



Chapter Two: West Africa Ebola Epidemic

***Author's Note:** The analysis and comments regarding the communication efforts described in this case study are solely those of the authors; this analysis does not represent the official position of the FDA. This case was selected, because it is a highly relevant and recent example of the challenges of communicating about medical countermeasures (MCMs). The West Africa Ebola epidemic posed unique challenges in that the only available MCM options were still in development, requiring special messaging to address the relevant authorization and approval processes and uncertainty regarding the products' safety and efficacy. This case study does not provide a comprehensive assessment of all communication efforts. The authors intend to use this case study as a means of highlighting communication challenges strictly within the context of this incident, not to evaluate the success or merit of individual investigational products or any changes made as a result of these events.*

Abstract

In late 2013, an Ebola outbreak began in Guinea, quickly growing to become the largest Ebola epidemic on record. Widespread transmission occurred in Guinea, Liberia, and Sierra Leone with imported cases and limited transmission occurring in other countries, including the United States. The absence of approved medical countermeasures (MCMs) and a severely limited supply of investigational drugs—in early stages of development and with limited production capacity—compounded delays in the global response to the epidemic. Several of the major communications challenges for the West Africa Ebola epidemic concerned the development, testing, and use of investigational MCMs. Questions arose in the media, public, government, and even the scientific community regarding the status of individual—often highly publicized—MCMs, specifically calling for increased transparency for the testing, approval, and production processes; challenging traditional requirements for testing; and questioning allocation of limited supplies of these products in the context of the growing Ebola epidemic.

Background

In December 2013, an Ebola outbreak began in Guinea,¹ and three months later, it was officially reported by the World Health Organization (WHO).² The epidemic peaked in late 2014, and cases continued through 2015 and into 2016, resulting the largest epidemic of Ebola virus disease (EVD) in history.³ By March 2016, the epidemic had resulted in more than 28,000 cases, including more than 11,000 deaths, in the West African countries of Guinea, Liberia, and Sierra Leone. Additional cases were identified in Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom, and the United States.⁴

In contrast to past Ebola outbreaks, which typically occurred in small, remote villages in Central Africa, the outbreak quickly took root in densely populated urban areas in West Africa, where the disease had not been seen before. A context of uncertainty, fear, and public mistrust of both local and international interventions resulted in difficulty identifying and isolating patients and facilitated rapid spread of the disease.⁵ Without effective MCMs to combat the outbreak, efforts to control the epidemic were based largely on the ability to improve supportive care for Ebola patients and deliver—and engage the public to accept—non-pharmaceutical interventions. In addition to these efforts, considerable resources in the United States were dedicated to the rapid development, production, testing, and approval of investigational MCMs to support response activities in West Africa, including international coordination to navigate complex regulatory requirements, implement clinical trials, and facilitate access to these investigational products.

Widespread transmission of EVD occurred in Guinea, Liberia, and Sierra Leone, with imported cases also arising in the United States and elsewhere.

The index case of Ebola Zaire for the West Africa Ebola epidemic was a two-year-old child who acquired the disease in early December 2013 in a Guinean village near the border between Sierra Leone and Liberia. The disease spread from there to nearby villages and towns in all three countries over the next several weeks.¹ The WHO

reported the outbreak on March 23, 2014, and by mid-July, the epidemic had reached the capital cities of Sierra Leone, Liberia, and Guinea.^{2,6,7} On August 8, 2014, the WHO declared the Ebola outbreak in West Africa to be a Public Health Emergency of International Concern (PHEIC). The epidemic peaked in all three countries in December 2014 and January 2015. As of March 27, 2016,



a total of 28,646 cases and 11,323 deaths had been reported across all affected countries,⁴ dwarfing the next largest Ebola outbreak by a factor of more than 67.⁹ While the epidemic has not yet been declared over—as of this writing—only sporadic cases have been identified since late in 2015.

In West Africa, implementing public health interventions and tracking patients and exposed persons proved to be extremely difficult, especially amid reports of attacks on aid workers and clinics.^{10,11,12,13}

Additionally, there were numerous reports of communities hiding sick friends and family members as well as reports of ill persons fleeing to evade medical care, fearing doctors as the source of the infection or hospital admission as a death sentence.^{14,15,16,17,18,19} At the time of death, Ebola victims have extremely high viral load, and the severe hemorrhaging that often accompanies the disease leaves victims' bodies highly contagious. As a result, local burial practices that involve intimate contact with the deceased accelerated the spread of the epidemic.^{20,21,22} In an effort to prevent the infection from spreading beyond the affected countries, several other nations issued border closures and travel bans to West Africa, even as far away as Australia. Border closures led to concerns that canceled flights would impede transportation of aid to the region and that those crossing the borders would simply avoid security checkpoints.^{23,24,25,26}

