Blurring Lines: Complexities of Ethical Challenges in the Conduct of West African Ebola Research

A Review of the Literature

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EXECUTIVE SUMMARY

CONTEXT

- The 2014-16 West African Ebola outbreak was the world's largest and longest outbreak of Ebola Virus Disease (EVD).
- It was particularly damaging as it arose in the context of countries (re)building their healthcare systems following decades of under-funding and armed conflict.
- Although WHO determined ethical criteria for use of unregistered interventions, ethical challenges surrounded the conduct of clinical trials.
- These challenges have not been systematically documented

NARRATIVE REVIEW OVERVIEW

- This review provides a three-year snapshot of ethical challenges in the scholarly literature pertaining to the conduct of research during the 2014-2016 West Africa Ebola outbreak.
- Peer reviewed literature from January 2014 to January 2017 was retrieved through 5 indexes
- 145 articles were included in the review.
- Articles were coded based on topics from WHO recommendations, as well as new insights

RESULTS

Five levels of challenges: Discussions of ethical challenges in EVD research emerged at five differing yet intersecting levels.

- *Global level challenges* situate the ethical challenges that stem from weak healthcare systems and underfunded research landscapes within the context of colonialism, global inequality, and transnational disadvantage.
- This challenge represented a large and unmentioned gap in the majority of reviewed articles.
- *National level challenges* highlighted resource and communication limitations, including lack of infrastructure, poor documentation practices, and lack of research experience and research ethics board support.
- *Community level challenges* emphasized cross-cultural confusion, lack of follow up, and high levels of distrust that occurred as a result of poor communication.
- *Trial design challenges* included two main areas: 1) the use of experimental interventions and 2) randomization, as well as how concentrated debate on those areas detracted from larger ethical discussions.
- *Individual level challenges* highlighted the difficulties of obtaining informed consent in extremely vulnerable situations, as well as the exclusion of vulnerable populations from trials.

Overwhelming complexity of ethical challenges

- *No research challenge* during a public health emergency is *purely ethical or practical*: they are both. Ultimately, many ethical challenges of research will only become apparent in the process of enacting protocols within specific socially, historically, logistically complex settings.
- Woven throughout the four levels of ethical challenges was a constant tension: between *ideals* of rigorous and ethical health research, and the *practical realities* of conducting research in a humanitarian emergency shaped by transnational differences in power and resources.

BACKGROUND

The 2014-15 West African Ebola outbreak was the world's largest and longest outbreak of Ebola Virus Disease (EVD). It resulted in 11315 deaths and the care management of 26350 persons over two years (Folayan et al., 2016). It was particularly damaging as it arose in the context of countries (re)building their healthcare systems following decades of under-funding and armed conflict (Upshur and Fuller, 2016). The Ebola case fatality rate is very high (Bellan et al., 2014). While recommendations do exist at this point for supportive treatment that have been shown to optimize patient chances of survival (Lamontagne et al., 2018), there exists no evidence-based treatment to cure the disease. In August 2014, WHO deemed the use of unregistered interventions to be ethical under certain conditions (Landry et al., 2015). It laid out criteria for use including urgency, transparency, fair distribution, and informed consent, and met to discuss acceptable study designs (Landry et al., 2015). WHO recommendations could only go so far in anticipating and delineating appropriate responses to the ethical challenges that emerged as clinical trials were rolled out.

The objective of this narrative review was to identify ethical challenges in the scholarly literature pertaining to the conduct of research during the 2014-2016 West Africa Ebola outbreak. Specifically, our aim was to catalogue anticipated and unexpected ethical challenges faced by research teams in the course of planning and implementing studies during this public health emergency, with the goals of producing a concise record of these that can inform preparedness for research in future similar events.

