Ethical considerations of experimental interventions in the Ebola outbreak

Annette Rid, Ezekiel J Emanuel

Published **Online**
August 21, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61315-5

Department of Social Science, Health & Medicine, King's College London, London, UK (A Rid MD)**; and Department of Medical Ethics & Health Policy, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA** (Prof E J Emanuel MD)

Correspondence to:
Dr Annette Rid, Department of Social Science, Health & Medicine, King's College London, London WC2R 2LS, UK
annette.rid@kcl.ac.uk

Background

The outbreak of Ebola virus raging in west Africa is special in two respects. First, with more than 2100 infections and 1100 deaths,[1] it has already become the most severe and largest documented Ebola outbreak. It is also occurring in some of the world's least developed countries,[2] and is therefore extremely complex to address. Second, experimental interventions that are still in the preclinical trial phase—and hence untested in human beings—were first given to health-care workers from high-income countries, focusing extensive attention and controversy on investigational treatments and vaccines for Ebola.[3–5]

The rapidly evolving situation raises three fundamental questions: how much emphasis should the international community place on experimental interventions in response to the Ebola epidemic; what are the ethical considerations if experimental treatments or vaccines are deployed; and if any interventions prove safe and effective, how can they be made more widely available?

Prioritising the strengthening of health systems

The international community has both humanitarian duties of assistance and duties of global justice to address the Ebola epidemic and its causes.[6] Although the prospect of specific Ebola treatments or vaccines is enticing, the current unproven interventions should have a marginal role in the global response. Fundamentally, this Ebola outbreak—and future ones—need focus on strengthening of health systems and basic infrastructure, rather than experimental treatments and vaccines.

The major challenge of Ebola is containment—implementation of isolation of suspected Ebola cases, infection control and universal precautions, contact tracing and monitoring, surveillance, and raised awareness in local communities and internationally.[5,7] Containment measures are not high-tech, but they have a proven track record of controlling infectious outbreaks.[5] Importantly, they require the basics of a functioning and trusted health system. For example, identification and isolation of suspected Ebola cases is impossible if basic health care is not offered to, and accessed by, all members of society. The most effective way to curb the Ebola epidemic is to adopt containment measures with a view to strengthen health systems and other infrastructure—eg, training and hiring of health professionals, deployment of basic medical supplies such as gloves, community engagement, investment in clinics and hospitals, and ensuring prompt and safe burial.

Improved health systems and infrastructure also have important collateral health benefits.[8,9] They not only help to prevent future outbreaks of Ebola and other diseases, but also improve the care for many other diseases. Although Ebola's rapid spread and high rate of mortality capture our attention, the disease needs to be put into perspective. Cumulatively in the past four decades, Ebola has claimed less than 3000 lives.[1,10] By contrast, the death toll in sub-Saharan Africa was 547 322 from diarrhoeal diseases and 222 767 from pneumococcal pneumonia in 2010 alone;[11] many of these deaths could have been prevented through access to basic health care, including cheap vaccines, and improved sanitation. Thus, strengthening of health systems and infrastructure will have positive externalities for health promotion after this epidemic subsides.

Furthermore, experimental Ebola treatments or vaccines are unlikely to have a decisive effect. The first issue is supply. Because the existing interventions are still in the earliest phases of development, supply is extremely restricted. For example, the "handful of doses"[5] of Zmapp (Mapp Biopharmaceutical, San Diego, CA, USA)—a cocktail of antibodies aimed to treat Ebola—has already been exhausted.[12] Further production is expected to take months to produce a substantial amount.[13]

The second issue is that, irrespective of hope, we need to be realistic. The distance between preclinical promise and clinical use is vast and littered with failed compounds. Only 10% of new molecular entities succeed from the point of preclinical candidate selection to commercial launch.[14] Although promising in non-human primates, there is no reason to believe that the experimental Ebola interventions will be more successful. In other words, it is more likely than not that the interventions will not improve or save patients, and might even weaken them as they battle a life-threatening disease.