In addition to Guinea, Liberia, and Sierra Leone, there were a number of cases of EVD diagnosed in other countries. Nearly thirty cases, including 14 deaths, and localized transmission were reported in Nigeria and Mali, and an imported case was identified in Senegal; however, intervention efforts were able to prevent further spread of the disease.^{27,28} A nurse in Spain contracted the disease in October 2014 while caring for an infected missionary who had returned from West Africa for treatment, the first transmission of the Ebola virus outside of Africa.²⁹ The first patient diagnosed with EVD in the United States was a Liberian national visiting family in Dallas, Texas, where he became symptomatic in September 2014 and was admitted to Texas Health Presbyterian Hospital. The patient ultimately died, and two healthcare workers were infected during his treatment. One healthcare worker was transported to Emory University Hospital in Atlanta, Georgia for treatment, and the other was treated at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. Both of these patients recovered and were discharged in October 2014. The final case of Ebola diagnosed in the United States to date was a doctor from Médecins Sans Frontières (MSF) who had recently returned from Guinea. He was diagnosed in October 2014 and successfully treated at Bellevue Hospital Center in New York.³⁰ The United Kingdom's first Ebola patient, a Scottish nurse returning from work in Sierra Leone in December 2014, was successfully treated in London.^{31,32} Finally, a healthcare worker who had recently returned to Italy from Sierra Leone was diagnosed with EVD in May 2015 and recovered a month later.^{33,34}

At the outset, health authorities were hamstrung by a lack of approved Ebola drugs and vaccines and turned to the limited options available in the MCM development pipeline.

Readily available prophylactic or therapeutic MCMs could have mitigated the impact of the West Africa Ebola epidemic by preventing new infections, reducing patients' infectiousness, or decreasing morbidity and mortality. When the outbreak struck, however, the only available drugs and vaccines for Ebola were still in early, preclinical stages of development and had yet to be tested in humans. Multiple factors contributed to a lack of approved Ebola drugs and vaccines at the start of the West Africa outbreak. First, previous Ebola outbreaks were infrequent, small-scale events that occurred primarily in isolated rural settings. The paucity of cases—along with a lack of infrastructure in West Africa for recruiting, treating, and testing human patients—meant that randomized controlled trials (RCTs)—beyond Phase 1 safety trials—were not feasible. As a result, the efficacy and safety of investigational Ebola MCMs in human subjects remained uncertain, although several products had shown promising results in animal testing.^{35,36,37,38} Additionally, the low number of Ebola cases prior to the West Africa epidemic provided little incentive to invest significant resources in the development of Ebola treatments and vaccines for pharmaceutical companies seeking to turn a profit.³⁹ Due to a combination of inadequate funding support, inefficient research and development cultures, and cumbersome procurement and contracting processes, responsible federal entities had also failed to sufficiently spur the private sector to develop investigational Ebola MCMs in the years leading up to the West Africa epidemic.⁴⁰

Though there were no Ebola MCMs at the time that had been shown to be both safe and effective in humans, several investigational drugs existed in various early stages of the development pipeline. Notable among these drugs were ZMapp, a combination of monoclonal antibodies;⁴¹ TKM-Ebola, a combination of small interfering RNAs;⁴² brincidofovir, an antiviral drug being assessed for the treatment of smallpox, cytomegalovirus, and adenovirus;⁴³ and favipiravir, an antiviral under investigation as a treatment of influenza.⁴⁴ Investigational vaccines against Ebola included a single-dose vaccine from the Public Health Association of Canada/NewLink/Merck,³⁶ a recombinant vector vaccine derived from a chimpanzee adenovirus developed by NIAID/GlaxoSmithKline,⁴⁵ a multivalent immunization against filoviruses from Janssen/Johnson & Johnson,⁴⁶ and a glycoprotein recombinant nanoparticle vaccine from Novavax.⁴⁷ At the time the West Africa epidemic rose to global attention, none of the vaccines had yet demonstrated efficacy in human trials, and while several of the

investigational therapeutics showed promise in animal models, only a very limited supply was available for use in humans^{48,49,50,51} let alone sufficient volume to conduct clinical trials.

A common desire to help those most affected by the epidemic nonetheless led to split opinions and controversy over how best to make use of scarce investigational Ebola MCMs.

As vaccines and therapeutics were explored for activity in animal studies and for preliminary safety and tolerability in early-phase human trials, many experts and vocal members of the public called for widespread compassionate use of these products in affected communities in West Africa, arguing that it was unethical to withhold potentially life-saving MCMs. Many others, including the FDA,

countered that it was, in fact, unethical to provide widespread access to MCMs without knowing whether the products would help, do nothing, or even harm those who took it. Additionally, they argued that widespread use of investigational products outside of RCTs would not provide usable data for determining their effect, positive or negative, and that this posed an additional risk of perpetuating the use of these drugs in future outbreaks without



knowing whether they helped or harmed patients.⁵² Compounding the ethical questions surrounding RCTs and compassionate use was the provision of the initial limited supply of ZMapp to treat two American aid workers, three Liberian medical doctors, a British nurse, and a Spanish priest.⁵³ The decision to allocate a scarce drug in this manner fueled perceptions that wealthy American and European aid workers were being prioritized over poorer West African patients, thereby leaving fewer drugs available for communities struck hardest by the outbreak.^{54,55} Additionally, cases of Ebola treated in the United States received a variety of investigational treatments; however, because initial patients were not part of clinical trials, they yielded no usable efficacy data.^{52,56,57} To some critics, the fact that Westerners could access investigational products outside of clinical trials while West Africans could not was indicative of prevailing inequities between Africa and the West. While the FDA is only responsible for responding to requests for compassionate use, not for identifying or selecting who receives the investigational products, they received a significant portion of the criticism by virtue of their presumed role in the authorization process.