METHODS

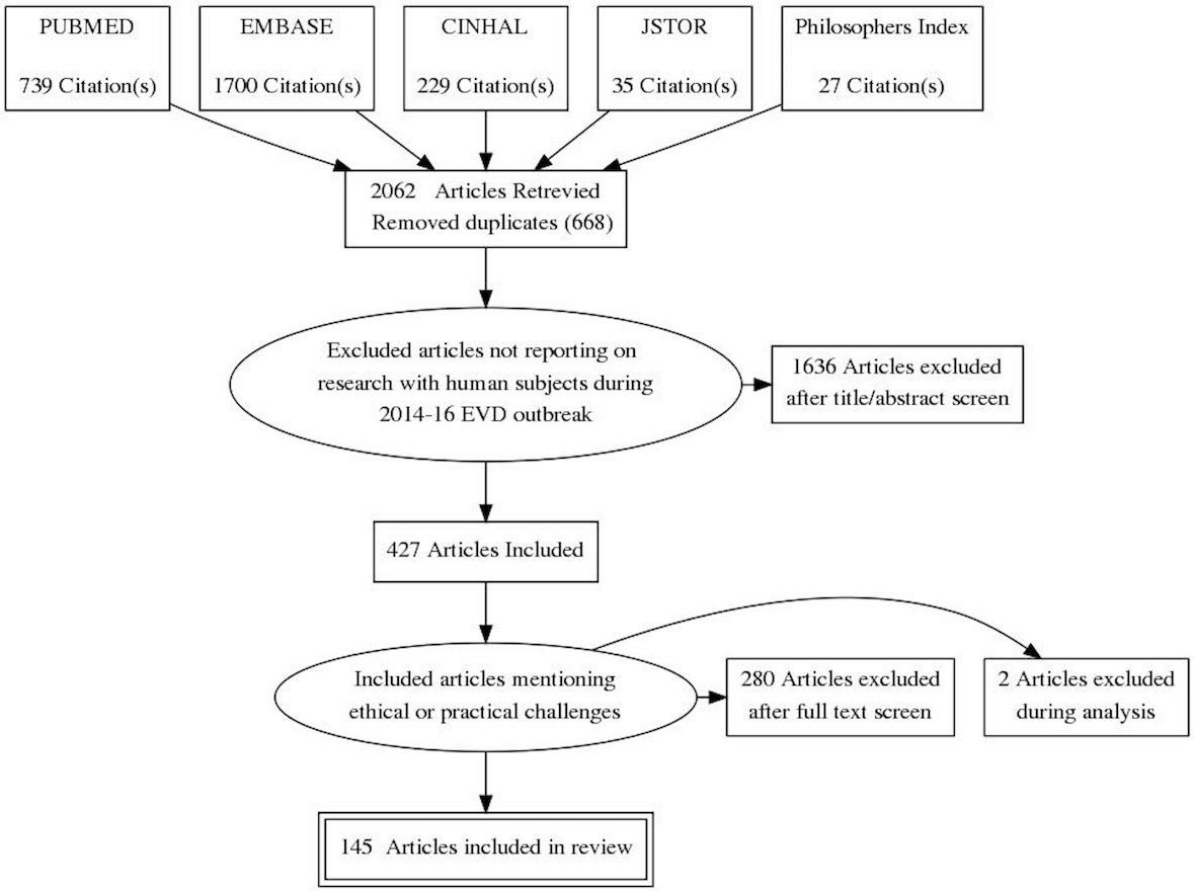


Figure 1. Flow Diagram for EVD Literature Search

This narrative review provides a three-year snapshot from the ever-growing literature pertaining to research conducted during the 2014-16 Ebola epidemic. Relevant peer reviewed literature published in French and English from January 2014 to January 2017 was retrieved via MeSH and keyword searches through 5 indexes (See **Figure 1**). Four stages of screening were undertaken (See **Table 1**) based on inclusion and exclusion criteria (See **Table 2**). Articles included both those presenting extended ethical discussion, as well as briefer references to ethical challenges reported in articles primarily dedicated to study/trial findings. Furthermore, while the majority of articles were included based on explicit references to ethical or practical challenges, this review also includes articles that did not explicitly refer to ethical problems. In our reading of the literature, some articles referenced challenges that we deemed to be practical or ethical problems, and therefore included in this discussion. Many articles were excluded for their focus on clinical care as opposed to research. After full text screening, reference checking, and exclusion during analysis, 145 articles were included in this review.

Stage of Search	Activities Involved
Stage 1: Search and Duplicate Removal	Search Terms: “Ebola” with “trial” or “trials” or “ethics” or “ethical” or “study” or “studies.” Excluded all article titles referring to pigs, monkeys, chimpanzees, or mice. Two rounds of duplicate removal, reduced 2730 initial results to 2062.
Stage 2: Title/Abstract Screening	Title/ abstract screening, excluded titles not reporting on research involving human subjects during the Ebola outbreak, leaving 427 articles
Stage 3: Full Text Screening	Full text screening with detailed inclusion/exclusion criteria was applied, leaving 145 articles
Stage 4: Reference Checking and Exclusion	Reference checking of key articles found 2 other relevant articles, while 2 articles were excluded during analysis, bringing the final total of articles included in the review to 145.

Table 1. Search Stages

DATA ANALYSIS

A team of three researchers, including and led by an experienced medical anthropologist, conducted the thematic coding. First, all three researchers independently coded the same six articles, using NVivo 11.0 software. Coding was initiated using a list of topics of ethical debate that were outlined in the 2014 WHO recommendations on the conduct of trials (WHO, 2014b). However, this initial list was significantly expanded as a codebook was put together that inductively derived additional codes as this work progressed (e.g. North-South power dynamics).

Comparison and discussion of this parallel coding process generated consensus on a codebook, organized into three main areas: practical, ethical, and community engagement challenges (see **Table 3**). Practical challenges included human and technical resources, healthcare systems, time length factors, bureaucracy and politics, flexibility and modifications, and logistics and recruitment. Ethical challenges included areas related to use of experimental interventions, use of randomization, informed consent, inclusion of vulnerable populations, other trial designs, and use of biosamples. Lastly, community level challenges focused on the imperative to engage communities, and successes and challenges of community engagement.

The coding team met bi-monthly throughout the coding process to resolve how best to code the most complex sections of articles, discuss potential additions or merges of codes, and to ensure interpretations remained grounded in the data. Finally, to validate the coding and involve the wider expertise of the authorship team in analysis, other contributing authors audit coded and summarized the contents of key themes in the codebook.

Inclusion Criteria	Exclusion Criteria
Articles had to feature discussions of ethical challenges, or practical challenges with ethical implications, in the conduct of health research with human subjects during the West Africa Ebola crisis, or have referred to it in relation to the unique Ebola crisis context or public health emergency. Articles discussing diagnostics were included due to their related discussion of biological samples.	Excluded: all studies that were not conducted in Sierra Leone, Liberia or Guinea; "animal" (non-human) studies; clinical outcomes description that were chart reviews, retrospective cohort studies, case studies, observational studies of care; summaries of morbidity and mortality; descriptions of results of care; descriptions of public health strategies (case finding or community health force descriptions); computer modelling research (no humans), brief reports on research; descriptions of symptoms and risk factors; quality improvement studies or program assessments; articles calculating effectiveness of a therapy; Articles exclusively about compassionate use and off label drug use; news articles.
	Passing references to the conduct of research or simple mentions of obtaining informed consent were insufficient for inclusion.
	Articles exclusively focused on clinical care
	Articles with only an abstract, non-peer reviewed articles, and research protocols were excluded.

