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Target Article

A Radical Approach to Ebola: Saving Humans and Other Animals

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As the usual regulatory framework did not fit well during the last Ebola outbreak, innovative thinking still needed. In the absence of an outbreak, randomised controlled trials of clinical efficacy in humans cannot be done, while during an outbreak such trials will continue to face significant practical, philosophical, and ethical challenges. This article argues that researchers should also test the safety and effectiveness of novel vaccines in wild apes by employing a pluralistic approach to evidence. There are three reasons to test vaccines in wild populations of apes: i) protect apes; ii) reduce Ebola transmission from wild animals to humans; and iii) accelerate vaccine development and licensing for humans. Data obtained from studies of vaccines among wild apes and chimpanzees may even be considered sufficient for licensing new vaccines for humans. This strategy will serve to benefit both wild apes and humans.

Keywords: international/global health; human subjects research; philosophy; public health; regulatory issues; research ethics

The largest ever outbreak of Ebola in humans was declared over in spring 2016. But although it disappeared from newspapers' headlines, Ebola has not been eliminated. Indeed, there continue to be regular outbreaks in Democratic Republic of Congo in Spring 2017, and we are currently in the midst of another which started only a week after the last was declared over in May 2018 (Centers for Disease Control and Prevention 2018). Ebola continues to circulate in nonhuman animal (hereafter "animal") populations, posing a grave risk to wild animals as well as humans (Olival et al. 2017). Nonhuman animals constitute a key vector of the virus's transmission to humans.

Recognizing that Ebola poses a common threat to humans and animals, we advocate for a response to Ebola rooted in a One Health approach to infectious disease prevention and control. One Health recognizes that human, animal, and environmental health are interdependent, acknowledges shared disease risks between humans and animals that occupy the same environments, and seeks to regulate the human–animal–environment interactions that contribute to infectious disease emergence and expression (Degeling et al. 2015; Landford and Nunn 2012). It moves us away from an anthropocentric approach to public health—one that puts humans' health at the center of public health campaigns—and toward an ecological approach—one that looks to control or mitigate common threats to organisms within shared environments through innovative and integrative measures. While the global health community is justifiably concerned about preventing Ebola in humans, it would be wise to consider ways of preventing Ebola in animals, too, thereby interrupting predictable chains of transmission of Ebola from animals to humans (and vice versa). Furthermore, conservationists are rightly concerned about Ebola's effect on apes, as populations of wild apes have, in recent years, substantially diminished due to Ebola outbreaks. Preventing Ebola in wild apes, in other words, also protects apes from endangerment and extinction.

This means there is an urgent need for researchers to assess what we already know about Ebola, and to think about innovative, integrative approaches to Ebola virus prevention. An anthropocentric approach to infectious disease

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prevention would prioritize developing an Ebola vaccine for humans. But this will not work in the case of Ebola because the usual regulatory framework, which can require evidence from human studies, taking up to 14 years to complete, does not fit well (Thielman et al. 2016). In the absence of an outbreak, randomized controlled trials of clinical efficacy in humans cannot be done, while during a future outbreak such trials will continue to face significant practical, philosophical, and ethical challenges associated with limiting access to new medicines to the research context when there is an immediate widespread public health crisis (Edwards 2013).

We argue that in relation to vaccination, researchers should also test the safety and effectiveness of novel vaccines in wild apes, employing a One Health approach to public health and a "pluralistic" approach to evidence. There are three reasons to test vaccines in wild populations of apes: (i) reduce interspecies Ebola transmission; (ii) protect apes; and (iii) accelerate vaccine development and licensing for humans. Data to help validate surrogate outcomes in humans obtained from studies of vaccines among wild apes and chimpanzees may be considered by regulators to be desirable and sufficient for licensing new vaccines for humans ahead of the next outbreak. At the very least, evidence from trials of new vaccines in wild animals will contribute to the evidence base for a new vaccine's clinical outcomes in humans: safety, efficacy, and effectiveness. Owing to challenges in mounting large-scale vaccine trials in humans, pluralism about evidence is warranted. This strategy will serve to benefit both wild apes and humans. In this way, we seek to make beneficial connections between the One Health approach (which provide opportunities to gather evidence from various species and sources), on the one hand, and what is known in philosophy of science as methodological or epistemic pluralism, on the other hand.