Product developers resorted to various approaches when testing MCMs, owing to complex circumstances surrounding the West Africa Ebola epidemic. The desire to provide help to a desperate population was complicated initially by insufficient supplies of investigational MCMs, and by the time clinical trials were ready to commence, the epidemic was waning, providing progressively fewer opportunities to gather data on MCM safety and efficacy. This variegated approach to testing led to a wide range of outcomes. For instance, TKM-Ebola was evaluated in Sierra Leone in a non-randomized controlled trial, but the trial ended after enrolling only 14 patients due to early indications that the drug was not beneficial. A trial of brincidofovir in Liberia, designed in conjunction with the University of Oxford and MSF, ended after enrolling only four patients, owing in large part to the overall low numbers of Ebola patients.^{59,60} A trial of favipiravir in Guinea yielded seemingly “encouraging” preliminary indications of efficacy; however, the trial was not a randomized controlled design, so many experts questioned the quality of the results. The recovery of several infected healthcare workers treated with ZMapp provided highly publicized anecdotal evidence of its efficacy, despite the fact that it was impossible to separate the drug’s effect from that of the intensive supportive care that the initial recipients received. By the time the RCT for ZMapp began in Liberia, however, there were few patients available to enroll in the study. The study was expanded to Sierra Leone and Guinea to increase the data pool; however, all patients in Guinea also received favipiravir, complicating the study’s ability to identify the independent effect of ZMapp.⁶⁰

Investigational vaccine products faced similar challenges in their trial designs. The GlaxoSmithKline vaccine trial began just as the epidemic in Liberia was winding down, and low enrollment relegated the Phase 3 trial to Phase 2; as of December 31, 2015, the trial was still ongoing and collecting data. The Merck vaccine was assessed utilizing a ring vaccination trial design—vaccinating close contacts of identified cases—that used a control group consisting of similar populations that received the vaccine several weeks later. Results indicate that the vaccine was 100% effective in preventing new cases of Ebola (zero cases within ten days of receiving the vaccine compared to 16 in the control group over the same time period); however, due to concerns with the innovative trial design, it remains to be seen whether this effort yields sufficient data to support product approval. In a Phase 1 clinical trial of a prime-boost vaccine combination from Johnson & Johnson and Bavarian Nordic, the vaccine combination demonstrated safety in humans and provided evidence of both initial and sustained immune response. Despite many efforts to evaluate investigational Ebola MCMs, tragically little progress has been made in determining their effect.⁶⁰

DILEMMA #1

Given a strong desire to combat the outbreak, tension developed around the best way to enable access to investigational MCMs: clinical trials versus broad availability.

As anecdotal evidence seemed to show that the investigational vaccines and therapeutics appeared safe to use in humans, the debate began regarding how to best utilize them as they became available. Although there were many nuances of argument and proposed trial designs, various viewpoints emphasized differences in how and when the MCMs should be distributed. Some felt that, due to the severity of the disease and the outbreak, the investigational products should be made available as widely as possible to provide the greatest potential benefit to those populations ravaged by the Ebola virus. Others maintained that, in order to determine safety and efficacy, RCTs should be conducted. Further complicating MCM use for the epidemic, making the investigational products available to affected populations in West Africa required adhering to regulatory authorities in the affected countries. FDA regulations would apply if the product was provided under a US Investigational New Drug protocol (IND);^{63,i} however, not all products were being developed under a US IND.

Under specific circumstances, the FDA can authorize use of unapproved products, including MCMs, for an individual (or use of an approved product in an unapproved manner) under a provision called expanded access, commonly known as “compassionate use.” Similarly, use in small groups or wider populations is designated as “under treatment protocol.” In all cases, the patients must be affected by a “serious or immediately life-threatening disease or condition” for which there is “no comparable or satisfactory alternative therapy.” Additionally, there must be some evidence that the product will provide benefit without unreasonable risk “in the context of the disease.”⁶⁴ Specifically with respect to vaccines, the expanded access provision does allow for the use of unapproved vaccines even though the condition is not technically present in those who receive it as prophylaxis.⁶⁵ Although West Africa is outside of FDA jurisdiction, those in favor of compassionate use cited the sheer volume of cases and deaths in the West Africa region and the high case fatality rate as justification for providing the experimental vaccines and therapeutics broadly to the affected populations.^{58,66} They made the argument that clinical trials were unnecessary, because historical data from Ebola outbreaks would be sufficient to serve as a control group to assess the efficacy of the new vaccines.⁶⁷ Proponents

ⁱ Some regulations also apply if the product is manufactured in the United States, even if not being developed under a US IND.

of widespread compassionate use viewed the broad distribution of vaccines and therapeutics as the best way to provide the most benefit to the most people and address widespread suffering in West Africa.