Table 2. Inclusion and Exclusion Criteria.

Type of Ethical Challenge	Specific sub-theme
Practical Challenges	
	Participant Recruitment
	Resources: Human, technical, therapeutic, REB
	Healthcare system
	Time length and urgency
	Bureaucracy and politics
	Document and share
	Flexibility, changes, modifications
	Logistics and communication
Ethical Challenges	
	Use of experimental interventions
	Use of randomization
	Informed consent
	Vulnerable populations
	Balancing realities with rigor
	Other trial designs
	Healthcare provision
	Biosamples
	North vs South power and resource relations
Community Level Challenges	
	Ethical imperative to engage community
	Actual community engagement
	Community engagement challenges

Table 3: Codebook of Themes for Analysis

RESULTS

After examination of the 145 articles in this review, we determined that articles fell into two distinct categories: “views from afar” articles (often more theoretical), and “on the ground” articles that described challenges within more extensive descriptions from those writing within West Africa, reporting on research results or experiences of conducting research during the outbreak. The former, almost exclusively written by scholars and researchers based outside West Africa, outweighed the latter two to one, with 99 articles from “afar” versus 46 “on the ground” articles. Articles from “afar” were often bioethicist commentaries primarily focused on two areas: determining whether the use of first, experimental interventions, as well as, second, randomized controlled trials were ethical, culturally acceptable, and scientifically valid. Several also discussed

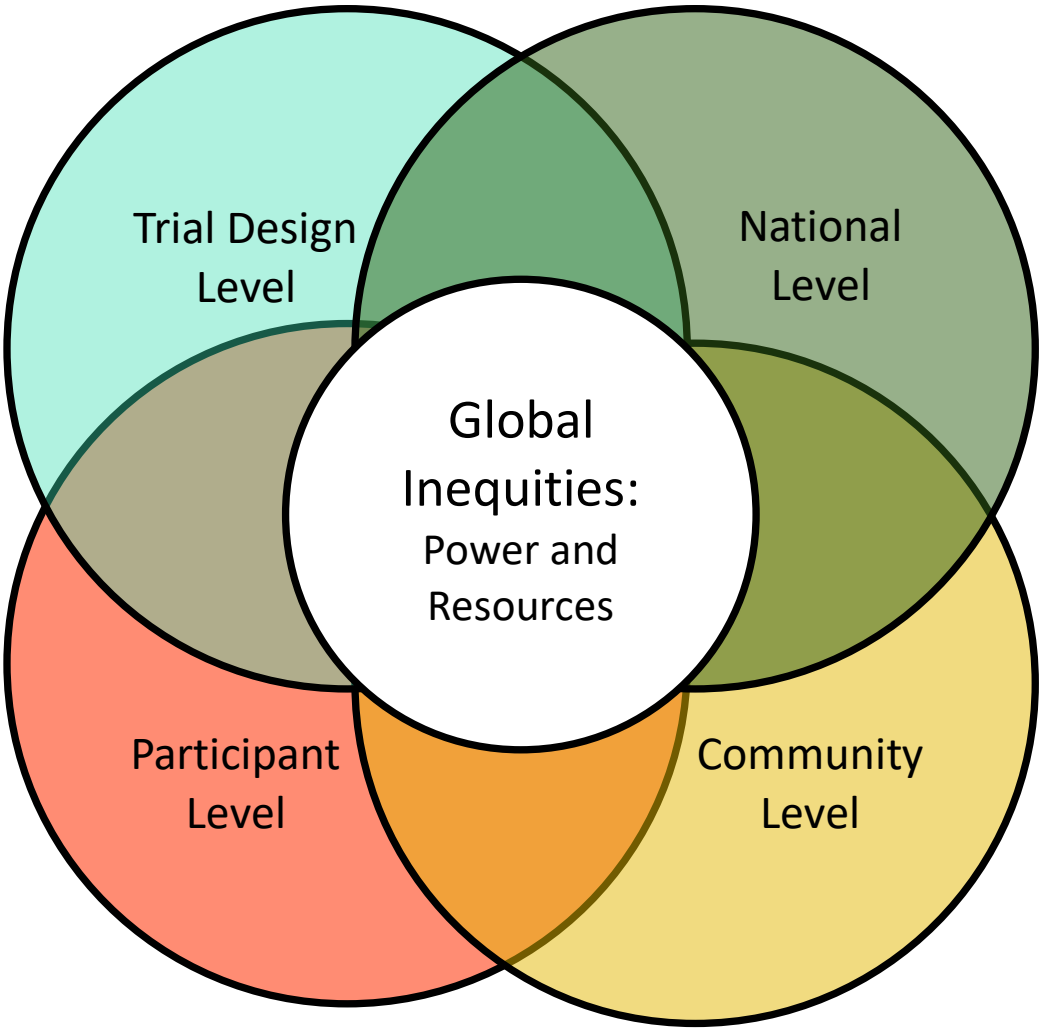
macro-ethical topics of political and economic inequities in EVD response and global health. Key challenges described in “on the ground” articles often stemmed from more practical issues (e.g. lack of resources, dwindling participant #s, community wariness, lack of time), requiring new skills or approaches. This latter category of articles also brought forward concepts such as the need for flexibility and changes throughout the research process, highlighting specific challenges of informed consent and exclusion of vulnerable populations during public health emergencies.