Ethical use of experimental interventions for Ebola

When thousands of people are confronted with a life-threatening disease, and no specific therapies or preventive measures exist, it can be ethically acceptable to assume greater risks and offer patients unproven interventions.[15] For example, patients with advanced cancer who do not respond to established therapies are routinely invited to participate in early-phase trials. Patients in the early HIV/AIDS epidemic successfully campaigned for fast-track trials because they faced imminent death. Moreover, countries affected by Ebola want access to the investigational drugs. For instance, the Liberian Government requested Zmapp for some health workers.[16] The Nigerian National Ethics Committee clarified guidance for use of non-validated treatments, partly "for the rapid

resolution of the current emergency".[17] Additionally, a WHO panel—regrettably without representation from the affected countries—stated in an announcement that it is ethical to offer unproven interventions "in the particular circumstances of this outbreak, and provided certain conditions are met".[18]

Panel:* Ethical principles for trials of experimental treatments or vaccines for Ebola (selected implications)

Collaborative partnership
- Involve local communities and stakeholders in planning, conducting, and overseeing of trials
- Ensure fair benefits from the conduct or results of trials (eg, contribute to strengthening health systems, help to ensure availability of any proven treatments or vaccines)

Social value
- Ensure data are valid and robust (eg, to inform decisions about the need for additional research, marketing approval or withdrawal)
- Disseminate knowledge

Scientific validity
- Plan trials in view of all relevant data (eg, preclinical, compassionate use)
- Ensure that trials realise scientific objectives (eg, randomly assign participants to experimental interventions with supportive care or supportive care with placebo control)
- Ensure that trials are feasible (eg, adequate infrastructure to monitor participants and collect data)

Fair selection of study population
- Be transparent about selection criteria and ensure criteria are consistently applied
- Select study population to ensure scientific validity (eg, exclude patients with severe Ebola to reduce confounding of side-effects)
- Avoid prioritisation of well-connected and well-off individuals

Favourable risk–benefit ratio
- Evaluate the risks and potential benefits to participants based on all relevant data
- Minimise risks to participants (eg, provide supportive treatment, monitor for side-effects, establish data and safety monitoring boards)

Independent review
- Ensure public accountability through ethical review or oversight
- Ensure public accountability through transparency and, as appropriate, reviews by other international and non-governmental bodies

Informed consent
- Disclose information and obtain voluntary and informed consent in culturally and linguistically appropriate formats
- Implement supplementary community and familial consent procedures if appropriate
- Ensure freedom to refuse or withdraw

Respect for recruited participants and study communities
- Monitor for and treat medical disorders (eg, side-effects and research-related injuries arising from the trial)
- Protect the confidentiality of recruited and enrolled participants
- Provide enrolled participants with relevant information in the course of the research study
- Provide compensation for research injuries
- Inform participants and the study community of the results of the research

*Adapted from Emanuel and colleagues.[23]

If experimental Ebola interventions are deployed in this outbreak, their use needs to comply with important ethical principles. The first principle is that the interventions should only be used in clinical trials, so that researchers can learn whether they work or not. At present, all investigational agents are in the earliest phases of development, hence their risks and potential benefits are largely unknown. Expansion of their use without additional testing would be irresponsible. Moreover, it would be wasteful to use the small amount of experimental interventions with no collection of systematic data about safety and efficacy.

Consequently, these interventions should not be distributed for compassionate use outside clinical trials—which might also undermine the feasibility of trials. If compassionate use nonetheless occurs, transparency is key and data about patient outcomes should be collected and shared in full. Of concern, it appears that the existing stock of Zmapp has been used only for compassionate use, and details about patient outcomes are not (yet) readily available. To ensure that data from compassionate use and clinical trials are rapidly integrated, a neutral body should oversee the use of experimental interventions during this epidemic.

When investigational drugs are used in this Ebola emergency, research ethics must be upheld to avoid exploitation of affected individuals and communities;[19–22] the eight ethical principles for research must be met (panel).[23] Although compliance with all principles is necessary, three need special attention. First, we agree with bioethicist Steven Joffe (personal communication) that, to enhance social value and scientific validity, clinical trials should be randomised with participants receiving either experimental interventions with supportive care or supportive care and placebo. Randomisation and placebo controls are the best means to control for confounding factors and determine whether interventions work or whether patients have recovered by chance.

Second, because of the scarcity of investigational agents, fair selection of participants is essential and must be ensured. Especially in a dire emergency such as this one, well-off and well-connected patients should not be further privileged.

Some have suggested prioritisation of health-care workers for receipt of the experimental treatments or vaccines.[3,24] Indeed, the limited supply of Zmapp has been given almost exclusively to health-care workers.[16,24] Because health professionals put themselves at risk to care for patients and could help more patients once recovered, the principles of reciprocity and helping the largest number of people could justify their prioritisation.[25] However, health-care workers are often well-off and have special ties to the medical establishment. Their priority might therefore be viewed as further privileging of the already well-off, especially by contrast with those who provide care without being trained as health professionals.

