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CRITICAL PERSPECTIVES

Ebola Virus in West Africa: Waiting for the Owl of Minerva

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Abstract The evolving Ebola epidemic in West Africa is unprecedented in its size and scope, requiring the rapid mobilization of resources. It is too early to determine all of the ethical challenges associated with the outbreak, but these should be monitored closely. Two issues that can be discussed are (1) the decision to implement and evaluate unregistered agents to determine therapeutic or prophylactic safety and efficacy and (2) the justification behind this decision. In this paper, I argue that it is not compassionate use that justifies this decision and suggest three lines of reasoning to support the decision.

Keywords Ebola virus disease · West Africa · Epidemic · Compassion

As I write this, the Ebola virus (EV) outbreak in West Africa is in its sixth month since first being reported in Guinea in March 2014. Previous EV outbreaks have typically been associated with high mortality but relatively brief duration. The current outbreak now accounts for more cases and deaths than all previous Ebola outbreaks combined. Current models forecast increasing case loads and high likelihood of spread beyond the currently afflicted nations of Liberia, Sierra Leone, Guinea, and Nigeria. There is a very real possibility that rather than a pathogen associated with sporadic and brief but deadly forays into human populations, EV will become endemic across a large populous geographic area. The scale and scope of this outbreak is unprecedented.

That this outbreak has found the world unprepared to respond is not surprising to many who have been closely watching trends in global health. Ebola took root in a context with barely functional health systems in nations emerging and building democratic structures after years of civil strife. Those who claim that tried-and-true public health measures would have prevented this outbreak must be cognizant of the fact that the infrastructure required to implement such measures did not exist in the first place. The response to the outbreak was critically dependent from the outset on the work of nongovernmental organizations (NGOs), Médecins Sans Frontières (MSF) in particular. As exemplary as MSF's work has been, it is not a public health agency with the responsibility of health protection and disease control in populations. Budget cuts to the World Health Organization (WHO)—particularly in outbreak response—explain, in part, the anemic reaction from the international community.

I think it is premature to write the story of the ethics of this outbreak as there is still much to unfold. Some

In response to the recent Ebola virus outbreak, the World Health Organization (WHO) in August convened a panel of experts "to consider and assess the ethical implications for clinical decision-making of the potential use of unregistered interventions" (see the WHO statement of August 12, 2014, at http://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/). Ross E. G. Upshur was a member of this panel.

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elements bear strong resemblance to other infectious disease outbreaks, for which much has been written: Do health care providers have an unlimited duty to care? What is the legitimate scope and application of restrictive measures to control an outbreak? How are scarce resources allocated in an outbreak? How do we evaluate global response and governance? These and many other questions have been examined in the context of pandemic influenza and drug-resistant tuberculosis. The analysis and recommendations found in these documents are likely applicable. Minimally they provide a point of departure for discussions on many of the ethical issues associated with this EV outbreak. There are predictable ethical issues in infectious disease outbreak response that should be planned for and integrated into outbreak response plans. Alas, this seems not to have happened, and the reasons for this ought to be explored once again when and if this outbreak is controlled.

International attention and concern about the EV outbreak intensified in early August 2014. Two American medical missionaries received an experimental monoclonal antibody. The means by which the NGO Samaritan's Purse was able to access the experimental agent remains obscure. Shortly after, a Spanish missionary and two Liberian physicians also received the agent. In each case the language of compassionate use was invoked as justification. As a result no ethical criteria, protocol, or reasons of any kind were used to determine who would get the very small supply of the untested agent. Ethics seemed to have vanished. Furthermore, there has been no mention of a standardized data set to evaluate the impact of the untested agent. Hence the goals of science were similarly undermined.

The lack of transparency for access and the rapid deployment of "novel therapies" triggered an immediate outcry in the media. The World Health Organization promptly announced that it would convene a panel of ethicists to address the issues associated with the use of investigational agents. The panel was tasked with answering five questions, but the questions essentially boiled down to whether it was permissible to use unregistered interventions with no human data to support safety or efficacy.

