

[157] *Id.*

[158] Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use, 68 Fed. Reg. 6062, 6073 (Feb. 6, 2003).

[159] Aaron S. Kesselheim & Kevin Outterson, *Improving Antibiotic Markets for Long Term Sustainability*, 11 YALE J. HEALTH, POL'Y, L. & ETHICS 113 (2011) (describing the ways patient and provider behaviors contribute to resistance); *see also* CTRS. FOR DISEASE CONTROL, FACT SHEET, *supra* note 148.

prescription requirements.[160] However, any effective restrictions would likely exceed FDA's REMS authorities, making the ability for FDA to address the issue without congressional action unlikely.[161]

ii. Agricultural Contributions to Antibiotic Resistance

The use of antibiotics in agriculture is likely even more important for antibiotic resistance. Most people are unaware that antibiotics are used on plants, particularly in fruit trees, causing significant environmental effects.[162] For example, in Florida, about 90% of citrus trees have been affected by a bacteria that causes "citrus greening."[163] An invasive insect, the Asian citrus psyllid, arrived in the United States within the last twenty-five years and spreads the bacteria through the trees.[164] Without treatment, the trees become less productive and eventually die.[165] That means that much of the nation's citrus crop is threatened. EPA, not FDA, regulates the use of antibiotics on plants.[166] And EPA has authorized the use of streptomycin and oxytetracycline for "emergency use" on the citrus trees.[167] Both drugs are medically important for human use.[168] Whether they will be effective against the bacteria involved in citrus greening, however, is not clear.

Despite objections from CDC and FDA, EPA has proposed allowing as much as 650,000 pounds of streptomycin, ten times the annual human use in the United States,

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[160] Brad Spellberg, Martin Blaser, Robert J. Guidos, Helen W. Boucher, John S. Bradley, Barry I. Eisenstein, Dale Gerding, Ruth Lynfield, L. Barth Reller, John Rex, David Schwartz, Edward Septimus, Fred C. Tenover & David N. Gilbert, *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives*, 52 CLINICAL INFECTIOUS DISEASES S397, S402 (2011).

[161] FDAAA gave FDA authority to require a REMS to assure that benefit exceeds risk in the use of a medical product. Food and Drug Amendments Act of 2007, Pub. L. No. 110-85, § 901 (codified at 21 U.S.C. § 355-1 (2007)). FDA has used REMS in areas where physician prescribing has been problematic, especially in the context of opioids. REMS can be used to educate prescribing patterns, but FDA is severely limited in expanding REMS beyond voluntary requirements. The opioid experience does not bode well for any similar expanded efforts with antibiotics. *See, e.g.*, Jeffrey Eric Rollman, James Heyward, Lily Olson, Peter Lurie, Joshua Sharfstein & G. Caleb Alexander, *Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products*, 321 JAMA 676 (2019), https://jamanetwork.com/journals/jama/fullarticle/2725233 [https://perma.cc/SHL5-HWJE]. Moreover, there have long been questions about whether FDA has authority to use REMS to extend the longevity and effectiveness of the product rather than to provide safety for the users of the product. *See* Ben Moscovitch, *Antibiotics REMS Floated as Option to Curb Resistance, Protect Efficacy*, 16 INSIDE WASHINGTON'S FDA WEEK 1, 10–11 (May 14, 2010).

[162] Tetracyclines and streptomycin are used for treatment and prophylaxis of bacterial infections in apples and pears. *See* Anne K. Vidaver, *Uses of Antimicrobials in Plant Agriculture*, 34 CLINICAL INFECTIOUS DISEASE S107, S107 (2002).

[163] Andrew Jacobs, *Citrus Farmers Facing Deadly Bacteria Turn to Antibiotics, Alarming Health Officials*, N.Y. TIMES (May 17, 2019), https://www.nytimes.com/2019/05/17/health/antibiotics-oranges-florida.html [https://perma.cc/TP42-WQCE].

[164] *Id.*

[165] *Id.*

[166] EPA regulates antibiotics used as pesticides under the statutory authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). 7 U.S.C. §§ 136–136y; *Antimicrobial Pesticides*, ENV'T PROT. AGENCY (Sept. 2, 2020), https://www.epa.gov/pesticides/antimicrobial-pesticides [https://perma.cc/9577-JLAZ].

[167] Jacobs, *supra* note 163.