 Published online August 21, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61315-5

Third, because reasonable people will probably disagree about who should have access to trials and other ethical questions, collaborative partnership with local communities and stakeholders is essential also in times of an epidemic. Local communities should be involved in trial planning, and trials should be implemented in a transparent and accountable way. Moreover, although standard procedures for ethics review might be inappropriate, some form of ethical oversight is necessary.[19,23] Oversight and community involvement are also vital to address distrust of clinical research from high-income countries, which has resulted from past abuses and misconduct,[26] and only augments the general distrust of health-care systems.

Additionally, the principle of collaborative partnership requires that communities receive fair benefits from the research. Contribution to strengthening of local health systems and infrastructure is a benefit that trial funders should consider first, because it reinforces the general response to the epidemic and its causes. Moreover, because where the next Ebola outbreak will strike is not known, strengthening of health systems and infrastructure could be the best way to ensure that communities obtain fair benefits from research in this epidemic.

Planning for future Ebola outbreaks

Even if clinical trials happen during this Ebola outbreak, additional research will probably be needed in a future epidemic. To better anticipate the surrounding ethical dilemmas, and to build consensus about potential solutions with representatives from affected regions, future trials should be carefully planned and reviewed in advance.[19] One model for this is offered by Médecins Sans Frontières, an international network providing emergency medical aid. The research ethics committee of Médecins Sans Frontières has a practice of pre-approving some generic research protocols.[27–30]

Furthermore, plans should be made to make any proven Ebola interventions available in affected regions, as part of providing fair benefits from research and promoting global justice regarding access to essential medicines.[6,23] Ebola vaccines should be fairly cheap to produce and implement, and could be covered by existing health partnerships such as the GAVI Alliance. By contrast, it is difficult to see how complex treatments like Zmapp—which is expensive to produce and requires intravenous administration—can be implemented in resource-poor settings in the near future. Together with the low odds of success for all experimental Ebola interventions, this issue underscores the importance of providing fair benefits to communities who participate in research in this outbreak.

Conclusions

The global response to the current Ebola outbreak has initially been slow and inadequate. Now that the response is picking up, the international community needs more focus on strengthening of health systems and infrastructure and less on experimental treatments. Adoption of containment measures with a view to strengthen health systems and infrastructure is the most effective way to curb this epidemic and prevent future ones; it has positive externalities for health promotion and offers fair benefits to communities who engage in research in this outbreak. Experimental Ebola treatments or vaccines should only be deployed in clinical trials. If trials are done, they must meet the eight ethical principles for research. The international community needs to show that it can meet the challenge of this public health emergency, while learning the lessons for future Ebola and other epidemics.

Contributors

AR conceived the idea for the paper and wrote the first draft. EJE revised the paper critically for important intellectual content. Both authors approved of the final version and agree to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Peter Smith, Sridhar Venkatapuram, and Verina Wild for comments on an earlier version of this Viewpoint, and Katherine Chockley and Thomas Huelskoetter for research assistance. AR received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007–2013) under REA grant agreement number 301816. This work was submitted for publication on Aug 17, 2014.

References

1 WHO. Ebola virus disease, West Africa—update 15 August 2014. http://www.afro.who.int/en/clusters-a-programmes/dpc/epidemic-a-pandemic-alert-and-response/outbreak-news/4256-ebola-virus-disease-west-africa-15-august-2014.html (accessed Aug 15, 2014).

2 UNDP. Human Development Report 2014: sustaining human progress: reducing vulnerabilities and building resilience. http://hdr.undp.org/sites/default/files/hdr14-report-en-1.pdf (accessed Aug 15, 2014).

3 Arie S. Ebola: an opportunity for a clinical trial? *BMJ* 2014; **349:** g4997.

4 Gostin LO, Lucey D, Phelan A. The Ebola epidemic: a global health emergency. *JAMA* 2014; published online Aug 11. DOI:10.1001/jama.2014.11176.

5 Fauci AS. Ebola—underscoring the global disparities in health care resources. *N Engl J Med* 2014; published online Aug 13. DOI:10.1056/NEJMp1409494.

