Evolving Challenges and Research-Needs Concerning Ebola

As the recent Ebola outbreak and global responses to it have continued to evolve, several major questions concerning research in developing countries arise, about which social science research is critically needed. Much of the debate about deployment of Ebola treatments and vaccines has focused on whether randomized clinical trials or other study designs or compassionate use should be employed (e.g., whether, in studies, standard of care or an alternative intervention should be a control arm).[1,2] Recently, favipiravir was found to decrease death rates from 30% to 15% among patients with low to medium viral levels,[3] leading to calls to use this drug more widely—to administer it instead of placebos in other studies and to roll it out more broadly in the population as a whole—which poses additional key questions. Vaccine trials are also advancing, with the completion of phase I trials.[4] Several additional dilemmas are thus emerging concerning ethics and public health that have still received little, if any, attention.

In general, responses to this recent Ebola outbreak serve as a very valuable case study, poignantly highlighting several larger ongoing challenges concerning research in the developing world. In these contexts, difficulties surface because of limited resources; poor health infrastructure; barriers in researchers' abilities to follow-up with patients in isolated rural areas, and thus to obtain research data; recent or ongoing political instability; poorly functioning institutions of civil society; corruption; stigmatization of affected groups; and often very different beliefs concerning the causes and possible treatments of disease.

As a result of these phenomena, crucial questions emerge generally, and specifically concerning Ebola—importantly, how affected populations view and understand the possible treatments and vaccines under study, including issues regarding therapeutic misconception, potential selection bias, and informed consent. Much of the discussion about Ebola has also focused on experimental treatments, rather than vaccines, which pose both similar and different issues.

For vaccines, for example, various kinds of selection bias may occur in trials, since healthy individuals who choose to enter a vaccine study may be more worried and concerned than are other individuals about acquiring Ebola, and they may thus strive harder to avoid exposure to the disease. Similarly, for instance, willingness of HIV-negative individuals to participate in HIV vaccine trials has been strongly associated with perceived risk of HIV infection[5] and neuroticism,[6] suggesting that individuals who feel more vulnerable (beliefs that may or may not be supported by actual relative risks) feel more need for protection.

Other individuals who receive a candidate Ebola vaccine may develop a form of therapeutic misconception, thinking that they are now protected from the virus. "Preventive misconception" (PM) has been described, whereby participants in a disease prevention study overestimate the likelihood that they will receive personal protection from the study (i.e., the odds that they will get the intervention instead of placebo or that it will be personally effective).[7] In a shingles vaccine study, for instance, 32% of participants demonstrated evidence of PM, 24% overestimated the probable personal effectiveness of the vaccine, and 12% underestimated the chance of getting placebo.[2]

Behavioral disinhibition or risk compensation has also been described in HIV vaccine trials,[8] whereby participants place themselves at greater risks as a result of being in the trial, significantly increasing their high-risk behaviors, despite rigorous counseling and informed consent.[9] These misconceptions and increased risk behaviors may occur particularly among certain participants (e.g., those who enrolled because of the possibility of being protected from the virus[5] and believe they are now protected[10]). Ebola, HIV, and hepatitis vaccine trials clearly differ, but participants' views in each of these sets of trials may have some similarities. Importantly, experimental Ebola vaccines may also prove ineffective, in which case any participants with misunderstandings and risk compensation could end up engaging more in physically caring for, or interacting with, sick relatives, friends, villagers or others, resulting in physical harm. Ebola vaccine studies should thus seek to avoid such possible selection bias (e.g., possibly through use of placebo or other, appropriate controls).

Moreover, assessments of whether, how frequently, and among whom such views emerge concerning Ebola are imperative to know how best to understand and interpret the results of Ebola vaccine studies. These two possible views among participants (of feeling either very wary of Ebola or overly protected from it) may cancel each other out, but both can nevertheless skew results. Thus, social science research is urgently needed to examine the extents to which such misconceptions, risk disinhibition, and selection bias may occur.

Therapeutic and other misconceptions can also arise concerning Ebola treatments. Regarding

favipiravir, for instance, research is needed to assess whether patients who receive the drug may indeed think that they are more protected than they in fact are (given that the drug appears to be partially effective) and may thus risk exposing others to the virus more (e.g., through bodily fluids during sexual[11] or other activities).

This attitudinal and behavioral research will in itself take time to conduct and, hence, can and should commence soon. Studies can probe, for instance, how participants view, and do or may respond to these various interventions—how likely and among whom such misconceptions and disinhibition may occur, and how these obstacles might be predictable or avoided. Without data on the likelihood of these beliefs and misconceptions, the results and effects of intervention trials will be difficult to interpret.