[168] *See id.* (noting that the antibiotics are used to treat syphilis, tuberculosis, urinary tract infections).

to be sprayed on citrus crops each year.[169] EPA has said it will control against potential antibiotic resistance by limiting the use to seven years and through additional monitoring.[170] Public health advocates are not convinced.[171]

Antibiotic use in livestock has long been controversial, and FDA has been at the center of much of the controversy. Antibiotics are used in animals for the treatment, control, and prevention of disease (treatment use), as well as to hasten animal weight gain or for improving feed efficiency (production use).[172] Both are now contentious. While on its face, treatment use is not inappropriate, critics argue that much treatment use is required because of poor animal husbandry and overcrowding.[173] They argue this need for treatment is particularly true in concentrated animal feeding operations (CAFOs).[174] Production use of these drugs in animals is even more problematic. The drugs are administered to add growth factors that allow producers to bring animals to market more quickly.[175] Critics note that both treatment and production use leaves antibiotic residues in meat products that may lead to greater levels of resistance that are transferred via food consumption to the human population.[176] In addition, antibiotics are found in manure and water runoff near the facilities where the animals are raised.[177] Both manure and runoff are considered probable drivers of antibiotic resistance transmission to and from livestock to humans.[178] FDA regulates antibiotic use in animals as animal drugs.[179] After decades of uncertainty about the limits of FDA authority to reduce livestock use, sales trends in antibiotics show some evidence of progress, although critics maintain that more progress needs to be made.[180]

Laura Kahn describes many of the difficulties FDA experienced in determining how to regulate antibiotic use in livestock feed in the United States.[181] Animal producers began using penicillin in livestock feed soon after its discovery and use in humans, and FDA's existing authorities allowed it to approve use in animals for both treatment and production purposes.[182] As early as the 1960s, critics warned that use of antibiotics

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169 Jacobs, *supra* note 163.

170 *Id.*

171 *Id.*

172 *See* JIM O'NEILL, ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT: REDUCING UNNECESSARY USE AND WASTE 1 (2015).

173 *See id.* at 2–3.

174 *Id.*

175 *Id.* at 5.

176 *Id.*

177 *Id.* at 9; David W. Graham, Gilles Bergeron, Megan W. Bourassa, James Dickson, Filomena Gomes, Adina Howe, Laura H. Kahn, Paul S. Morley, H. Morgan Scott, Shabbir Simjee, Randall S. Singer, Tara C. Smith & Carina Storrs, *Complexities in Understanding Antimicrobial Resistance Across Domesticated Animal, Human and Environmental Systems,* ANNALS N.Y. ACAD. SCIS. 17, 19 (2019).

178 *See* Graham et al., *supra* note 177, at 17, 19.

179 Food, Drug, and Cosmetic Act, 21 U.S.C. § 201(g)(1)(B)–(C) (2018).

180 Karin Hoelzer, *Antibiotic Sales for Animal Agriculture Increase Again After a Two-Year Decline*, PEW (Jan. 16, 2020), https://www.pewtrusts.org/en/research-and-analysis/articles/2020/01/16/antibiotic-sales-for-animal-agriculture-increase-again-after-a-two-year-decline [https://perma.cc/F3QU-7EDW].

181 LAURA H. KAHN, ONE HEALTH AND THE POLITICS OF ANTI-MICROBIAL RESISTANCE (2016) (ebook).

182 *Id.*

in livestock was causing antibiotic resistance. As a result, Great Britain invoked partial bans of such use.[183] In the United States, FDA created an ad hoc Committee on the Veterinary Medical and Nonmedical Uses of Antibiotics.[184] However, in 1970, during congressional hearings on the use of antibiotics in animal feed, Senator Bob Dole of Kansas proposed a requirement that proved to be a barrier to FDA's action to limit uses of antibiotics in animal feed for the next four decades, stating: "Once FDA approves a feed additive it should then be FDA's responsibility to prove what the new hazards are before taking action to ban the use of the approved additive. This proposed ban assumes a human health hazard that scientists cannot agree exists."[185] Congress continued to periodically hold hearings. Congress's Office of Technology and Assessment evaluated the risks and benefits of the use of antibiotics and diethylstilbestrol in animal feed.[186] FDA co-sponsored a report by the National Research Council that recommended enhanced global surveillance and that FDA ban use of medically important antibiotics used to enhance growth in livestock.[187] But comprehensive data supporting a safety threshold, never mind a ban, for such uses was limited. In the meantime, producers continued to obtain antibiotics for livestock, usually without a prescription.[188] With no congressional financial support for surveillance, eventually FDA, CDC, and USDA created their own surveillance systems. First, USDA created the National Animal Health Monitoring System (NAHMS), designed to be acceptable to industry, which included antimicrobial resistance among other health data collected.[189] Soon after, in 1996, FDA led the establishment of the National Antimicrobial Resistance Monitoring System (NARMS).[190] NARMS monitors evidence of antimicrobial resistance among four major foodborne bacteria: Salmonella, Campylobacter, Escherichia coli, and Enterococcus.[191] NARMS also monitors evidence of resistance among Vibrio species other than V. cholera, the non-foodborne enteric organisms Shigella, and typhoidal Salmonella.[192] NARMS monitors this evidence from three sources: humans (CDC),