One of the key findings of this literature review is that it is extremely difficult to differentiate between what constitutes a practical challenge and what constitutes an ethical challenge in the 2014-16 EVD outbreak research context. Although we coded practical and ethical challenges separately (see Methods), this distinction ultimately became less significant. Across both types of articles, but especially in the on the ground articles, there is a clear implication that figuring out best or most ethical research practices requires first and foremost recognizing and figuring out how best to navigate material and social realities particular to the affected country contexts. Defining, striving towards and/or achieving ethical research in these settings hinges on creative and sometimes critical engagement with conditions and relations that originate well outside the time, place, and methods of any trial: challenges formed through trans-national resource and research inequalities, weak national and sub-national infrastructure, socio-political tensions, and context-specific patterns of (mis)trust and authority. Emphasized time and again by many authors, this inter-connection between practical and ethical challenges of research is a key finding of this review.

Discussions of ethical challenges in EVD research emerged at differing yet intersecting levels, from the global system to the participant level. These included political deliberations on the macro-level ethics of non-Africans controlling Ebola research, debates over trial designs, descriptions of overwhelmed research ethics boards, and concerns over the validity of consent obtained from desperate patients, to name a few. Woven throughout these discussions was a constant tension: between the ideals of rigorous and ethical health research, and the practical realities of conducting research in a high stress humanitarian emergency shaped by transnational differences in power and resources. Researchers and commentators consistently highlighted the importance of embracing flexible approaches to trial designs and research ethics (Waldman and Nieburg, 2015, Edwards et al., 2016, Widdowson et al., 2016, Vandebosch et al., 2016, Saxena and Gomes, 2016). Of utmost priority was understanding and adapting clinical trials for the context of West African communities and using innovative thinking to “balance scientific rigor in design and conduct, with what could be achieved in the challenging field conditions” (Edwards et al., 2016).

Therefore, in what follows, we introduce the literature review organized into five main categories: global-level challenges, national-level challenges, community-level challenges, trial design challenges, and individual-level challenges. These categories are not intended to demark sharp boundaries: it is only by deepening understanding of the singularity and connection between layers of interlocking ethical challenges related to research in public health emergencies that robust solutions for mitigating these can be developed (see **Figure 2**).

Figure 2: Interlocking Levels of Ebola Research Challenges



GLOBAL INEQUITIES: POWER AND RESOURCES

Some of the articles made apparent the centrality of global inequalities in the shaping of the West African EVD research landscape and its ethical challenges; however, many articles neglected to situate their research within this broader context. In 2014, the health and public health systems of Liberia, Guinea, and Sierra Leone were amongst the most fragile in the world, having slowly eroded over the previous 40 years (Hooker et al., 2014, Komesaroff and Kerridge, 2014).These weak health care systems with limited physical structures, equipment, and human resources were completely overwhelmed when Ebola hit (Thompson, 2016). From the outset, these conditions clearly positioned researchers and research consortiums based in well-resourced and respected research institutions at an advantage over their West African counterparts to lead EVD research in the region.

As Folayan et al. (2016) state, the ethical debates that arose during the West Africa EVD outbreak were intrinsically global in nature, in that these were “situated within the overarching

moral problem of severe transnational disadvantage." This problem of transnational disadvantage, as many articles acknowledged, connected to historical and ongoing relations of global inequality. The economically fragile landscape upon which internationally funded EVD research was grafted was one in which roads, communication, and electricity infrastructure were widely unreliable or non-existent. It was one in which investments in research could be glaring in the face of so many having no access to routine healthcare. This was a landscape where, in the face of relatively recent histories of colonialism, ongoing post-colonial resource extraction industries, and rumors of government self-serving collusion with these industries, mistrust of authorities and outsiders was widespread. These factors, at once global in origin and highly localized, were often neglected in the literature, and yet are intrinsic to figuring out "how best to" conduct research within the particular context of the West Africa Ebola epidemic.

NATIONAL RESOURCE AND COMMUNICATION CHALLENGES: LOCAL MEETS GLOBAL

All three countries shared several characteristics that amplified the challenges of conducting research during a public health emergency: weak and understaffed health systems, poor general infrastructure, under-resourced researchers, and largely research naïve populations. Limited human resources and a lack of training in numerous areas (see **Table 4)** created ethical concerns for research implementation. Most staff working in Ebola Treatment Centers (ETCs), both national and international, were trained as front line workers, not researchers (Osterholm et al., 2016, Rid and Emanuel, 2014). Some trials, such as the Favipiravir trials in Guinea, took place in rural centers, hiring and training community members with no previous experience of research (Sissoko et al., 2016). Varied capacity for research across study sites posed difficulties for the design of multi-sited clinical trials (Folayan et al., 2016b). What ultimately transpired across the region, more in answer to a practical need than an ethical imperative, was the training of dozens and sometimes hundreds of staff for specific trials, often by foreigners (Doe-Anderson et al., 2016). While capacity building of research personnel is one positive outcome of the epidemic, it is also a reminder of the vast global inequities in opportunities and resources to lead health research. Lastly, in order to be ethical, clinical research could not coopt limited healthcare personnel for research (Shuchman, 2014). This required research to be flexible in its design, for example, decreasing the number of additional blood samples taken from participants (Edwards et al., 2016).