EBOLA VACCINE DEVELOPMENT SO FAR

Though several are in development, there is still no licensed Ebola vaccine. There simply are not many opportunities to pursue vaccine trials in the real world because large outbreaks in humans, thankfully, do not occur very often. Testing the safety and effectiveness of a new vaccine typically involves a randomized controlled trial (RCT), in which many thousands of people who are at risk of exposure to the disease are vaccinated and compared to controls. The impossibility of predicting when the next outbreak will occur, and in which geographic areas, presents a practical challenge to testing candidate vaccines in human subjects.

The Ebola outbreak of 2014–2016 provided an opportunity to test the safety and effectiveness of promising vaccines, as well as treatments, while thousands of people were at risk of exposure to the devastating illness. However, the outbreak also saw the international community struggle with questions of research methodology to test the novel agents' safety and effectiveness (Calain 2016). In the context of having no standard medical treatments available and of having several candidate medicines only just becoming ready to "test" in humans for the first time, questions surrounded how to amass safety and effectiveness evidence about novel therapeutics and vaccines. Some argued that an RCT ought to be performed in order to produce the most reliable evidence base (Rid and Emanuel 2014). Others advocated the use of "alternative" trials that, for example, do not randomize research subjects to a placebo arm on the basis that randomization to a placebo arm was unethical because of high mortality and morbidity associated with illness (Adebamowo et al. 2014; Caplan et al. 2015; Edwards 2013). Research groups that began trials during the outbreak ultimately abandoned them, in part due to under-enrollment as the outbreak waned (Gates 2015). Concerns about the incompatibilities in the methods favored by different stakeholders are likely to complicate effectiveness research in humans either before or during any future outbreak.

Two experimental vaccines show promise in humans: Merck's vaccine and Janssen's vaccine. Merck and Janssen have both undertaken trials with human subjects, although neither has provided sufficient evidence for licensing. Merck has patient outcomes data for rVSV-ZEBOV live vaccine. With Emergency Use Authorization by the World Health Organization (WHO), it administered the experimental vaccine to nearly 800 people within 1 week in 2016, including 182 who were considered to be high-risk contacts, to contain a flare-up of Ebola in March 2016 as the outbreak waned (World Health Organization 2016). Merck introduced an additional arm of its vaccine with a booster, which is not always possible to administer in the field. A follow-up phase 3 trial of the rVSV vaccine adopted a "ring" design, which was declared a success in terms of preventing disease transmission. A ring design seeks to treat only those in close contact with a cluster of known cases, thereby forming a "ring" of protection around an outbreak. Nonetheless, the FDA did not find the data compelling enough to fully license the vaccine (Henao-Restrepo et al. 2017). Merck's still-experimental vaccine is currently being used in DRC but not always adhering closely to the ring method due to the difficult social conditions in the region.

Janssen's vaccine was deployed in a trial toward the end of the 2014/16 outbreak and yielded data on immunogenicity alone—an evidential facet that makes some regulatory bodies cautious. Immunogenicity tests the body's ability to mount an immune response, but does not necessarily mean that one is immune to the disease in question. Thus, data on a vaccine's immunogenicity does not entail that the vaccine in question prevents illness. A large comparative trial in humans (PREVAC), led by the Partnership for Research on Ebola Vaccination, is now recruiting and will use immunogenicity as a

surrogate endpoint for effectiveness in the absence of a human outbreak (National Institute of Allergy and Infectious Disease [NIAID] 2017). Currently, any marketing license would need to appeal to data validating immunogenicity data with clinical outcomes but only in nonhuman animal studies. While each vaccine will be compared with a placebo control, the hope is that recruitment rates will be high enough to allow a head-to-head comparison between them. Given pragmatic constraints associated with severity of the situation on the ground (e.g., refrigeration required for certain drugs), evidence of effectiveness—not efficacy—has more value for medical practitioners, who need multiple tools as they face multiple tasks and multiple impediments. Drug companies naturally wish to be the lead market provider on the basis of evidence of superiority, but for public health agencies and doctors, multiple treatments are a better resource for treating populations, especially when so much is still unknown.