6 Millum J, Emanuel EJ, eds. Global justice and bioethics. New York, NY: Oxford University Press, 2012.

7 WHO. WHO statement on the meeting of the international health regulations emergency committee regarding the 2014 Ebola outbreak in West Africa, 8 Aug 2014. http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/ (accessed Aug 15, 2014).

8 WHO. Everybody's business: strengthening health systems to improve health outcomes. WHO's framework for action. 2007. http://www.who.int/healthsystems/strategy/everybodys_business.pdf (accessed Aug 15, 2014).

9 WHO. A conceptual framework for action on the social determinants of health. 2010. http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf?ua=1&ua=1 (accessed Aug 15, 2014).

10 WHO. Ebola virus disease, fact sheet No 103, updated April 2014. http://www.who.int/mediacentre/factsheets/fs103/en/ (accessed Aug 15, 2014).

11 Institute for Health Metrics and Evaluations. Global burden of disease database. http://www.healthdata.org/search-gbd-data (accessed Aug 15, 2014).

12 Mapp Biopharmaceutical. Focus: August 12, 2014 at 8:30 AM. http://www.mappbio.com (accessed Aug 15, 2014).

13 Bernstein L, Dennis B. Can we give that experimental Ebola drug to West African victims? Washington, DC: *The Washington Post*, Aug 5, 2014. http://www.washingtonpost.com/news/to-your-health/wp/2014/08/05/can-we-give-that-experimental-ebola-drug-to-west-african-victims/ (accessed Aug 15, 2014).

14 Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov* 2010; **9:** 203–14.

15 Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research. *Kennedy Inst Ethics J* 2011; **21:** 141–79.

16 Fink S. 3 Liberian health workers with Ebola receive scarce drug after appeals to US. New York, NY: *The New York Times*, Aug 16, 2014. http://www.nytimes.com/2014/08/17/world/africa/three-liberian-health-workers-get-experimental-ebola-drug.html (accessed Aug 19, 2014).

17 National Health Research Ethics Committee, Nigeria. Statement on the use of innovative or non-validated medical treatment in Nigeria, 9 Aug 2014. http://nhrec.net/nhrec/statement-on-the-use-of-innovative-or-non-validated-medical-treatment-in-nigeria/ (accessed Aug 15, 2014).

18 WHO. Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD): summary of the panel discussion, 12 Aug 2014. http://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/ (accessed Aug 15, 2014).

19 WHO. Research ethics in international epidemic response, meeting report. 2010. http://www.who.int/ethics/gip_research_ethics_.pdf (accessed Aug 15, 2014).

20 London AJ. Clinical research in a public health crisis: the integrative approach to managing uncertainty and mitigating conflict. *Seton Hall Law Rev* 2009; **39:** 1173–202.

21 Edwards SJ. Ethics of clinical science in a public health emergency: drug discovery at the bedside. *Am J Bioeth* 2013; **13:** 3–14.

22 Viens AM, ed. Emergency research ethics. Ashgate: Rumford, 2013.

23 Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis* 2004; **189:** 930–37.

24 Pollack A. Ebola drug could save a few lives. But whose? New York, NY: *The New York Times*, Aug 8, 2014. http://www.nytimes.com/2014/08/09/health/in-ebola-outbreak-who-should-get-experimental-drug.html (accessed Aug 15, 2014).

25 Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. *Lancet* 2009; **373:** 423–31.

26 Lenzer J. Secret report surfaces showing that Pfizer was at fault in Nigerian drug tests. *BMJ* 2006; **332:** 1233.

27 Médecins Sans Frontières. Research ethics framework: guidance document. 2013. http://fieldresearch.msf.org/msf/bitstream/10144/305288/5/MSF%20Research%20Ethics%20Framework_Guidance%20document%20%28Dec2013%29.pdf (accessed Aug 15, 2014).

28 Calain P, Fiore N, Poncin M, Hurst SA. Research ethics and international epidemic response: the case of Ebola and Marburg hemorrhagic fevers. *Public Health Ethics* 2009; **2:** 7–29.

29 Schopper D, Upshur R, Matthys F, et al. Research ethics review in humanitarian contexts: the experience of the independent ethics review board of Médecins Sans Frontières. *PLoS Med* 2009; **6:** e1000115.

30 Ford N, Mills EJ, Zachariah R, Upshur R. Ethics of conducting research in conflict settings. *Confl Health* 2009; **3:** 7.