Alongside human resources, a lack of infrastructure and technical resources in the affected countries generated its own set of ethical challenges (see **Table 4**). Poor road infrastructure slowed movement in and out of remote areas, and resulted in researchers often being uncertain when EVD had developed in individuals who presented to treatment facilities (Dodd et al., 2016, Sissoko et al., 2016). Few courses of experimental treatments were available (Dodd et al., 2016, Griffiths, 2014, Mohammadi, 2014, Dunning et al., 2016b), and it was suggested that manufacturers in the global North felt little responsibility to respond (Arie, 2014, Berry et al., 2015, Sykes and Reisman, 2015). By March 2015, as trials were beginning to launch, the number of infected individuals had declined. This generated another challenge: a shortage of potential participants and competition between teams to recruit them (Arie,

2014, Kombe et al., 2016). The sample sizes, designs, and research sites originally planned for were adjusted in response to the shrinking numbers of infected individuals (Beavogui et al., 2016, Doe-Anderson et al., 2016, Kennedy et al., 2016, Rid and Miller, 2016, Schieffelin et al., 2016, Semper et al., 2016), but ultimately no trial was sufficiently powered to be conclusive (Dodd et al., 2016, Sissoko et al., 2016, Van den Bergh et al., 2016, Walker et al., 2015, Dunning et al., 2016b). This is another place practical and ethical challenges come together as critics have suggested that this was avoidable: with the right political will and economic investment globally, experimental treatments could have been implemented earlier in the epidemic (Arie, 2014).

Table 4: Lack of Human and Technical Resources
Sources: Human resources (Schieffelin et al., 2016, Beavogui et al., 2016, Delamou et al., 2016, Allen et al., 2015, Thielman et al., 2016), and technical resources (Brown et al., 2017, Rezza, 2015, Semper et al., 2016, Tambo, 2014, Van den Bergh et al., 2016, Widdowson et al., 2016, van Griensven et al., 2016a).

Resource Deficiencies	
Human Resources/Training	**Technical Resources**
1. Lack of nationals trained as specialized lab technicians	1. Lack of consistent water, electricity, and internet
2. Lack of practical knowledge of or training in the safe management of biohazardous materials	2. Lack of mobile cold chain systems (for biosamples, plasma and vaccines)
3. Lack of training in informed consent	3. Lack of office space for data management
4. Lack of good clinical and lab practices (GCP)	4. Lack of blood collection capacity
5. Staff at ETCs trained as front-line workers, not researchers	5. Lack of refrigeration and air-conditioning units
	6. Lack of biosafety level 4 laboratories
	7. Lack of computers

Coordinating and conducting studies was impeded by the lack of reliable communication and transportation between research sites and organizations (Van Vuren et al., 2016). Data collection, storage and sharing were described as a “scientific and moral imperative” (Donovan, 2014) to ensure researchers could make informed decisions about proceeding with studies, and to determine effectiveness of treatments (Dunning et al., 2016a, Fedson et al., 2015). However, weak documentation practices were reported (Delamou et al., 2016). These were in part due to factors such as poor communication and data systems (Van Vuren et al., 2016) as well as difficulty re-locating trial participants (Folayan et al., 2015b), but commitments to sharing data were also not always honored, possibly to prioritize national self-interest (Smith and Upshur, 2015). In response, researchers have advocated for standardized documentation practices (Butler, 2014, Delaunay et al., 2016, Folayan et al., 2015a); however, whether or not this issue can be resolved without investment in

communication systems and changes to norms of communication in affected countries remains to be seen.

Research ethics boards in all three countries had limited experience in the evaluation of clinical research, let alone novel designs for implementation during a public health emergency (Schopper et al., 2017). They faced new responsibilities to evaluate the merit of protocols in a context where potential participants were making decisions while fearing for their lives (Saxena, 2014). The responsibility they shouldered for research ethics review in a context of intense humanitarian and political urgency was further exacerbated by the absence of institutional clinical care ethics committees to which they might have otherwise turned for advice, both an ethical and practical challenge (Saxena, 2014). As the research and research ethics communities grappled with these issues, winning the trust of affected villages, towns, and neighborhoods became essential.

COMMUNITY LEVEL CHALLENGES: DISTRUST IN A POSTCOLONIAL CONTEXT

This section outlines how widespread distrust impacted the conduct of specific studies and rendered community engagement both a practical and ethical imperative for research teams.

During the epidemic, panic and confusion arose due to beliefs of the causes of EVD, including those who believed national or international governments had infected West Africans with Ebola for their gain (Doe-Anderson et al., 2016). As Smith and Upshur (2015) assert, in the context of West Africa, trust has historical and systemic elements, situated in "decades of social and personal risk, vulnerability and powerlessness" that extend far beyond the immediate outbreak. Fear and violence further complicated trials, as some patients "[refused] to be transferred to an Ebola treatment center" (Sissoko et al., 2016) "or were violently freed out of isolation units by their worried families" (Schuklenk, 2014). Thompson (2016) describes these events as arising due to "profound mistrust and failure to communicate with a frightened public." Stigma was pervasive for EVD survivors. Fearing discrimination, some study participant survivors gave fake contact information on discharge from ETCs, rendering study follow-ups, important for research results but also for participants, more difficult or impossible (Delamou et al., 2016). Confusion related to the difficulty of translating words or concepts across linguistic and cultural lines were also noted as challenges at the community level (Doe-Anderson et al., 2016).