On the opposite side of the argument were those calling for RCTs for all new vaccines and therapeutics. The placebo-controlled, randomized trial is widely accepted as the “gold standard for determining the efficacy of a new treatment,” although several additional trial designs were debated.⁶⁸ While compassionate use advocates claimed that it would be unethical to give someone a placebo, delay



treatment, or withhold treatment during an epidemic such as Ebola, others, such as FDA Office of Counterterrorism and Emerging Treats Director Dr. Luciana Borio, asserted that a trial using unreliable historical controls would be an invalid study design and that, by definition, invalid trials cannot be ethical.⁵² The use of historical data would not necessarily provide a legitimate control group, as differences in population demographics, treatment regimens, and virus virulence or lethality would significantly impact the ability to assess the efficacy of vaccines or treatments.⁶⁷ Moreover, without a proper placebo control group, it would be difficult to gather sufficient evidence regarding the safety and efficacy of these products.⁶⁸ Further, Dr. Borio noted that random allocation would provide a fair means of deciding who could access limited quantities of investigational MCMs,

which could still cause more harm than benefit. And due to low inventory of investigational MCMs, not everyone would be able to receive a vaccine or treatment anyway, so conducting a placebo-controlled trial would not actually deprive anyone of a product.⁶⁷ In a region where the outside medical community is treated, at best, with skepticism, conducting trials in the most ethical manner possible is vital to earning and maintaining the trust of the West African people.¹²

In July 2014, two American aid workers in Liberia who contracted Ebola were treated with the investigational product ZMapp and transported to specialized medical facilities at Emory University Hospital in Atlanta, Georgia, where they later made full recoveries. Because they received high levels of supportive care at the same time, there was unfortunately no way to determine how much, if any,

benefit the ZMapp provided.^{69,70,71} Initial supplies of ZMapp yielded only enough doses to treat a handful of patients, and it would take months to produce more.^{57,72,73} Without enough ZMapp or human subjects to conduct a randomized trial, scientists remained uncertain about the MCM's true efficacy in treating Ebola.

Despite the lack of scientific evidence needed to justify broad use of ZMapp and other investigational Ebola MCMs, the media, the healthcare and public health communities, and the general public continued to criticize what they perceived to be inefficient, ineffective institutional responses to the escalating outbreak. For example, access to ZMapp was arranged by the drug's manufacturer to treat Ebola patients prior to the establishment of clinical trials, when clinical circumstances warranted its use. It was widely reported that the FDA authorized the use of ZMapp for these patients under the "compassionate use" provision due to the severity of the disease and the lack of other viable treatment options;^{74,75,76} however, some reported that initial use of ZMapp was outside of the FDA's jurisdiction due to it being administered in West Africa before the patients returned to the United States.⁷⁷ While the FDA is legally prohibited from discussing IND applications or commenting on whether individual patients receive products under IND protocols, a FDA representative did acknowledge that the initial patients treated at Emory University received investigational products under emergency IND (eIND) protocols and that all Ebola patients treated in the United Statesⁱⁱ received at least one investigational product.^{78,79} Some questioned why these few ZMapp doses were initially provided to Americans and not to those in West Africa.^{80,81,82} Specific concerns arose around the perceived disparity between Americans being given the investigational ZMapp serum outside of a controlled trial while mandating trials for investigational treatments and vaccines in West Africa.⁵⁸ Once clinical trials were established, both Americans and Africans were afforded access to investigational products in accordance with trial protocols,⁸³ but without the ability to comment directly on specific instances of compassionate use, the FDA was unable to deflect criticism from the media and public over early use of investigational MCMs outside of clinical trials.



ⁱⁱ As of October 16, 2014.

The FDA faced the challenge of conveying its message that RCTs are the best, fastest, and most ethical means of rapidly evaluating the safety and efficacy of investigational MCMs and ultimately providing products that work to patients in need. The perception of disparity in access and pushback from many respected experts made these communication efforts even more difficult.