Noticeably absent from the list of candidate treatments and vaccines reviewed by WHO during the 2014–2016 human outbreak was a vaccine developed by Peter Walsh purely for the purposes of conservation of chimpanzees (Walsh et al. 2017). The orally delivered vaccine was made up of the live, weakened rabies virus, with an added gene for the main surface glycoprotein from the Ebola virus. Walsh had promising preliminary data from a trial of the vaccine's safety and effectiveness using 10 captive chimpanzees at an animal facility in Louisiana. In 2015, however, the trial was cut short when amendments to the U.S. Endangered Species Act banned the use of chimpanzees in medical research. The law, which came into effect in 2016, places captive chimpanzees on the endangered species list, effectively banning invasive research using them.

Ebola is extremely difficult to model in other animals, and this presents another practical barrier to vaccine development. Mice, hamsters, and guinea pigs have all been developed as animal models of infection for a number of species and strains of Ebola virus and Marburg virus. Yet (as with most research on animal models) these rodent studies alone are insufficient to reliably guide human vaccine development, as they do not exhibit the symptoms of disease present in the typical human case of Ebola—that is, abrupt onset with flu-like symptoms, including fever, malaise, and myalgia, followed by anorexia, lethargy, nausea, vomiting, and diarrhea. Hemorrhaging can develop, particularly in severe cases at the peak of illness, and include petechiae, uncontrolled bleeding from venipuncture sites, epistaxis, and other mucosal hemorrhages. Fatal cases are accompanied by hypovolemic shock and multiple organ failure.

As nearly all aspects of filovirus infection in humans are replicated in rhesus macaques and other primates, some have concluded that nonhuman primates are the most valuable animal model of human disease (Shurtleff and Bavari 2015). Several nonhuman primate species have been used to model human Ebola infection, including African green monkeys, marmosets, baboons, cynomolgus macaques, and rhesus macaques (Nakayama and Saijo 2013). There are some notable limitations, but nonetheless, the features of disease in both cynomolgus and rhesus macaques appear to best model, in the laboratory, the progression of Ebola disease in humans.

As stated, the confluence of several factors complicate Ebola vaccine development. Primates provide an opportunity to model and study Ebola virus in the lab setting; however, some primates are banned from invasive research, and animal welfare concerns should give us pause when it comes to using nonbanned primates (Barnhill et al. 2016). Alternative evidence bases of new vaccines' safety and effectiveness are sorely needed to guard against another outbreak, as is an approach to handle different evidence types in more resourceful and beneficial ways. This need motivates our call for expanding vaccine research to include study of wild apes and chimpanzees that are at risk of exposure to Ebola virus. Three further moral reasons for doing so are reviewed in what follows.

Reducing Interspecies Ebola Transmission

A One Health approach to controlling infectious disease emphasizes that animal health and human health are intimately intertwined, and this is especially the case for Ebola virus. As humans infringe upon animals' natural habitats through urban sprawl, deforestation, tourism, need for new food sources, and anthropogenic climate change, humans and animals increasingly encounter each other. They increasingly share not only spaces, but also diseases.

As noted in the preceding, wild gorillas and chimpanzees in central Africa have experienced occasional Ebola outbreaks. Yet like their human counterparts, they are too ravaged by the virus to serve as its host over the long term. Experts say that a nonprimate reservoir species is likely to harbor the virus only at low levels, and without becoming sick (Groseth et al. 2007; Saéz et al. 2015). Animals ranging from rodents to livestock to domestic dogs and cats may not be victims of Ebola, but they could contribute to transmission to humans and apes. It is thought that Ebola spreads from apes to humans when a hunter kills and eats an animal, or when someone meets an infected ape corpse (Whitfield 2003). Recognizing the ways in which the Ebola virus lives and circulates within shared environments is critical to control and mitigation efforts.