To reduce the risk of misunderstandings, disillusionment, and frustration, several researchers emphasized the importance of trust building, community dialogue, and transparency (Folayan et al., 2016). Strategies employed by research teams included anthropological research on community knowledge and acceptability of EVD therapies (Delamou et al., 2016, Widdowson et al., 2016); participant follow up; and wide dissemination of results (Klitzman, 2015, Kombe et al., 2016). Social mobilization was broadly used to increase community acceptability, awareness, and trust (Delamou et al., 2016, Doe-Anderson et al., 2016, Ebola ça suffit consortium, 2015, Kennedy et al., 2016, Sissoko et al., 2016, Widdowson et al., 2016) by communicating and collaborating with local stakeholders including Ebola survivors (Beavogui et al., 2016, Delamou et al., 2016), government officials (Doe-Anderson et al., 2016,

Widdowson et al., 2016), and community leaders. Many research groups described approaching community leaders before trials started to seek consent, garner support, and to facilitate ongoing feedback (Delamou et al., 2016, Doe-Anderson et al., 2016, Ebola ça suffit consortium, 2015, Widdowson et al., 2016). A number of researchers highlighted importance of North-South collaborations prioritizing the voices of West African researchers, as essential not only for effective research but also to prevent perpetuation of neocolonial mistrust, and thus further unethical research situations (Gulland, 2014, Konde et al., 2017, Osterholm et al., 2016, Tangwa, 2017).

Ensuring research benefits are shared equally (Rid and Emanuel, 2014) and community members have decision-making power requires work (Folayan et al., 2016b, Rid and Emanuel, 2014). Some researchers went to great effort to put in place respectful and careful community engagement strategies, but it is clear that these practices were not widespread. The next section, trial design challenges, unravels how key elements such as community engagement were given a back seat to major debates that happened across the globe.

TRIAL DESIGN CHALLENGES: IMPACT OF GLOBAL DEBATES

Discussions on the ethics of trial designs, while most common in the articles "from afar," was a recurring and key theme in the literature. Two questions dominated debates in this area: whether or not it was ethical to use untested experimental interventions, and whether or not randomization was appropriate and feasible. Out of a total of 145 reviewed articles, 43 touched on experimental interventions, 52 discussed the ethical challenges of randomization, and many (80) did both.

The Use of Experimental Interventions

The WHO's 2014 report stated that there was an "ethical imperative to offer the available experimental interventions" to patients with EVD (WHO, 2014a), which highlighted ethical issues, particularly around the notion of false hopes (Goodman, 2014, Antierens, 2015, Doe-Anderson et al., 2016, Klitzman, 2015). Authors emphasized several ethical concerns, including the diversion of resources from important supportive measures and infrastructure, and the relaxing of protective measures due to a belief that one was "protected" (Donovan, 2014, Goodman, 2014, Millum, 2015, Shah et al., 2015, Widdowson et al., 2016). As such, many contended there was also a moral imperative to investigate the novel interventions used during the outbreak (Donovan, 2014, Griffiths, 2014, Upshur, 2014, Brown et al., 2017). While acknowledging the inherent risks of going straight to human studies, forgoing animal trials and double blind randomized control trial (RCT) models, authors argued that such risks were mitigated by infrastructure benefits gained by a community participating in a trial (Doe-Anderson et al., 2016) and using a randomized control trial design as an ethical way to address issues of priority setting when resources are in short supply (Goodman, 2014). To some, these nods to mitigation left untouched the responsibility to address ongoing patterns of colonialism: as Tangwa (2017) wrote, "African scientists and experts working with Western funding…are at the service of Western global dominance and hegemony." As such, central to the debate of experimental interventions were longer term issues including the possible erosion of trust should interventions not be successful (Arie, 2014, Goodman, 2014, Hooker et al., 2014). Even when authors asserted that conducting trials with unregistered

interventions was ethical, they still highlighted ethical issues including that developing strong evidence may not be possible given the limitations of trial design (Lanini et al., 2015, Folayan et al., 2015b, Griffiths, 2014, Klitzman, 2015).

Although several authors suggested that the principle of beneficence justifies compassionate use of experimental treatments outside of clinical trials (Goodman, 2014, Shah et al., 2015, Singh, 2015), others stressed that when the risks of the intervention are actually unknown (Upshur, 2014), treatment should only occur in the context of a study (Donovan, 2014, Landry et al., 2015, Rid and Miller, 2016). Compassionate use had the possibility of undermining trial feasibility, depleting scarce experimental resources needed to collect data (Rid and Miller, 2016).

The Use of Randomization

The scramble to develop an effective EVD treatment exposed methodological rifts and ethical uncertainty, bringing forward questions about randomization. In the international planning of clinical trials, two camps emerged: proponents of RCTs maintaining that scientific rigor should prevail, and opponents of randomization insisting that unproven but potentially effective treatments should be made available to all patients. For the first camp, RCTs were the quickest and most efficient way to establish safety and efficacy for the benefit of future patients. Opponents of randomization emphasized that the use of randomization was unacceptable to local communities (Beavogui et al., 2016). Care providers saw a humanitarian imperative to treat current patients with anything that might offer benefit apart from supportive care (De Crop et al., 2016, Upshur and Fuller, 2016). For these reasons, arguments were made for the monitored emergency use of unregistered and experimental interventions (MEURI) (Kombe et al., 2016, Calain, 2016), single arm studies using historical controls (Fleming and Ellenberg, 2016, Sissoko et al., 2016), and alternative trial designs (Caplan et al., 2015). Multi-stage approaches and adaptive designs such as Bayesian methods were presented as better aligned with the urgency of the crisis (Adebamowo et al., 2014, Cooper et al., 2015, Lanini et al., 2015), “rather than doggedly insisting on gold standards that were developed for different settings and purposes” (Adebamowo et al., 2014). Randomization also raised the question of comparators, whether they be placebo, supportive care, or another unproven treatment. Placebo-controlled trials were quickly deemed ethically unacceptable to the communities (De Crop et al., 2016, Ebola ça suffit consortium, 2015, Edwards et al., 2016, van Griensven et al., 2016b, Rid and Miller, 2016): “with EVD considered a death sentence, randomization would have been perceived of as an unacceptable ‘lottery system’” (De Crop et al., 2016). Comparing treatment to supportive care was also questionable because supportive care varied and remained undefined. Therefore, some thought it “ethically preferable” to compare unproven interventions against each other (Caplan et al., 2015, Waldman and Nieburg, 2015).