Participants' potential misunderstandings can also pose challenges in obtaining informed consent for Ebola intervention trials. As Adebamowo et al. wrote:

> Populations who are terrified by the progress of the epidemic, and who lack trust in health-care and aid workers, and in public authorities in the aftermath of civil wars, cannot be expected to offer informed consent to such randomised trials.[12(p1423)]

Misunderstandings can further contribute to fear and mistrust; yet, since informed consent is essential, examination of these and other specific obstacles is crucial to know how to address such barriers. Hence, research on how best to convey the complexities of these trials in participants' local languages—what terms and concepts to use—is critical to avoid these miscomprehensions. Participants will have to understand, in their own languages (several of which are spoken in the three countries most affected by this outbreak) the particular experimental nature of these interventions—the fact that these products may not work. Participants in the developing world and elsewhere often miscomprehend key aspects of studies, and forward and back translation do not always ensure effective communication and comprehension.[13] For instance, even after providing informed consent through a detailed process, more than 80% of participants in a malaria vaccine trial did not understand basic concepts such as placebo, randomization, and the ability to withdraw from research participation without negative consequences to themselves.[14] In some sub-Saharan African languages, for example, a word may exist only for "cure," but not for "experimental drug trial," "placebo," "randomization," or "vaccine."[11] Hence, determining how best to convey these concepts in local languages will take considerable effort, and will not necessarily be easy.

If favipiravir (with its only partial, but not complete effectiveness), or other early tested drugs that may also prove to have only limited effectiveness, are used more broadly, research will be especially vital to ensure that local populations do not assume that these products are more protective than they in fact are. Such overestimations of these products' benefits could lead not only to additional exposures of oneself or others, but to demand for these drugs that could undermine beneficial ongoing and future trials of other possible treatments (e.g., serum transfusions). Potential participants might decline to enroll in studies examining other experimental treatments that may prove to be even more effective. These issues are important since the disease incidence may be decreasing somewhat (though remaining at worrisome levels), making recruitment of participants into studies more difficult.

Decreased incidence creates needs, too, for close coordination of current and future trials. Currently, sponsors of trials of each of these products may launch their own studies, which may then compete with each other for participants. Instead, ideally, these various trials could and should be prioritized, and potentially be redesigned, pending each other's results (e.g., to use, as comparators, other new agents found to be effective, rather than placebos). Moreover, informed consent forms of ongoing and new studies may periodically need to be revised to incorporate information about the results of studies of other agents that may prove somewhat effective.

Wider dissemination of appropriate messages to affected communities about the results of each study will also be critical to avoid misconceptions. But social science research will be vital to design and frame these messages, to know how to convey optimally potential benefits and limitations of such new interventions. Diffusion of such messages will be crucial, especially since preliminary results of studies are often leaked through world media and become transmitted through word-of-mouth in ways that may or may not be wholly accurate, and may affect attitudes of current and future participants and others in affected regions.

All of these trials of interventions against Ebola need to be conducted as ethically as possible. Specifically, research must respect individuals' autonomy (as reflected in efforts to obtain and full valid informed consent) and promote beneficence (by making new treatments available when they are proven to be effective), nonmaleficence (e.g., through efforts to avoid harm occurring by participants mistakenly thinking they are more protected than they are), and social justice (by making any effective interventions available as widely and expeditiously as possible to affected populations). Yet the dilemmas posed by Ebola can involve conflicts between these principles (e.g., in weighing how best to make treatments available while minimizing the possible harms of PM).

Social science research can be indispensable to know how best to address these issues. Data collected on participants in intervention trials should thus include surveys probing affected individuals' attitudes, understandings, and expectations concerning these products (e.g., the effectiveness of the vaccines or treatments being studied and participants' reasons for entering the study). Structured questionnaires and ethnographic methods can be either added to these intervention studies or employed separately and independently to inform subsequent trials. Many observers have argued that interventions should only be administered in the context of research. Surveys of these attitudes should thus be incorporated as part of such research. These additional, social science investigations need not delay intervention trials, and should begin now to understand the extent of these challenges and how best to overcome them. One could argue that current responses to Ebola are performed as "public health emergencies" and that consequently, such additional social science research is unimportant or

unfeasible. But the attitudinal studies suggested here are crucial to know how to interpret and understand the results of intervention trials. Moreover, the epidemic has been continuing for more than a year and, though appearing to lessen overall, does not appear about to end; and other such outbreaks could easily occur in the future. The fact that research is being conducted in an emergency situation thus poses additional concerns that should be considered, rather than ignored, concerning how to adapt research designs and ensure the highest possible ethical standards.