Since the disease first emerged in Zaire, now Democratic Republic of the Congo, 40 years ago, efforts to trace the exact nonhuman origins of human outbreaks, including the most recent one, have been inconclusive. What is clear, however, is that mass animal deaths act as an early warning system for human outbreaks (Funk and Piot 2014). Researchers are now modeling past

outbreaks for common ecological and environmental factors, such as vegetation, elevation, and the presence of suspected reservoir species such as fruit bats and insect-eating bats, and carriers such as apes, to create a map showing high risk of human transmission (Bisson et al. 2015; Redding et al. 2016). By intervening in either the vector animals, like apes and chimpanzees, or reservoir species, like bats and rodents, the risks to human health might be reduced.

Developing an Ebola vaccine that is safe and effective for both nonhuman primates and human primates intervenes in a known vector of Ebola and achieves the vision of "inter-species herd immunity," as recently proposed by Capps and Lederman (2015). Herd immunity refers to resistance to infectious diseases within a population that results from having a sufficiently high proportion of individuals immune to the disease through vaccination. When herd immunity is achieved, even unvaccinated individuals are protected. Interspecies herd immunity would be agnostic as to which animals—human or otherwise—are vaccinated. The important goal would be achieve population-level resistance to the Ebola virus. Reliance on developing "model organisms" of Ebola, which attempt to replicate human disease in animals, represents an unfortunately partitioned view of the intimate connections between human and animal health. Animals are not merely models of Ebola; they are victims. In these cases, humans and apes share a common disease threat against which multifaceted and integrated vaccine research might be marshaled (Capps and Lederman 2015; Olival et al. 2017; Reed et al. 2014).

Protecting Wild Apes and Chimpanzees

Several studies have tracked the impact of Ebola on wild apes, gorilla, and chimpanzee populations (Barmejo, 2006; Caillaud et al. 2006; Genton et al. 2017; Pilcher 2004; Ryan and Walsh 2011; Walsh et al. 2003). As early as 2003, Walsh and colleagues referred to an "ape Ebola epidemic," calling it "a major conservation crisis" (2003, 613). Bermejo et al. (2006) studied wild gorillas for more than a decade at a gorilla sanctuary near the Gabon–Congo border and found that between 2002 and 2003, Ebola killed more than 5000 gorillas in their study area, with gorilla mortality rates between 90 and 95%. Not to be overlooked, they also estimate that the chimpanzee population in the same area and time period declined by 89% (Pilcher 2004). The authors conclude: "We hope this study dispels any lingering doubts that [Ebola virus] has caused massive gorilla die-offs." What's more, Caillaud et al. (2006) tracked gorillas in a different study area in the Democratic Republic of Congo, reporting that between December 2003 and July 2004, 95% of gorillas in their study area died from the disease. Data from these gorilla studies led the International Union for Conservation of Nature (IUCN) to classify the species as "critically endangered" in 2008.

Ebola therefore represents a threat to wild ape and chimpanzee populations, and this fact supports an urgent argument from conservation of the species for developing Ebola vaccines suitable for use in apes and chimpanzees (Ryan and Walsh 2011). All the early work by Walsh on captive chimpanzees was intended to benefit the conservation effort with no ambition for application in humans.

Humans have exacerbated the threat Ebola poses to wild apes and chimpanzees through deforestation, urban sprawl, tourism, and other means. We would be remiss not to point that chimpanzees' and apes' health also depends on humans' activities. Humans structure their environments, intentionally or unintentionally. It is incumbent upon us to create shared environments that also promote the health and well-being of other animals. Vaccination is certainly not the only way to promote the health of wild apes, gorillas, or chimpanzees that share our planet, but it may be one way.

Accelerating Vaccine Development in Humans

Morbidity data show that great apes and chimpanzees experience a disease trajectory very similar to that of humans. Thus, it is reasonable think that vaccine safety and effectiveness data obtained from wild great ape or chimpanzee populations might inform vaccine development in humans. Biologically, immunologically, pharmacokinetically, and otherwise, apes and chimpanzees and humans are remarkably similar. Put another way, the "translational distance" between apes and humans is very short (Kimmelman 2010). Data from wild ape and chimpanzee populations may provide evidence of the vaccine's safety and effectiveness in humans, and may even contribute to a regulatory license for an Ebola vaccine for humans ahead of the next outbreak, depending on the type of evidence sought and how it is assessed alongside data from humans.