Implications for the future:

Recent experience with the Ebola epidemic revealed a range of expert and public views about the appropriate use and clinical study of unproven therapies during a major infectious disease emergency. Whether investigational MCMs should be provided via RCTs that would require some patients be administered placebos is a debate likely to be repeated in future health emergencies, especially because US government investments in MCM development are now expanding the pipeline of candidate therapies. The FDA will confront an ongoing challenge of communicating persuasively about the value of RCTs during a health emergency. To communicate most convincingly about clinical trials—and to a range of audiences that include the media, Congress, and the general public—the FDA should approach this topic as one where technical and normative issues are inextricably linked, competing values about the public good are in play, and the merits of the opposition’s arguments deserve to be acknowledged.⁸⁴

From a risk communication perspective, when and how to provide potentially life-saving MCMs to affected populations is a public health question that has a strong moral component (eg, the duty to address mass suffering) and one that elicits public desire for a compassionate, humanistic response rather than a dispassionate, technocratic one.⁸⁴ In the context of Ebola, the FDA produced two notable resources outlining its rationale for RCTs: a strong science-based article by FDA leadership in *The New England Journal of Medicine*⁶⁷ and a compelling TEDx talk delivered by Dr. Luciana Borio to a broader audience.⁸³ Arguments in each case were heavily weighted toward the technical merits afforded by RCTs in efficiently producing critical knowledge about the safety and efficacy of investigational MCMs, specifically contrasting them against historically controlled trials, while the larger social and moral aspects of MCM access went largely unaddressed. Commentators on the RCT debate regarding experimental Ebola drugs help illustrate two different ways of framing the case:

“It sounds inhumane to give sick and dying people placebos when testing experimental treatments, but it is tragic on a different scale to conduct a study that doesn’t tell us clearly where, or how well, a new treatment works.”⁸⁵

versus

“The blinded randomized control trial is the most robust study design for testing the efficacy of a treatment.”⁸⁶

While the complex debate over RCTs during the Ebola epidemic touched on an array of scientific and practical matters, differing values and understanding attached to the placebo seemed to underpin much of the controversy. For instance, regulators and investigators may see a placebo as strengthening the reliability of data on whether a therapy helps, harms, or does nothing, while patients and the larger community may perceive a placebo as missing out on a treatment that offers hope and that could possibly extend life or lessen pain, regardless of the slim odds of it doing so or the chances of it causing an adverse reaction instead.⁸⁷ The value of scientifically defensible data and the value of hope amidst mass tragedy may involve competing ideas about the public good. During the Ebola response, an important value for those who rejected the RCT approach was a desire to reduce suffering. By acknowledging this objective and, more importantly, highlighting how this and other values are reflected in FDA policy, the FDA could greatly improve the impact of its messages.

To speak credibly and meaningfully on the topic of RCTs to a broad audience requires that a science-driven agency like FDA be responsive to opposing arguments grounded in cultural norms, social values, and a moral perspective. In the Ebola case, effective communicators outside of the FDA were promoting a strategy counter to that promoted by the FDA. A rich body of literature on competing message frames highlights the importance of effective communication through framing issues, such as the need for clinical trials, using language that is salient (ie, relevant) to potential audiences and using strong messages that tap the power of emotion.⁹⁰ In addition, the frequency and timing of these messages also play a role.^{91,92} From a risk communication standpoint, it is sensible to work the opposition’s strongest points (eg, facts, arguments, emotions) into one’s own statements.⁸⁴ Speaking in ways that show genuine appreciation for alternate viewpoints and for a range of deeply held values, particularly how those underlying values are already incorporated into existing policy, can enhance the legitimacy of FDA positions. Framing current policy in terms of the opposition’s values provides the audience context in which to evaluate, understand, and appreciate these positions. It is important that

It is important that communication efforts be made in the midst of the debate, rather than after attention has drifted from the issue, since many audiences will no longer be primed to receive information. In this case, Dr. Borio's TEDx talk—one of the FDA's principal efforts to communicate with the broader public—did not take place until October 2015, more than a year after the RCT debate began.⁸³ The use of familiar language and arguments in well-timed and regular communications can help effectively overcome competing message frames and improve overall communication efforts.

ACTION ITEMS FOR FDA

- 1) In advance of future crises, commission research that would elicit public views and values about the appropriate use and clinical study of unproven therapies, and on this basis, develop informational materials designed to help broaden support for the use of RCTs during health emergencies.
- 2) Embed any technical claims about the advantages of placebo-controlled clinical studies in the context of a larger values-based narrative that reflects the common, overarching desire to provide assistance to affected populations. In this case, express the moral convictions that sick and dying people deserve appropriate care and that populations under duress deserve society's best efforts at support, both for current and future epidemics.
- 3) During periods of active debate, listen to opposing arguments to discern the cultural norms, social values, and moral perspectives relevant to the audience, and craft messages that incorporate and reflect these important underlying priorities. Use opposing views as important data points to understand where empathy and reflection of values are important in producing a message that resonates with the target audience.
- 4) Deliver these messages early and frequently in order to compete effectively with opposing message frames. Late messaging occurring after the period of active debate is not as effective as messaging that is applied when audiences are paying attention to the issue.