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[183] *Id.*; HC Deb (20 Nov. 1969) (791) cols. 1525–31 (UK) (conducted by the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine), http://hansard.millbanksystems.com/commons/1969/nov/20/use-of-antibiotics-in-animal-husbandry [https://perma.cc/KFJ7-SBEU]. The report discussed is also known as the "Swann Report."

[184] *Id.*

[185] *Id.* (This argument was also combined with an argument that FDA has since rejected—that in making such a decision, FDA should consider the benefits, i.e., the economic benefits to industry, in any ban on an approved use.).

[186] OFF. OF TECH. ASSISTANT STAFF, DRUGS IN LIVESTOCK FEED (1979), https://www.princeton.edu/~ota/disk3/1979/7905/7905.PDF [https://perma.cc/F9BK-CYP2].

[187] THE NAT'L ACADS. PRESS, MICROBIAL THREATS TO HEALTH (Mark S. Smolinski, Margaret A. Hamburg & Joshua Lederberg eds., 2003).

[188] Prescription requirements were not mandated until 2015. *Veterinary Feed Directive (VFD)*, U.S. FOOD & DRUG ADMIN. (Feb. 8, 2021), https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-feed-directive-vfd [https://perma.cc/HH86-R4WP].

[189] KAHN, *supra* note 181, at loc. 1351, 5823.

[190] *Id.* at loc. 1285.

[191] *About NARMS*, U.S. FOOD & DRUG ADMIN. (Dec. 11, 2020), https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/about-narms [https://perma.cc/7JZ7-8YEG].

[192] *Id.*

retail meats (FDA), and food animals (USDA).[193] From a One Health perspective, these monitored sources do not include a crucial sector—soil and water.[194]

In 2003, FDA itself concluded that the risks of antibiotic use in livestock were neither proved nor disproved, but FDA did not deny that there was some degree of risk and could not conclude that continued production use of penicillin and tetracycline in food animals was safe.[195] For new drug applications, FDA issued the Guidance that sets up the basic framework for review that is still used by FDA today.[196] FDA applies a risk-based assessment process for evaluating new antimicrobial animal drug applications.[197] It creates what would come to be called the requirement of "judicious use" of "medically important antibiotics."[198] The assessment requires consideration of the importance of the drug in human therapy, whether the use is selectively targeted or broadly applied to entire flocks or herds, and the degree of veterinarian involvement in the decision to use the drugs.[199] Animal drugs approved after 2003 must generally meet these standards for approval. But FDA's Guidance did not provide a satisfying framework for dealing with antibiotics that were approved prior to 2003, and those were often both medically important and the most likely to be used because they were less costly.

Over time, the drumbeat for FDA to act on antibiotic use in livestock became more insistent. A federal court ordered FDA to hold hearings and reissue a notice of withdrawal of approval for the subtherapeutic use of the antibiotics penicillin and tetracycline in food animals.[200] However, Congress failed to pass legislation clearing a path for FDA's withdrawal of those pre-2003 approvals. Without congressional

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193 *Id.*

194 *See* Graham et al., *supra* note 177 (demonstrating that monitoring soil and wastewater are crucial indicators of the existence of antimicrobial resistance.); H. Morgan Scott, Gary Acuff, Gilles Bergeron, Megan W. Bourassa, Shabbir Simjee & Randall S. Singer, *Antimicrobial Resistance in a One Health Context: Exploring Complexities, Seeking Solutions, and Communicating Risks*, ANNALS N.Y. ACAD. SCIS. 3, 3–7 (2019).

195 *See generally* U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY #152: EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS WITH REGARD TO THEIR MICROBIOLOGICAL EFFECTS ON BACTERIA OF HUMAN HEALTH CONCERN (Oct. 23, 2003), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-152-evaluating-safety-antimicrobial-new-animal-drugs-regard-their-microbiological-effects [https://perma.cc/PXJ6-DQH6] [hereinafter GUIDANCE FOR INDUSTRY #152].

196 *Id.*

197 Margaret Foster Riley, *The Regulation of Antibiotic Use in Animal Agriculture*, JURIST (May 26, 2012), https://www.jurist.org/commentary/2012/05/margaret-riley-antibiotics-fda/ [https://perma.cc/C986-TBTZ].