Stressing the benefits to humans that might result from vaccination trials in wild apes and chimpanzees does not undermine our commitment to a One Health approach to public health. On the contrary, protecting humans from shared threats is also part of the complex puzzle of creating environments and ecosystems that are more resilient to infectious diseases. Vaccinating humans is likely be essential to achieving interspecies herd immunity.

Questions remain about what sort of evidence would be regarded as sufficient to gain a full market license and when that evidence could practically and ethically be sought. In terms of both speed and effectiveness, RCTs are still awarded a privileged status when methods of collecting evidence are considered during an outbreak (U.S. National Academies 2017). For half a century or so, RCTs have been thought to provide evidence with the fewest biases so had become the "gold standard." By the time the candidate treatments were ready for human use during the 2014–2016 outbreak, there were epidemiological

data emerging from the field that showed variation in the accumulating case facility rates from 50% to 80% between individuals and between reporting treatment centers (mainly facilities run by Médicins Sans Frontières), such as they were early on. On this basis, the Food and Drug Administration (FDA) concluded that sound science required a concurrent control (of best available supportive care) to reduce an anticipated bias associated with using historic controls (Cox et al. 2014). Variation between centers, the FDA argued, also ruled out randomized trials at the cluster level, including any step-wedge approach (which allocates new clusters to the intervention sequentially until all clusters receive the intervention). Establishing efficient statistical associations between treatment and clinical effect was the FDA's primary concern. However, variation in outcomes might suggest the existence of subpopulations that are not yet well understood—notably pregnant women—which could be disguised by aggregated data. Thus, their results could be ambiguous and misleading, while there is significant and unidentified heterogeneity between subpopulations. Radically different methods for designing clinical trials were ultimately used during the human outbreak of 2014–2016, but mainly due to pressure from past colonial partners and for different reasons, with mixed and inconclusive results (Gates 2015).

Strikingly, where RCTs are not feasible (as in cases of rare disease) or are unethical to carry out (as in Ebola exposure studies involving healthy humans), the FDA has been willing to license new drugs and vaccines based on other types of evidence. For example, where clinical effectiveness studies would require deliberately exposing humans to potentially lethal pathogens, the Animal Rule permits the FDA to license a new drug based on effectiveness data from animals alone—that is, without any clinical trials in humans (Edwards 2015).

Even if data from wild ape and chimpanzee trials were not sufficient for licensing a new vaccine, at the very least, evidence from other sources such as ape and chimpanzee studies (and using multiple methods) would contribute to the evidence base for the three vaccines (and others) currently in development, and would guide global health experts in their decision about whether, when, and how to mount trials in humans. Indeed, evidence specifically from wild apes and chimpanzees could help reevaluate the perceived scientific need for RCTs in humans during the next outbreak. In this way, an overall causal picture could be better formed by the beginning of the next outbreak in humans, and later completed by considering observational or pragmatic trials in humans alongside evidence of mechanisms gathered via laboratory studies. Finally, studies in wild apes might clarify how immunogenicity measures change clinical outcomes in humans. Outcomes in great apes potentially contribute to alleviating uncertainty more than evidence gleaned from rodent studies, or laboratory studies of cynomolgus and rhesus macaques.

Far from being problematic, in the longer run, multiple methods for gathering clinical evidence of the effects of novel vaccines could provide more robust scientific inferences regarding causal relationships. Unreflective reliance on clinical effects observed from large RCTs is beginning to wane (Bothwell et al. 2016). Those who are charged with coordinating research in the context of a public health crisis should do it with an eye to the possibility of bringing it all together. Given the plurality of evidence available, Ebola deserves an equally pluralistic approach to how we analyze and assess the suitability of new vaccines under regulatory approval.

PLURALISM: IS IT FEASIBLE?

A One Health approach to public health, and the three specific reasons reviewed, motivate our argument for mounting vaccine studies in wild apes and chimpanzees already at risk of Ebola exposure in the absence of another human outbreak. These trials would stand to benefit both wild populations of animals under threat of endangerment from Ebola outbreaks, and humans, who also suffer greatly and may die from the disease.