DILEMMA #2

The need to protect confidential commercial information relating to emergency MCMs against Ebola created communication barriers between FDA and

In addition to the challenges that emerged during the Ebola MCM development process, the FDA also fielded concerns around potential disclosures of confidential commercial information (CCI), some of which stemmed directly from ongoing communication dilemmas around perceived inequities in MCM distribution. For example, following news that two American clinicians working in West Africa received ZMapp after contracting Ebola, the Goldwater Institute (a public policy think tank) sent the FDA a Freedom of Information Act (FOIA) request in August 2014, seeking information about the agency's process for approving use of ZMapp.⁹¹ Concerned about potential disclosures of industry trade secrets or CCI, the FDA denied the FOIA request. After unsuccessfully appealing the decision to the US Department of Health and Human Services, the Goldwater Institute filed a lawsuit against the FDA in June 2015, citing the importance of ensuring equitable access to potentially life-saving drugs.⁹² The FDA also encountered blowback from Congress over CCI during the clinical trials process for investigational Ebola MCMs. For instance, during a hearing before the US House Committee on Foreign Affairs in September 2014, members of Congress asked witnesses representing the FDA and the NIH why certain investigational MCMs were placed on clinical hold.⁹³ However, the FDA could not acknowledge the existence of the investigational applications for the MCMs in question. Though in each of these instances, the FDA was complying with legal requirements to protect CCI, the agency's actions were perceived as being obstructionist and privileging industry needs over those of other stakeholders—namely, Congress and the general public.

Given the tension between the FDA's legal obligation to protect CCI submitted by pharmaceutical developers and a public that demands transparency, the FDA faces considerable challenges around publicly sharing information about MCMs that could result in competitive harm to industry. Under Title 21 of the Code of Federal Regulations (CFR), the FDA is prohibited from disclosing CCI without written authorization from a product sponsor. The regulations, in 21 CFR §20.88, do allow the FDA Commissioner (or his or her designee) under certain conditions to authorize disclosure of CCI to state government officials without sponsor permission if doing so is in the interest of the public's health.^{94,95}

However, it remains unclear as to whether state officials invoked this regulation during the Ebola outbreak.

The FDA does employ other mechanisms for facilitating non-public information sharing with foreign government officials in the midst of an international public health emergency, as authorized by CFR 21 §20.89, for example. In September 2014, for instance the International Coalition of Medicines Regulatory Authorities (of which the FDA is a member) affirmed its commitment to cooperate with the World Health Organization (WHO) and regulatory agencies “to encourage submission of regulatory dossiers and evaluation of the submitted information on potential new medicines...to accelerate access to investigational treatments for patients most in need during the current outbreak,” as well as to ensure that affected communities could access safe, efficacious medicines in the event of future outbreaks.⁹⁶ Furthermore, the FDA made a mutual confidentiality agreement with the WHO in 2014 to facilitate interagency exchanges of CCI while ensuring public non-disclosure of such information.⁹⁷ The FDA made similar commitments to protecting CCI with the Ministry of Health and Public Hygiene of Guinea, the Pharmacy Board of Sierra Leone, and the Liberian Medicines and Health Products Regulatory Authority during the West Africa Ebola epidemic.^{98,99,100}

Implications for the future:

The FDA’s dual role as both a regulatory body and a protector of the public’s health confers the agency with the difficult tasks of handling industry considerations, ensuring the safety of emergency MCMs, and responding to the needs and concerns of its partners in government, healthcare, and the general public. The FDA has already taken important regulatory steps to ensure that select partners are privy to certain types of CCI during a public health crisis, but without concurrently strengthening channels of communications with other, non-industry stakeholders—namely, members of Congress, healthcare providers, and consumers—the agency will likely continue facing the repercussions of perceived non-transparency as it strives to satisfy its public health mission.

The disclosure of CCI could certainly discourage pharmaceutical companies from pursuing development of MCMs for critical public health threats. However, the perception that the FDA’s legal obligation to protect CCI is obstructionist could fuel distrust among the aforementioned stakeholders, and potentially result in future lawsuits, low uptake of MCMs among consumers, frustration among healthcare providers and public health officials contributing to emergency response efforts, and

ongoing Congressional pressure to divulge proprietary information—consequences that would require the FDA to continue depleting its already limited pool of resources. The FDA could mitigate some of these challenges by including acknowledgements of public anxiety and concern in its communications about the importance of protecting CCI, as well as by hiring personnel with the expertise necessary to craft messages about MCM risks for its various audiences. Finally, it is critical for the FDA to assume a more proactive approach to setting public expectations around the scope of its legal and regulatory powers during public health crises. During such events, misperceptions of obstructionism could exacerbate existing anxieties around the health threat in question; the public, in turn, might be less receptive to explanations of the FDA's legal constraints in the midst of an ongoing threat. Therefore, in advance of a public health emergency, the FDA might consider collaborating with sister agencies and industry partners to increase awareness of its legal obligations and other CCI challenges among members of Congress, Congressional staffers, and consumers.

ACTION ITEMS FOR FDA

- 1) Engage with industry partners developing emergency MCMs to explain the FDA's challenges in protecting CCI and underscore the immense public health value of disclosing relevant CCI (eg, clinical trial data) during a crisis. Collaborating with industry partners to develop prepositioned messages for Congress, healthcare providers, and consumers about MCM safety to deploy during crises could also further facilitate emergency communication.
- 2) Reach out to relevant members of Congress to explain the legal restrictions that prohibit the FDA from publicizing certain details about investigational MCMs. Partnering with sister agencies/offices bound by less-restrictive confidentiality laws—eg, the NIH, the CDC, and the ASPR Biomedical Advanced Research and Development Authority—to describe regulatory challenges around CCI could help provide context and details that the FDA may be unable to disclose.