The panel came to affirmative answers on this question and recommended further work be done on the criteria and conditions of use in the field. The panel has been criticized for the haste in which it was brought together and the lack of representativeness of the panel. These shortcomings have been acknowledged; however, there has been little disagreement with the substantive decision. The subsequent larger panel is well represented by ethicists and social scientists from West Africa and the report of their deliberations will be released sometime in late September 2014.

This outbreak has left the global community struggling for appropriate language to frame thinking around addressing the ethical issues. The language of compassionate use is a good example. It represents the need to find a conceptual structure to explain and justify choices. In the context of using unregistered interventions in the current Ebola outbreak, the language of compassionate use seemed appropriate. I think this may be misleading and should be resisted going forward. I think this is incorrect for several reasons:

1. Compassionate use has a specific technical meaning in many regulatory frameworks, such as those of the U.S. Food and Drug Administration, the European Union, and in Canada. These regulatory frameworks all differ in subtle ways, so compassionate use does not denote a concept upon which there is universal agreement.
2. Compassionate use typically refers to releasing agents that are being evaluated in a clinical trial to persons with severe disease, who are out of therapeutic options, and do not meet inclusion criteria to the trial. There exists, then, some data on safety in humans. It is an example of the rule of rescue.
3. As a result, compassionate use is not primarily oriented to evaluating effectiveness.
4. With many of the agents under consideration, there is no data on human use. It is misleading, therefore, to label what is in essence a first in human experimentation compassionate. Any such experiment must be structured to learn as much as possible about the effects on the human subject. There is no reason to presume benefit, and harms are very much a possibility.
5. Many of the agents will be used in the context of pre- and post-exposure prophylaxis, and it most assuredly stretches language too far to speak of compassionate pre-exposure prophylaxis!

It is also important to have a very clear justification for the precedent that is being set in this case. There are many diseases with relentless natural histories and few effective therapeutic modalities for which claims to rapid access of therapies shown to be promising in

animal models could, by analogy, be demanded on compassionate grounds. There are at least three prima facie considerations to support this precedent, but this issue should be rigorously examined.

First, it is not really compassion that ultimately justifies the decision to move forward with assessing these agents. Historically, research into therapy and prevention for EV has not been robust. While safety of various modalities can be assessed in the interim between EV outbreaks, efficacy can only be determined in the context of an Ebola outbreak. Calls have repeatedly been made to have protocols ready to assess therapeutic modalities in Ebola outbreaks, but this has not occurred. Addressing this historical injustice is a relevant consideration.

Second, the public health significance of EV is germane. In the discourse on emerging and re-emerging infectious diseases, EV and other hemorrhagic viruses are singled out for particular public health concern. It is a Level 4 pathogen, requiring impeccable infection control to manage clinically. Patients with EV disease rapidly become completely dependent on health care providers as the illness takes hold. Contact tracing must be meticulous and complete. It must be remembered how taxing and difficult control of SARS was in well-resourced health systems.

Finally, I think there is a humanitarian imperative to move forward on evaluating these agents. Health care providers responding to the outbreak are weary of watching patients and colleagues die. A high proportion of health care workers has become ill and died. This is highly dispiriting and hampers efforts to recruit needed human resources. Even if only of symbolic value, evaluating these agents indicates a willingness to explore all avenues that may promise relief.

My own personal view is that there is a very low probability that these agents will make a difference in the short-term. As the case numbers rise, though, it becomes clearer that an effective vaccine will likely be required to halt this outbreak. So the sooner the process to evaluate the candidate vaccines gets started the faster we will know whether they are effective. In the meantime we are left with nothing.

I think it is the sincere hope of everyone not to see an outbreak of this magnitude again. It rapidly overwhelmed local resources and has clearly exceeded the capacity of the global community to mount an effective response. There are many more ethical lessons to be learned in this outbreak, but just how harsh these lessons will be remains to be determined. “Only when the dusk starts to fall does the owl of Minerva spread its wings and fly.”