Randomization also highlighted ethical issues of North-South justice. Authors pointed out that Western medical workers offered unproven treatments were not randomized (Adebamowo et al., 2014), and that “few of us would consent to be randomized when facing utterly lethal circumstances” (Caplan et al., 2015). However, randomization did become more locally acceptable as time went on (Beavogui et al., 2016). As the epidemic was waning—and because there was still no viable cure— the tide turned towards randomization: RCTs were

agreed upon as “the most expedient and definitive means of establishing the absence of a harmful effect and … translate directly into lives saved ” (Davey et al., 2016). As noted in a book published outside the scope of this review, protocols for RCTs were quickly drafted towards the end of the epidemic; but, by then, too few cases meant insufficient participants for clinical trials (Rid and Antierens, 2017). It becomes clear how differing levels of ethical challenges intersect, as national, community, and trial design challenges build on each other to create insurmountable complexities, halting Ebola research.

In response to these two major debates occurring globally, a smaller group criticized these debates, arguing that by focusing solely on a few ethical elements of clinical trials, scant attention was given to other topics these critics regarded as more urgent to address in the context of the outbreak (Dawson, 2015). For example, Gericke (2015) argued that the debates on the use of experimental interventions “not only sidetracked relief efforts but led medical ethicists from all over the world sheepishly down the wrong path.” Instead, he argued that international organizations and governments needed to use a wider public health perspective, focusing on infection control methods such as case identification and containment, supportive care, and contact tracing, alongside health system preparedness (Gericke, 2015). Similarly, speaking about the vaccine debates, Schuklenk (2014) asserted that debates “were not the most pressing ethical issues because these vaccine candidates, even if they turned out to work effectively, would not make a dent in the current pandemic.” Others highlighted that interventions and design ethics should have been addressed before the outbreak (Hayden, 2014). Lastly, many stressed that flexibility in trial design and implementation was essential (Kieny and Rägo, 2016, Thielman et al., 2016, Dodd et al., 2016), without compromising ethical integrity (Kombe et al., 2016). Running a few Phase 1 vaccine trials in parallel in case there were delays at sites to enroll enough subjects (Kieny and Rägo, 2016) was one example. In the face of complex ethical and methodological debates, a small minority continued to emphasize that greater attention to health system strengthening and infection control at the global and national level was needed. The interconnection between ethical challenges at numerous levels continues within participant level challenges including informed consent.

PARTICIPANT LEVEL CHALLENGES

As Caplan (2015) highlights, “…the dying cannot be asked to bear the entire moral weight of deciding on whether or not to try new remedies and interventions.” Two final areas of discussion focused on informed consent, and inclusion of specific vulnerable populations. In accordance with its roots in Western modern bioethics, informed consent and evaluation of participant vulnerability is primarily about the individual research participant; however, as is highlighted in this section, community context and cultural sensitivities also influence these processes.

Informed Consent

Informed consent ensures that participants engage in a clear discussion of benefits and risks to make an informed decision about study participation. However, during the outbreak, Ebola patients were often extremely sick, and it was not clear whether they had the psychological or physical ability to assess immediate or lifelong potential side effects of the study agent (van

Griensven et al., 2016a). Furthermore, comprehension of informed consent information was questioned in some studies due to low literacy rates (Doe-Anderson et al., 2016, Schieffelin et al., 2016, Kennedy et al., 2016, Widdowson et al., 2016). Concerns of providing culturally inappropriate information were also raised (Goodman, 2014). Other consent issues included coercion, where patients may have been provided with overly optimistic information on the risks and potential benefits of a vaccine trial (Widdowson et al., 2016). Many mentioned the potential for therapeutic misconception—with study participants confusing research as therapy—in this context of low literacy and high optimism for experimental interventions (Kombe et al., 2016, Folayan et al., 2015a, Folayan et al., 2016b, Mohammadi, 2014, Saxena, 2014, Schopper et al., 2017). This brings forward the importance of addressing communication challenges at the community level in order to ensure informed consent at the participant level. In response to these challenges, some studies provided information to a group of participants using flip charts, before taking individuals to private settings to obtain consent (Doe-Anderson et al., 2016, Kennedy et al., 2016). Public health emergencies require flexible applications of ethical principles (Saxena and Gomes, 2016): in response, some studies used short written documents (Konde et al., 2017) or verbal consent after patients were presented with the study's purpose and procedures (Sissoko et al., 2016, Schieffelin et al., 2016). For the most part, clinical research articles provided some description of consent processes but ethical challenges of informed consent were rarely reported.