One might read our call for increased research involving apes and chimpanzees as a return to a dark time of biomedical research involving healthy captive primates in the laboratory, before protections of chimpanzees and great apes from research went into effect. But that is not our suggestion. A more pragmatic and arguably more ethical approach is to identify certain groups in the wild and adopt the testing methods for conservation purposes as already planned by Walsh et al. (2017) and refined subsequently by others (Willyard 2017). Testing vaccines' effectiveness against a naturally occurring Ebola challenge (within geographically contained environments) rather than sacrificing healthy apes in the laboratory is more consistent with the accepted ethical approach to both animal and human experimentation. Moreover, the current trial of two vaccines in humans (PREVAC) could be compared and combined with data from wild apes.

Walsh and others have already proposed an experimental design in the wild but only for conservation purposes. In 2013, Walsh's short-lived studies involving captive chimpanzees had shown some immunogenicity without adverse side effects, and he had long planned to pursue conservation work in wild chimpanzees and gorillas endangered by the Ebola virus (Walsh et al. 2017). In an overview of what those trials might look like, he proposed oral vaccination delivery in response to the challenges of traditional hypodermic dart methods of inoculation. The densities of forests in which gorillas and chimpanzees live often make it difficult to track and inoculate them in the wild. The promise of noninvasive, oral vaccinations is not only practical, but also induces less stress for the animal. Stress can be known to trigger a strong immunosuppressant reaction, thus hindering

the effectiveness of the drug post inoculation. A live-virus Ebola vaccine might be preferable because it can be eaten, unlike killed-virus vaccines, which require injection through targeted darts. Walsh also designed the trial using a dispenser from which apes could get sweet vaccine-laced treats, monitored by a camera recording those who took some. The effectiveness of the vaccine could then be tested by measuring antibodies in the apes' excretions. The conservation work was seemingly abandoned but is worth resurrecting, especially in light of the growing public health threat to, and from, wild animals with Ebola.

It is important to note that research with wild animals that is aimed to benefit the animals is exempt from U.S. protections of great apes and chimpanzees. An exception to the U.S. Endangered Species Act is made for research that benefits chimpanzees in the wild or aids in the chimpanzees' propagation or survival, including work to improve chimpanzees' habitats or management of wild populations. Researchers seeking to use chimpanzees for allowed purposes must apply for an exemption. While this process can be time-consuming, the exception would seem to allow for vaccine trials like the one Walsh proposed.

Some have noted that it might be necessary to use captive primates to obtain safety and immunogenicity data on vaccines in development, ahead of deploying the experimental vaccine in a field test on primates as allowed by the U.S. exemption (Capps and Lederman 2015). However, it is worth noting that immunogenicity data could also be obtained from human subjects, as in the trial currently underway. Evidence of mechanisms as an auxiliary type of evidence, such as pharmacokinetic data, might be obtained from other animals (e.g., mice or rodents), and while a model organism is not necessary. Notwithstanding, studies of vaccines in wild apes and chimpanzees need not entail increased use of apes and chimpanzees in a laboratory setting prior to the field tests, if, say, prior data in humans show that they are safe and potentially beneficial to conservation efforts. Humans would be treated as models for studying the drug's effects in primates, flipping the way biomedical researchers typically think about the relationship between animal and human subjects of research.

CHALLENGES TO THE NATURAL EXPERIMENT

Use of vaccination in the wild is already controversial, so the prospect of testing unproven vaccines in the wild needs careful thought (Osofsky et al. 2016; Walsh et al. 2017; Willyard 2017). For example, the tragic case of invasive research (specifically handling-induced stress) on a population of Serengeti-Mara wild dogs still looms large in the consciousness of conservationists (De Villiers et al. 1995). Between 1985 and 1991, the entire study population of endangered wild dogs (*Lycaon pictus*), comprising 14 packs of 200 individuals, died in Tanzania and Kenya where the species had been identified for intensive conservation efforts. It was never shown exactly what caused the dogs to die, but the work was very invasive and disruptive for a long period of time, causing incalculable distress to the animals. However, there is probably enough evidence on the safety of current Ebola vaccines to provide the scientific rationale to test them in targeted wild populations of apes.