198 *FDA's Strategy on Antimicrobial Resistance—Questions and Answers*, U.S. FOOD & DRUG ADMIN. (Dec. 2013), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdas-strategy-antimicrobial-resistance-questions-and-answers#question4 [https://perma.cc/2JYA-WQDL] ("Medically important antibiotics" are those antibiotics that are especially important for human use—either because they are the best option for disease or condition or because the alternatives are suboptimal or non-existent.); *Judicious Use of Antimicrobials*, U.S. FOOD & DRUG ADMIN. (Jan. 2021), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/judicious-use-antimicrobials (explaining that "judicious use," which typically requires veterinary supervision, is "an approach to maximize therapeutic efficacy and minimize selection of resistant microorganisms") [https://perma.cc/C4UR-KNHV].

199 GUIDANCE FOR INDUSTRY #152, *supra* note 195.

200 Nat. Res. Def. Council, Inc. v. U.S. Food & Drug Admin., 872 F. Supp. 2d 318 (S.D.N.Y. 2012), *rev'd*, 760 F.3d 151 (2d Cir. 2014). The decision itself is rather curious, and as the Second Circuit later held, the court misunderstood some aspects of the administrative procedure.

support, FDA faced fruitless years of administrative hearings with industry stonewalling.[201] Instead, FDA offered a voluntary program for approval withdrawals to reduce subtherapeutic use of medically important antibiotics in livestock.[202] Unfortunately, a voluntary program made no one happy. Finally, on September 18, 2014, President Obama issued Executive Order 13736,[203] making reduction of antibiotic resistant bacteria a national security priority. Although not explicit, the order takes a One Health approach to the problem. It requires FDA and USDA to work together to eliminate subtherapeutic use of "medically important" antibiotics in livestock.[204] The order also requires USDA, EPA, and FDA to improve coordination in areas such as research into and surveillance of antibiotic use and resistance patterns in food-producing animals and inter-species disease transmissibility.[205]

Executive Order 13736 gave FDA's voluntary withdrawal plan real teeth.[206] In 2017, FDA completed the implementation of the program, resulting in eighty-four new drug applications (NDAs) withdrawn by their sponsors.[207] Ninety-three of the remaining applicable NDAs were converted to prescription status from over-the-counter status, and the remaining 115 NDAs now require veterinary supervision.[208] FDA is currently gathering data for use in a draft guidance for labeling to provide veterinarians guidance on appropriate duration of use.[209] It is also running a pilot program to gather "on-farm" data in poultry, swine, and cattle.[210] The full proof of success has yet to be realized. Critics argue that the same number of antibiotics are being used, but that they are just now authorized by veterinary supervision as treatment use when they were before being openly used for production use.[211] NARMS data should show over the next couple of years whether that argument is true.

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[201] KAHN, *supra* note 181, at loc. 1491.

[202] U.S. FOOD & DRUG ADMIN., CVM GFI #209 THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS (Apr. 13, 2012), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-209-judicious-use-medically-important-antimicrobial-drugs-food-producing-animals [https://perma.cc/V4QA-KABP]; U.S. FOOD & DRUG ADMIN., CVM GFI #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 (Dec. 2013), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-213-new-animal-drugs-and-new-animal-drug-combination-products-administered-or-medicated-feed [https://perma.cc/H3MY-ZW8H].

[203] Exec. Order No. 13,676, 3 C.F.R. (2014). It also set up a coherent government response. S*ee infra* Section III.B.2.iii discussing CARB.

[204] *Id.*

[205] *Id.*

[206] The plan is still voluntary.

[207] U.S. FOOD & DRUG ADMIN., CTR. FOR VETERINARY MED., SUPPORTING ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS, GOALS FOR FISCAL YEARS 2019–2023 5 (2018).

[208] *Id.*

[209] *See FDA-Track: Progress on FDA's Support of Antimicrobial Stewardship in Veterinary Settings*, U.S. FOOD & DRUG ADMIN. (Apr. 1, 2021), https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-progress-fdas-support-antimicrobial-stewardship-veterinary-settings [https://perma.cc/JSC7-8LVY].