Vulnerable Populations

Ethical debates arose around the exclusion of specific populations from clinical trials. While there were reasons for excluding pregnant women (Kennedy et al., 2016, Schopper et al., 2017), women at risk for pregnancy (Dunning et al., 2016a, Dunning et al., 2016b, Kombe et al., 2016), or lactating mothers (Dunning et al., 2016a, Dunning et al., 2016b, Kennedy et al., 2016) as it was uncertain whether the experimental agents were teratogenic (Kombe et al., 2016), there were calls that this exclusion breeched principles of equity (Dunning et al., 2016b, Edwards et al., 2016, Kombe et al., 2016, Konde et al., 2017, Schopper et al., 2017, Sissoko et al., 2016, Van den Bergh et al., 2016, van Griensven et al., 2016a, Walker et al., 2015, Gerlier, 2015, Richardson et al., 2017). In order to address issues of justice in the face of a disease with very high mortality rates, authors argued data on pregnant women is required (Kombe et al., 2016). Ebola infection is associated with high fetal mortality even if the woman survives (Davey et al., 2016), and if the woman dies, then the fetus will also die. Therefore, excluding pregnant women left them without access to the potential benefits of novel agents (Kombe et al., 2016, Dunning et al., 2016a). Vulnerability and consent was also an issue with children: one option was the use of substitute decision makers, but in many situations this did not provide a solution as either there was no such person or that person was also a child (Folayan et al., 2016).

In response to the above debates, authors including Dawson (2015) as well as Gericke (2015) asserted that ethical analysis was overly attentive to the level of the individual participant. Dawson highlighted that six of the seven criteria produced by the WHO for experimental intervention use were focused at the person level (Dawson, 2015). He argued for ethical criteria to have more engagement at the community and public health infrastructure level, which would bring the intersection of participant level challenges into conversation with broader contextual elements (Dawson, 2015).

CONCLUSION

KEY LESSONS

1) Ethical challenges must be understood as embedded within global inequities and weak health systems.
2) Unanticipated and unique circumstances should be anticipated in epidemic research in low- and middle-income countries. Research teams must be prepared to troubleshoot and develop flexible study designs and ethical procedures.
3) It is only by deepening understanding of how factors at the participant, community, study design, national, and global levels intersect to produce ethical challenges for clinical research in public health emergencies that robust solutions for mitigating these can be developed.

This narrative review's objective was to identify and examine ethical challenges in the scholarly literature pertaining to the conduct of research during the EVD outbreak in West Africa. This review revealed that the majority of the articles were written by bioethicists and researchers not on the ground in West Africa, and the majority of ethical discussions centered around issues of trial design, including the use of experimental interventions and randomization. Many of these articles did not describe weak health systems or global inequities between African and non-African researchers as key ethical challenges while conducting research during the 2014-16 Ebola epidemic. In contrast, for a number of researchers leading trials on the ground during the epidemic, global inequalities, the need for greater equity in global health research, complexities of socio-political relations, and the very real impact on research of working in limited resource settings were framed as being of equal if not more important to defining "best practices" for research in these settings. Therefore, this review revealed that no challenge of research conducted during a public health emergency is purely ethical or practical. Principles, prohibitions, guidelines, and goals of ethical research can be discussed and defined outside the field, but ultimately many ethical challenges of research will only become apparent in the process of enacting protocols within specific socially, historically, logistically complex settings. This reality implies the importance of all involved in the conduct of research during public health emergencies entering the field primed for and ideally skilled in navigating unanticipated challenges.

In case another public health emergency occurred tomorrow, what lessons could be drawn from the Ebola outbreak regarding the ethical conduct of research?

First, as mentioned above, ethical issues must be understood as embedded within patterns of global inequity that directly impact each level of public health emergency research. Past economic dependencies continue to this day, perpetuating current global inequities that impact all stages of research in public health emergencies.

Second, it is clear that ethical challenges at the global, national, community, trial design, and participant levels are intimately connected to each other, and cannot be fully separated. Therefore, a study with a soundly constructed approach to informed consent and data

sharing during a public health emergency will not be successful without an equally robust plan for community engagement. This narrative review demonstrated the extent to which challenges overlap and build on each other, complicating, slowing down or, in some cases, bringing public health research during emergencies to a complete stop.

Lastly, future epidemic research will benefit from an ability to be flexible in identifying means to adapt ethical procedures in response to contextual features while upholding principles of research ethics and implementing creative yet rigorous study designs. Our review highlights ethical implications of the lack of technical and human resources for research (see **Table 4**), information which can help researchers prepare moving forward. Robust mechanisms to facilitate communication and collaboration across research ethics boards, national and international organizations, and study sites are needed. Time is of the essence during an outbreak. It is clear that a lack of participants eligible to participate in trials in the later stages of the outbreak reinforce the need to initiate studies promptly. Social mobilization was a highly effective community engagement strategy that kept partners and stakeholders involved with the research process. Further empirical research will help guide researchers as they navigate producing flexible yet rigorous research protocols that are sufficiently embedded in local cultural contexts, deepening understanding of specific ethical challenges such as obtaining informed consent during dire circumstances.

This paper's focus on published ethical discussions during the Ebola epidemic reveals important issues, but also the inequality of voices and blinds spots in normative definitions of what counts as an ethical challenge worth discussing when it comes to public health emergency research in low-income countries. As Komesaroff and Kerridge (2014) state, "the Ebola epidemic, perhaps more than any other, reminds us that ethical questions depend on the positions and social roles of the persons asking the questions." Moving forward, more attention towards ethical issues around solidarity and trust (Dawson, 2015, Smith and Upshur, 2015), as well as respect for local knowledges (Tangwa, 2017) is imperative to enacting research that works against, rather than reinforces, legacies of colonial disempowerment and ongoing entrenched inequities.

LIMITATIONS

It is important to highlight that this narrative review offers only a three-year period (2014-2017) of published articles, and that many have published since 2017 on this topic. As such, this review provides a snapshot of what was being published during and immediately after the EVD outbreak.

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