DILEMMA #3

Initial authorization of investigational Ebola MCMs for use by Americans and Europeans outside of clinical trials fueled concerns over inequities experienced by West Africans affected by the Ebola epidemic.

One of the largest controversies involving Ebola MCMs was the act of providing limited quantities of investigational products to American and European responders rather than the affected West African population. On one hand, the extremely limited supply of investigational Ebola MCMs would likely have little impact on the growing Ebola epidemic, and many felt an obligation to help those who had voluntarily placed themselves in harm's way to respond to the outbreak. Health officials also feared that if West Africans were administered an investigational MCM that turned out to be harmful, it would be perceived that "Africans [were] used as guinea pigs" for the American pharmaceutical industry.⁵⁴ Opponents, including medical experts, argued that it was unethical to deprive the affected population of a potentially life-saving drug, even if it had not been previously tested in humans.^{58,101} Additionally, they argued that the lives of West African volunteers who contracted Ebola were equally as valuable as those who received the drugs, so the investigational products should be distributed accordingly, not just to white Westerners.¹⁰² A variety of challenges came into play in a debate that grew well beyond the act of authorizing the use of investigational MCMs to encompass larger perceptions of health inequities associated with the West African Ebola epidemic.

ZMapp provides a prime example of the controversy over the ethics involved in allocating scarce Ebola MCMs in the midst of the West Africa epidemic. The world first learned about ZMapp in early August 2014 when reports surfaced about the first use of the investigational drug in humans, two American missionaries fighting the Ebola outbreak in Liberia.⁷⁶ Use of the drug was presumed by many to have been authorized under the FDA's compassionate use (expanded access) protocol, because the drug was not yet approved for use in humans;^{74,75,76} however, the exact process by which early Ebola patients in the United States accessed investigational products and the extent to which the FDA was involved remains unclear.^{77,92} The survival of both of these patients, in conjunction with promising animal trial results, provided support for ZMapp's efficacy, if only anecdotal. ZMapp's subsequent and rapid rise to "miracle" drug status in the media sparked immediate demand for the product to be sent

to West Africa.^{75,103,104} Unfortunately, the supply of ZMapp at the time was limited to only a handful of doses, all of which were distributed by August 11.¹⁰⁵ In total, ZMapp was administered to seven people, five of whom survived. Among these were two patients from the United States, one from



Britain, and one from Spain;¹⁰⁶ the remaining doses were used to treat three healthcare workers in Liberia.¹⁰⁷ In the context of the unprecedented and growing epidemic in West Africa, many questioned providing the limited supply of the miracle drug to wealthy, white Americans and Europeans while thousands of poorer West Africans suffered and died.⁷⁵ Many others countered that the severely limited inventory of ZMapp, in and of itself, precluded its use among

the affected West African population, but some countered by questioning why Dr. Sheik Umar Khan—one of Sierra Leone’s leading Ebola physicians and a “national hero” who contracted Ebola and died the day before Americans Dr. Kent Brantly and Nancy Writebol received doses of ZMapp—was not given the drug or even informed of its existence.^{81,82,108} As the federal agency responsible for approving MCMs, the FDA bore the brunt of the public and media contempt, but there were many mitigating factors beyond their control.

Fueling the debate was a lack of transparency regarding the availability and distribution of investigational Ebola MCMs like ZMapp. As previously mentioned, the existence of drugs like ZMapp was largely unknown in the general public at the time, prompting demand from the media, the public, and government officials for more information on the products and their respective status in the FDA approval process. Legal constraints on the FDA, however, prohibited officials from discussing confidential information about these products, including approval status. FDA officials were not even permitted to acknowledge if compassionate use authorization had been requested, let alone discuss the process by which a product’s use was authorized or how the allocation was determined.⁷⁴ The FDA did acknowledge that the eIND protocol was used to provide investigational drugs to Ebola patients, but further details were not provided.⁷⁸ An NIH representative described in general the process by which ZMapp was obtained for the initial patients, in that Samaritan’s Purse, the organization that Dr. Kent Brantly worked for, contacted ZMapp’s manufacturer directly, via the Centers for Disease Control and Prevention (CDC) and NIH; however, explicit details—including how many requests were submitted

and approved, which patients received which products, and the extent to which FDA regulated the use of products outside the United States—have not been made public due to confidentiality restrictions.⁹² The opacity of this process led to questions regarding how the patients who received ZMapp were selected, and the perceived inequity in resource allocation—specifically providing Westerners, authorizing the limited supply of investigational products for use in Westerners outside of clinical trials while requiring placebo-controlled trials in West Africa—resulted in intense media scrutiny around the ethics of MCM distribution.^{111,112}