[210] *Id.*

[211] Hoelzer, *supra* note 180.

iii. A Broader One Health Approach to Antibiotic Resistance

The *National Action Plan for Combating Antibiotic-Resistant Bacteria* (CARB), 2020–2025 takes an explicitly One Health approach to its mission.[212] The CARB plan creates a task force that includes representatives from HHS, USDA, DOD, Department of the Interior, Department of State, EPA, USAID, and the Department of Veterans Affairs.[213] By including agencies focused on human, animal, and environmental health in an effort to reduce overall antibiotic resistance, the CARB plan thus represents a model for One Health pandemic preparedness in an important but discreet area. Especially important, it includes an expanded focus on antibiotic resistance in the environment, something that has been largely neglected until recently. The plan lays out five goals: 1) to slow the emergence of resistant bacteria and prevent the spread of resistant infections; 2) to strengthen national One Health surveillance efforts; 3) to advance development and use of rapid and innovative diagnostic tests; 4) to accelerate basic and applied research and development for new antibiotics, therapeutics, and vaccines; and 5) to improve international collaboration and capacity for prevention, surveillance, control, and antibiotic research and development.[214] Significantly, the plan operationalizes the five goals by establishing agency responsibility and requirements for collaboration with specific targets. Nonetheless, the devil will be in the details. For example, it is one thing to have an objective that FDA, CDC, and EPA engage "the animal health community, crop protection community, and other relevant stakeholders to advance strategies intended to foster the responsible use of medically important antibiotics in plants and animals."[215] It is another to outline the legal authorities and incentives to make that engagement effective. As the previous discussion of the use of medically important drugs for animal production use illustrates,[216] incentives in unconnected stakeholder groups can make progress extraordinarily difficult to achieve, especially absent additional legislative authority.

Perhaps one area for potential progress is in the CARB goals for surveillance. The plan calls for new capacities for surveillance data from animals, farms, production facilities, and the environment, including water and soil, and to establish a platform for more comprehensive understanding of the carriage of antibiotic resistance genes (resistome).[217] Leveraging and expanding existing NARMS and NAHMs capacities is a start. NARMS already uses whole genome sequencing in surveilling antibiotic resistant microbes.[218] That infrastructure is a good foundation for a resistome platform. Potentially engaging EPA inspections with Clean Water Act authorities could better meet environmental surveillance needs.[219] All of these are likely to be controversial.

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[212] FEDERAL TASK FORCE ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA, NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC RESISTANT BACTERIA 2020–2025 4 (Oct. 2020).

[213] *Id.* at 5.

[214] *Id.* at 11.

[215] *See id.* at 21.

[216] *Supra* Section III.B.2.ii.

[217] *Id.* at 17.

[218] *About NARMS*, *supra* note 191.

[219] Under the Clean Water Act, concentrated animal feeding operations (CAFOs) are defined as point source dischargers. 33 U.S.C. § 1362. EPA conducts inspections if alerted to a potentially illegal discharge and on a random basis. 33 U.S.C. § 1251, 1318. A broader and more systematic inspection including waste-

The CARB plan demonstrates both the value and difficulty of implementing a One Health plan to combat potential disease. A broader plan that includes monitoring and responding to many pathogens would be even more difficult to achieve. But if the current pandemic is a harbinger of more to come, then we have no choice. Antibiotic resistance is a growing problem, and solving this problem requires comprehensive surveillance and responsive mitigation even if those responses are likely to trigger the ire of industry.

3. Use of Gene Drives to Combat Potential Epidemics and Serious Endemic Disease

For pathogens that cannot be eradicated or even reasonably mitigated with vaccines and other containment measures, the new technology of gene drives might eventually be an option to consider. A One Health paradigm is essential to understanding all the implications that the technology may raise. Gene drives work to eliminate either the animal vector itself (e.g., some species of mosquito that carries disease) or permanently change genetic characteristics in an animal species (within a certain habitat) that make it a vector for emerging zoonotic disease.[220] Gene drives are also ethically fraught and carry uncertain risks—although potentially huge benefits. With gene drives, we might be able to eradicate a disease like malaria for which efforts to develop a vaccine have been unsuccessful and which still kills a half million people each year in the developing world. Gene drives create obvious implications for the targeted species. They may also incur significant ecological costs, and we do not fully understand what those may be.

One thing that sets gene drives apart from most biotechnology involving genomic engineering is that they are explicitly designed not to be fully contained.[221] Since the inception of the technology in the 1970s, biosafety was assured through a focus on containment. Thus, gene drives present a new paradigm and make One Health considerations even more imperative.[222] Gene drives, of course, are not limited to animals; they may eventually become an effective method for dealing with invasive plants.[223] In the context of zoonotic pathogens, though, the focus will be on animal applications. While not yet a fully mature technology, gene drives might be ready for implementation, subject to how regulation might play out, in the next couple of years.