Trials of possible Ebola vaccines and treatments are vital; but so, too, is research to inform how potential participants do and will perceive, understand, and respond to these experimental public health interventions, especially as preliminary results of intervention studies are increasingly released and discussed.

These considerations have critical implications beyond the current Ebola outbreak as well, given that in recent years, several epidemiological outbreaks of infectious diseases have arisen and spread across national borders (e.g., SARS, HIV, Avian Flu), and surely will continue to do so. Efforts to improve understandings of how best to address the ethical and public health challenges posed by Ebola can thus potentially enhance efforts to combat future such outbreaks. ■

Robert Klitzman, MD

About the Author

Klitzman is Professor of Psychiatry and Director of the Masters of Bioethics Program at Columbia University, New York, NY.

Correspondence should be addressed to: Robert Klitzman; Director, Masters of Bioethics Program, Columbia University; 1051 Riverside Drive, Mail Unit #15; New York, NY 10032 (e-mail: rlk2@cumc.columbia.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted May 1, 2015.

doi:10.2105/AJPH.2015.302757

References

1. Rid A, Emmanuel EJ. Ethical considerations of experimental interventions in the Ebola outbreak. *Lancet.* 2014;384 (9957):1896–1899.
2. Joffe S. Evaluating novel therapies during the Ebola epidemic. *JAMA.* 2014; 312(13):1299–1300.
3. Kupferschmidt K, Cohen J. "Positive" results for Ebola drug upsets plans for trials. *Science.* February, 2015. Available at: http://news.sciencemag.org/africa/2015/02/positive-results-ebola-drug-upsets-plans-trials. Accessed March 10, 2015.
4. Sarwar UN, Costner P, Enama ME, et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial. J Infect Dis. *J Infect Dis.* 2015;211(4):549–557.
5. Jenkins RA, Torugsa K, Markowitz LE, et al. Willingness to participate in HIV-1 vaccine trials among young Thai men. *Sex Transm Infect.* 2000;76(5): 386–392.
6. Johnson MO. Personality correlates of HIV vaccine trial participation. *Pers Individ Dif.* 2000;29(3):459–467.
7. Simon AE, Wu AW, Lavori PW, Sugarman J. Preventive misconception: its nature, presence, and ethical implications of research. *Am J Prev Med.* 2007;32 (5):370–374.
8. Eaton LA, Kalichman SC. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. *Curr HIV/AIDS Rep.* 2007;4(4): 165–172.
9. Chesney MA, Chambers DB, Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;16(4): 266–271.
10. Szmuness W, Stevens CE, Harley EJ. et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med.* 1980;303(15): 833–841.
11. Fink S. Signs Ebola spreads in sex prompt a CDC warning. *New York Times.* April 10, 2015. Available at: http://www.nytimes.com/2015/04/20/world/africa/signs-ebola-spreads-in-sex-prompt-a-cdc-warning.html?_r=0. Accessed April 27, 2015.
12. Adebamowo C, Bah-Sow O, Binka F, et al. Randomised controlled trials for Ebola: practical and ethical issues. *Lancet.* 2014;384(9952):1423–1424.
13. Klitzman R. The importance of social, cultural and economic contexts, and empirical research in examining "undue inducement." *Am J Bioeth.* 2005; 5(5):19–21.
14. Krosin MT, Klitzman R, Levin B, Cheng J, Ranney ML. Problems in comprehension of informed consent in rural and peri-urban Mali, West Africa. *Clin Trials.* 2006;3(3):306–313.

Disability as an Emerging Public Health Crisis in Postearthquake Nepal

Just before noon on April 25, 2015, a massive 7.8 magnitude earthquake occurred about 80 kilometers east of the Nepali capitol of Kathmandu, unleashing considerable destruction in one of the poorest countries in Asia. Then, just 17 days later, a second earthquake with a magnitude of 7.3 struck, this time about 40 kilometers west of Kathmandu. Although predictions of an impending large earthquake in Nepal had motivated the government and local and international nongovernmental organizations to create disaster preparedness plans in recent years,[1,2] this disaster affected rural and remote areas where the country's infrastructure

A Nepalese mother and child participate in a laughter yoga session to help relieve trauma among survivors of two earthquakes, which struck the country in less than three weeks, in Kathmandu on May 15, 2015. Photograph by Prakash Mathema. Printed with permission of AFP/Getty Images.