Another concern is the risk of a replicating virus unleashed in the wild, exacerbated by the use of a live vaccine. The remote risk of a live vaccine replicating unhindered in the wild population can be reduced or even eliminated (Osofsky et al. 2016). Specific wild populations could be identified as being at highest risk of Ebola and vaccines could be further tested to introduce a "ring" of protection around a known outbreak based on geography and known and contained territorial reach (Kucharski et al. 2016; Reed et al. 2014).

The counterarguments to the testing of vaccines in wild apes and chimpanzees center on exposing the animals and their ecosystem to harms, perhaps significant harms. The inability of chimpanzees or great apes to consent to research places a great responsibility on those deciding for them to what extent those harms are justified by benefits. Those decisions ought to be guided by the expectation of benefit to the wild animals, our ability to mitigate harms to the animals and to the ecosystem, and the ability to perform experiments that produce reliable data and knowledge about the vaccines' effectiveness.

While there are major issues concerning the way to balance risks and expected benefits to individual animals for the pursuit of aggregate benefit to the particular species, we are here interested in increasing the aggregate benefit across species through cross-species vaccination and perhaps even achieving interspecies herd immunity. Difficult questions about balancing risks and benefits remain, for example, about quantifying risks and benefits of research across species, and about balancing risks and expected benefits to individual animal subjects of research versus risks and expected benefits at the species or population level. Such tensions are inevitable within a One Health approach, and more research is needed to understand these tensions and ethically balance risks and benefits both across and within species (Rock and Degeling 2015).

CONCLUSION: A NEW ERA OF PLURALISTIC EVIDENCE

We are currently faced with a stark choice during an outbreak: deploy only the Merck vaccine and gather observational data on clinical effectiveness, test on imperfect animal models in laboratory "challenge" studies, or perform mutually beneficial work in great apes facing a natural exposure to Ebola. Merck's vaccine was awarded a breakthrough therapy designation by the

FDA, and was put on a fast track to licensure as more data accumulate. Considering data from studies with chimpanzees and great apes in the wild might aid and accelerate this process, perhaps removing the need for future RCTs during another outbreak. The impact on wild nonhuman primate populations is likely much worse.

Testing promising treatments and vaccines in chimpanzees and great apes is a prudent and justified next step in the development of Ebola virus vaccines. While it is not guaranteed that the FDA will embrace a more methodologically pluralistic approach to evidence, it is already open to the concept of adaptive licensing and has adopted the Animal Rule when evidence of clinical outcomes cannot be gained in particular, so it is already somewhat sensitive to context. In the meantime, a vaccine trial or treatment trial (if necessary) in wild populations would not only benefit the wild population, but also promote human, animal, and ecological health by identifying promising, if not already licensable, Ebola vaccines and treatments. More research is necessary to identify feasible and ethical approaches to experimenting on wild populations of chimpanzees and great apes, and Dr. Walsh's study design is a start. The ethical case, however, is already strong.

The current situation of Ebola vaccine research may seem somewhat unique, yet opportunities to gather specific evidence from our nearest living primate relatives under a One Health approach (which cannot be gained from humans) are nonetheless worth debating. That said, a more flexible approach to regulation of new drugs in humans generally may serve to provide more robust evidence by accepting data from other sources and at different stages of the development process. This may be especially important with the rise of zoonotic diseases.

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AUTHOR CONTRIBUTIONS

The article is based on an original combination of ideas by SE, following ethical difficulties with RCTs, recognizing the need to explore the philosophy of causation in science, associating conservation work in apes, OneHealth and Ebola research, and, with CHN, applying evidential pluralism to produce the first draft with reference material. CPN contributed work related specifically to the ethics of animal experimentation, and revised the structure of the article, including in final drafting. PI commented on drafts and made substantive points concerning the need for stratification and strength of evidential claims, while BC emphasized the importance of surrogate outcomes and the possibility of validating them in animal populations between outbreaks, showed how the pharmaceutical industry collects evidence to drive a commercial agenda, and greatly contributed to early versions of the article. ■

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