FDA likely has authority[224] over many gene drive organisms if they meet FDA's definition of "animal," which would implicate FDA's animal drug regulations. FDA

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water monitoring could prove a valuable surveillance method—not just for antibiotic resistance but for other potential pathogens.

220 *See* NAT'L ACADS. OF SCI., ENG'G & MED., GENE DRIVES ON THE HORIZON: ADVANCING SCIENCE, NAVIGATING UNCERTAINTY, AND ALIGNING RESEARCH WITH PUBLIC VALUES 15 (2016) [hereinafter NASEM, GENE DRIVES].

221 *See* Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin III & Maxine F. Singer, *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72(6) PROC. NAT'L ACAD. SCIS. 1981 (1975) (emphasizing containment in biotechnology); NASEM, GENE DRIVES, *supra* note 220, at 7.

222 Gene drives also may raise questions of intentional misuse. *Id.* at 159–61. For example, potentially a mosquito vector could be used to introduce and spread disease. That is outside the scope of this Article.

223 *See id.* at 154. USDA has primary authority over that technology and includes EPA. *Id.* at 152, 154. The limits of both agencies' full authority is ambiguous.

224 "It is likely, but not certain, that FDA has the authority under the Federal Food Drug and Cosmetics Act to regulate gene-drive modified organisms." NASEM, GENE DRIVES, *supra* note 220, at 156. Part of

treats the heritable genetic construct in a genetically engineered animal as a new animal drug.[225] FDA then treats all offspring of that animal, whether produced through normal sexual reproduction or other means, as containing that drug. This treatment in turn gives FDA the authority to determine "the safety and efficacy" of a gene drive through its authority to regulate the heritable genetic construct "drug."

Many of the regulatory concerns that affect gene drives are already discussed in FDA's Guidance for Industry applicable to genetically engineered animals.[226] FDA is concerned about the effect and durability of the genetic construct. Safety is focused not just on the animal itself, but on its effect on humans, other animals, and the environment.[227] In particular, the safety concerns include the potential of the genetic construct to "cause human or animal disease either intrinsically or by recombination."[228] As required under the National Environmental Policy Act (NEPA),[229] FDA also anticipates that any approval process involving genetically engineered animals will also include an environmental assessment (EA) and a finding of no significant impact (FONSI) (21 C.F.R. § 511.1(b)(10), 21 C.F.R. § 25.15) or an environmental impact statement (EIS) (21 C.F.R. § 25.22).[230] What remains unclear is whether gene drives will be subject to the full requirements of an EIS which is considerably more rigorous than an EA.[231] Since gene drives are by definition difficult to contain, a more thorough assessment of the potential environmental risks may be warranted.

One of the ambiguities surrounding the limits of FDA's authority on gene drives concerns the intended use of the gene drive. FDA's latest draft guidance on

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that uncertainty depends on the species involved and the indication specified; some uncertainty also emanates from ambiguity about the scope of FDA's authority. FDA has still not issued its revised applicable guidance, Guidance for Industry #187. A revised draft guidance was issued in January 2017; that means the 2015 final Guidance for Industry is still in effect. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY #187: REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS (2015), https://www.fda.gov/media/135115/download [https://perma.cc/RM6L-87LA] [hereinafter GUIDANCE FOR INDUSTRY #187].

[225] An article "(B) . . . intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals . . . ." 21 U.S.C. § 321(g)(1). *See also* GUIDANCE FOR INDUSTRY #187, *supra* note 224. This issue became more complicated during the last week of the Trump Administration. Citing public health concerns, FDA Commissioner Hahn refused to sign an MOU with USDA that would transfer authority of genetically modified animals to USDA. *See* Sam Hill, *Advocacy Groups Want FDA, not USDA, to Regulate Genetically Engineered Animals*, SEAFOOD SOURCE (Apr. 12, 2021), https://www.seafoodsource.com/news/food-safety-health/advocacy-groups-want-fda-not-usda-to-regulate-genetically-engineered-animals [https://perma.cc/2QQ6-GQVH]. As of this writing, that issue is not resolved and is outside the scope of this Article.

[226] GUIDANCE FOR INDUSTRY #187, *supra* note 224.

[227] *Id.* at 8.

[228] *Id.*

[229] National Environmental Policy Act of 1969, 42 U.S.C. § 4332 (2000).

[230] GUIDANCE FOR INDUSTRY #187, *supra* note 224, at 20.