Superficially, the initial allotment of ZMapp appeared to perpetuate health disparities between America/Europe and Africa; however, a number of factors played into its authorization and allocation. These factors were highlighted with the arrival of the United States' first diagnosis of Ebola in Thomas Eric Duncan in Dallas, Texas. In the wake of his death, accusations of racism and classism surrounded Duncan's treatment, ranging from the hospital sending him home from his initial visit to his clinical treatment once admitted. Many, including Duncan's friends and family and Reverend Jesse Jackson, decried withholding ZMapp from Duncan after its earlier use with Dr. Kent Brantly and Nancy Writebol^{113,114} despite the fact that the limited supply of ZMapp had been exhausted months prior.¹⁰⁵ Other considerations—such as Duncan's current health condition and blood type—also factored heavily into the treatment options available to him.^{115,116} Similarly, the authorization of ZMapp and other investigational products for individual patients depended on a number of considerations. First, compassionate use requests are submitted by treating physicians, not offered by the FDA. The FDA can only respond to those requests based on their merit, and allocation of the product is subject to availability from the manufacturer.¹¹⁷ Additionally, FDA has no standing international authority, and use of investigational products abroad must be coordinated through the appropriate national governments to ensure they are used safely and ethically. While providing investigational products to patients in need seems, on the surface, like a straightforward process, there are many factors—information for many of which remains confidential—that must be considered before this can occur.

Implications for the future:

Many aspects of the West Africa Ebola response prompted concerns over ethical treatment and health inequities between West Africa and Western nations. In this case, the high-profile use of limited supplies of investigational treatments in white Americans and Europeans that had not been made

available to West Africans was complicated by limitations on the FDA's ability to discuss specifics of the compassionate use requests. This instance is similar to historical examples involving health inequities and medical research. Unlike other scenarios, however, this case involves the perception that an investigational drug was being withheld from the affected population rather than being forced on a vulnerable population to test a new product, resulting in nuanced communications challenges. As discussed previously, the FDA is legally obligated to protect confidential information for investigational products. Under these restrictions, it was difficult to address questions regarding how and why the initial supply of investigational MCMs like ZMapp were provided to white Americans and Europeans. While federal agencies—including the NIH and the State Department—did an effective job at publicizing the process by which Samaritan's Purse obtained ZMapp for Dr. Kent Brantly, Nancy Writebol, and others,^{118,119,120} health officials did not effectively acknowledge the public's ethical concerns nor relate to them in a way that could help abate their frustration.

In situations such as this—where the media and public could perceive that certain people were given preferential treatment, particularly over a historically disadvantaged population—health officials need to address these concerns explicitly. Simply stating the inability to comment due to legal restraints or lack of information leaves a void that the media and public can fill with speculation and information—as well as misinformation—from unofficial sources.¹²¹ The first step is to provide the information that is available. As mentioned above, the process by which the initial doses of ZMapp were obtained was discussed in general terms by several federal sources, and this message was carried by numerous media outlets. Secondly, and most importantly, health officials need to acknowledge the public's grievance—in this case, that white Westerners received preferential treatment—and provide concrete support to clarify the situation. By specifically addressing concerns regarding fairness, health officials give themselves the opportunity to demonstrate why the actions taken were morally sound and in keeping with ethical principles and established protocols. Communications should also address any factors that are beyond the control of the applicable agencies and limitations on their scope of authority. In this case, for example, communications should have highlighted that the FDA can only respond to requests for compassionate use, not proactively issue them. Additionally, statements should have emphasized that the requesting organizations approached the CDC and FDA rather than these agencies working to actively identify Americans for whom investigational treatment options could be supplied.

ACTION ITEM FOR FDA

Train agency spokespersons to recognize variables known by risk communicators to provoke public outrage including perceived unfairness, moral indifference, and impacts on vulnerable populations. When these elements are present in a situation, recognize that they are central to public health objectives rather than dismiss them as mere misperceptions.⁸⁴ Instead, openly acknowledge these concerns and use values-based language with supporting evidence to diminish impassioned critiques, direct or indirect, of agency policies and actions.

Conclusion

While there were countless problems with the global response to the West Africa Ebola epidemic, much of the conflict focused on the availability of MCMs. With few products in development and none with demonstrated safety and efficacy in humans, traditional development and approval processes were called into question by the public, media, and government as well as public health and bioethics experts. The desire to provide much-needed aid to a population facing a devastating epidemic with limited medical and public health resources drove many to question the necessity of clinical trials, including RCTs, when they felt that more good could be done with widespread use of investigational products. These ethical concerns were bolstered by highly publicized reports of the use of some of these investigational products outside of clinical trials, increasing concern that Americans and Europeans were being prioritized over the struggling West African population. In addition to ethical challenges, there were also calls for increased transparency in product development and testing, challenging legal responsibilities to maintain confidentiality for products currently in development. These complex issues would be difficult to address even under ideal circumstances, but the rapidly expanding Ebola epidemic and rising global anxiety applied increased pressure to provide rapid solutions.

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