[231] An EA is a concise assessment that reviews the purpose and need of the proposal, any alternatives, and a brief review of the impacted environment, and provides a list of agencies and persons consulted. An EIS requires Federal Register notice and opportunity for public comment and collaboration. It involves a much more comprehensive review. *National Environmental Policy Act Review Process*, ENV'T PROT. AGENCY (2021), https://www.epa.gov/nepa/national-environmental-policy-act-review-process [https://perma.cc/L3G6-SFDA].

intentionally genetically altered animals no longer includes a statement of the "intended purposes of the genetic modification" that are subject to FDA jurisdiction.[232] But the NASEM committee that studied gene drives demonstrated how the use of the term "intended use" creates overlapping authorities between agencies.[233] If a species subject to a gene drive modification were to be considered a threat to animal health, it might be subject to USDA authority under the Animal Health Protection Act;[234] if it threatens plants, it is potentially subject to USDA's authority under the Plant Protection Act.[235] However, if the gene drive is designed to eradicate a "pest," it likely falls into EPA's jurisdiction under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[236] And how any of this authority might be affected by the Endangered Species Act[237] is still unclear.

While FDA has not yet approved any gene drive product, it did review the Friendly® Oxitec mosquito and eventually transferred authority for that product over to EPA.[238] The mosquito is a transgenic *Aedes aegypti*, the mosquito responsible for the transmission of dengue fever,[239] which affects millions of people worldwide.[240] The Oxitec mosquito is bred with a "lethal gene" inserted that permits adults to mate but renders it impossible for any of their eggs to mature unless they were provided with a small dose of the antibiotic tetracycline during larval development.[241] In theory, it is the type of disease most suited to experimentation with a gene drive; there is currently no vaccine or drug for the disease, and despite attempts to control the mosquito with standard means of insecticides and environmental management, the

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[232] GUIDANCE FOR INDUSTRY #187, *supra* note 224 (enumerating six classes of animals that would be subject to review based on "intended purposes": to enhance production or food quality traits, to improve animal health, to produce products intended for human therapeutic use, to enrich or enhance animals' interactions with humans, to develop models for human disease, and to produce industrial or consumer products).

[233] NASEM, GENE DRIVES, *supra* note 220, at 156–57.

[234] Animal Health Protection Act, 7 U.S.C. § 8301; *see also* Exec. Order No. 13874, 84 Fed. Reg. 27899 (June 11, 2019).

[235] Plant Protection Act, 7 U.S.C. § 7701 (2000).

[236] Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. § 136 (1996).

[237] Endangered Species Act, 16 U.S.C. § 1531 (1973).

[238] *See* Zahra Meghani & Jennifer Kuzma, *Regulating Animals with Gene Drive Systems: Lessons from the Regulatory Assessment of a Genetically Engineered Mosquito*, 5 J. RESPONSIBLE INNOVATION 1, 16, n.4 (2018). Such mosquitoes are deemed outside the jurisdiction of GUIDANCE FOR INDUSTRY #187, *supra* note 224. In Draft Guidance for Industry #236, "Regulation of Mosquito-Related Products," FDA has proposed to clarify that the phrase "articles (other than food) intended to affect the structure or any function of the body of man or other animals" does not include articles intended to prevent, destroy, repel, or mitigate mosquitoes for population control purposes. Instead, such products are pesticides regulated by the Environmental Protection Agency (EPA). U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY #236: CLARIFICATION OF FDA AND EPA JURISDICTION OVER MOSQUITO-RELATED PRODUCTS (2017), https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM533600.pdf [https://perma.cc/CM3B-BQYS] [hereinafter GUIDANCE FOR INDUSTRY #236].

[239] Alex M. Nading, *The Lively Ethics of Global Health GMOs: The Case of the Oxitec Mosquito*, 10 BIOSOCIETY 24, 1 (2015). *See also* Meghani & Kuzma, *supra* note 238, at 5.

[240] Nading, *supra* note 239, at 2.

[241] *Id.* at 1. *See also* Meghani & Kuzma, *supra* note 238, at 5.

disease continues to spread.[242] The Oxitec mosquito is not a true gene drive product; unlike a true gene drive which aims for close to 100% inheritance and at least theoretically accomplishes its goal with a few generations, use of the Oxitec mosquito would likely require continuous releases, and if those releases did not transpire, it would likely eventually disappear from the population.[243]

FDA originally took regulatory responsibility for the Oxitec mosquito and authorized a field trial, which is analogous to a clinical trial for this type of technology, in the Florida Keys.[244] At the time, the sponsor had already conducted field trials in the Cayman Islands, Brazil, and Malaysia, but critics claimed that the sponsor did not provide FDA data on the ecological surveillance of non-target organisms or broader environmental effects.[245] Further, they argued that NEPA requires the more rigorous EIS rather than the agency's submission of an EA and subsequent finding of no significant impact.[246] Moreover, critics argued that FDA must engage further public discourse and a normative democratically based regulatory review for all genetically engineered animals.[247] But on this last point, these critics misunderstand the limits of FDA's authority. FDA, as it has stated previously regarding genetically engineered animals, is limited to a science-based risk assessment; it does not have the authority to engage with non-science-based ethical or economic considerations.[248] Moreover, one of the problems of treating the regulation of all genetically engineered animals with the same brush as gene drives is that this treatment tends to diminish how different gene drives are from already existing technology. GE technology with animals is an emerged technology, with which FDA now has some significant experience. Gene drives raise more complex questions.

In 2017, FDA transferred the review of the Oxitec mosquito to EPA pursuant to Guidance for Industry #236.[249] But the Oxitec controversy has resolved little in terms of how FDA may regulate gene drives in the future. If FDA is correct about the limits of its authority, and it likely is, these limits leave loopholes and ethical gaps that a One Health approach may be able to ameliorate. A One Health approach breaks down regulatory silos and allows a holistic approach between collaborating agencies and other entities. The Coordinated Framework for Biotechnology[250] is based on the notion

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242 Nading, *supra* note 239, at 2.

243 *See* Meghani & Kuzma, *supra* note 238, at 5.

244 *See id.* at 5.

245 *See id.* at 6.

246 *Id.* at 5–6. Meghani and Kuzma's claim is weakened by the fact that they argue that an EIS is required for all genetically engineered animal approvals, including the already approved AquaBounty Salmon. *See id.* This requirement smacks somewhat of obstructionism. Unlike the Oxitec mosquito or gene drives, the AquaBounty salmon is significantly contained. *AquAdvantage Salmon Fact Sheet*, U.S. FOOD & DRUG ADMIN. https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/aquadvantage-salmon-fact-sheet [https://perma.cc/YE3U-TT8T] (last updated April 15, 2020).

247 *Id.*

248 *FDA's Response to Public Comments on Draft Guidance for Industry #187*, U.S. FOOD & DRUG ADMIN. (Sept. 19, 2008), https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/fdas-response-public-comments-draft-guidance-industry-187-released-9182008 [https://permma.cc/MD9C-XBLH].

249 GUIDANCE FOR INDUSTRY #236, *supra* note 238.

250 *The Unified Website for Biotechnology Regulation*, U.S. DEP'T OF AGRIC., U.S. FOOD & DRUG ADMIN., U.S. ENV'T PROT. AGENCY, https://usbiotechnologyregulation.mrp.usda.gov/biotechnologygov/home [https://perma.cc/84CS-UWPC]; Coordinated Framework for Regulation of Biotechnology, 51 Fed.

that USDA, FDA, and EPA will collaborate, and they will need to do so here. But with technologies like gene drives that are truly disruptive, some of the more intractable questions may go beyond any agency's authority, or even several agencies' combined authority. That may require other fora[251] to consider the issues. That needs to be done before the exigencies of a new emerging pandemic trigger preemptive actions that may not be well considered.

IV. CONCLUSION

A One Health paradigm is a useful—and likely necessary—paradigm to help us avoid the next pandemic. Only by developing systems that coordinate our responses to developments in human, animal, and environmental health will we avoid repeating our experience with SARS-CoV-2. But a paradigm without the necessary infrastructure and funding to fully operationalize its solutions cannot be successful. At FDA, the Center for Veterinary Medicine is poised to take a leadership role with One Health. But to be successful in that endeavor, the rest of the agency will have to take One Health seriously, both in focus and funding. Congress will have to provide the necessary funding. One Health needs to be better understood and targeted for real results. While FDA is not the lead agency in implementing many aspects of One Health, its prominence will be useful in leading public health solutions both within the United States and internationally. There are significant One Health platforms and infrastructure that the agency can adopt in its own preparation and in its coordination with other agencies. Once the current pandemic has dissipated, we risk reverting back to shortcutting funding and ignoring lurking natural threats. With appropriate support, One Health can help us make a global pandemic something that we endure only once in a century.

Reg. 23302, 23302–03 (June 26, 1986); Exec. Office of the President, Update to the Coordinated Framework for the Regulation of Biotechnology (2017), https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf [https://perma.cc/M2TQ-86FD].

[251] *See* NASEM, GENE DRIVES, *supra* note 220. As noted earlier, the National Academies has already opined on gene drives. The NIH's NExTRAC has also taken on gene drives, within the context of emerging and endemic disease and will hold a public workshop on those issues in November.