The American Journal of Bioethics

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/uajb20

The Goals of Research During an Epidemic

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Published online: 09 Apr 2015.

To cite this article: Annette Rid (2015) The Goals of Research During an Epidemic, The American Journal of Bioethics, 15:4, 47-50, DOI: 10.1080/15265161.2015.1009573

To link to this article: http://dx.doi.org/10.1080/15265161.2015.1009573

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The Ebola crisis provides a lens through which to focus on global health issues that have received insufficient attention. Hopefully, the lessons learned from other epidemics will help researchers and policymakers deliver needed relief in the form of new effective methods for prevention, treatment, and care, more quickly and effectively than in the past.

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The Goals of Research During an Epidemic

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The world is currently witnessing an unprecedented Ebola epidemic in West Africa. Weak health systems are primarily to blame for the scale of the events. Peter Piot, one of the discoverers of the Ebola virus in 1976, said before the present crisis that Ebola is "really a disease of poverty and neglect of health systems" (Piot 2012, 83). With adequate health systems and basic infrastructure in place, the epidemic would have likely been contained in its early stages.

Absent such systems and infrastructure, the outbreak has reached enormous proportions. Moreover, the lack of specific treatments and vaccines for a disease with a mortality rate of up to 90% (Beeching, Fenech, and Houlihan 2014) has become a key problem. It was therefore appropriate that the World Health Organization (WHO) endorsed the use of early experimental interventions in this epidemic (WHO 2014a)—even though these interventions arguably received too much attention too early in the international response (Rid and Emanuel 2014).

Heated controversy has now erupted over how the available interventions should be tested. Everyone agrees that generating more data about safety and efficacy has priority, so that beneficial vaccines or treatments can be identified as quickly as possible. But opinions about the most appropriate trial designs are divided, especially in treatment trials. Some commentators have recommended randomized controlled trials (RCTs) in which participants receive either experimental treatments and supportive care or supportive care and placebo (Cox, Borio and Temple 2014; Goodman 2014; Joffe 2014; Rid and Emanuel 2014), while others have rejected RCTs on both ethical and practical grounds (Adebamowo et al. 2014; Folayan et al. 2014).

In their target article, Arthur Caplan, Carolyn Plunkett, and Bruce Levin offer the first detailed argument against RCTs of investigational treatments for Ebola, such as convalescent blood products, monoclonal antibodies, or antiviral medicines, in the current epidemic (Caplan, Plunkett, and Levin 2015). The authors make three overarching claims to support their position. First, RCTs violate the ethical requirement of clinical equipoise that governs clinical

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April, Volume 15, Number 4, 2015
trials. Second, RCTs are based on the flawed assumption that trials must test whether experimental treatments are superior to best available supportive care for Ebola. Instead, Caplan and colleagues argue, the goal of research during an epidemic is to identify “winning treatments” as quickly as possible. Third, RCTs of experimental Ebola treatments are not feasible in the context of this epidemic. As an alternative, the authors advocate adaptive “randomized selection trials” (RSTs) in which candidate treatments are administered with supportive care and tested head-to-head without a concurrent control arm. Inferior treatments are sequentially eliminated until the “correct winner” stands. Although they do not make all of this explicit, the authors seem to believe that RSTs—unlike RCTs—satisfy clinical equipoise, realize the right goals of research during an epidemic, and are feasible to conduct. In the following, I argue against the authors’ second claim about the goals of research during an epidemic.

THE GOALS OF RESEARCH DURING AN EPIDEMIC

Caplan, Plunkett, and Levin (2015) claim that the goals of research during an epidemic differ from the goals of research under ordinary circumstances. Ordinary trials are rightly designed to test the “null hypothesis” that investigational treatments do not work better than available care, they say. By contrast, during an epidemic that is spiraling out of control, trials should aim to quickly “assess among potentially promising agents . . . which stand the best chance of working.” It follows that RCTs, because they test the null hypothesis, are not the “right tool for the job” in the current epidemic.

Imagine two schoolyard baseball captains, the authors write, who are choosing sides. It would be absurd for them to assume that no player is any better than any other player, or—to hone the authors’ presentation of their analogy—that no player is any better than someone who hardly knows how to play baseball. The captains should just try to select the best players for their team. “Testing the null makes no sense.” The analogy is intended to show that the goal of research during an epidemic is to identify, as quickly as possible, the “winning treatment” among available candidates. It is not to determine whether candidates improve patients over best available care, which is the goal of research during ordinary circumstances. However, the analogy is flawed because the schoolyard scenario does not reflect essential features of the current epidemic.

The schoolyard captains have a different task than the sponsors and investigators who are currently planning trials of investigational Ebola treatments. The captains have to make do with whoever happens to be in the schoolyard and constitute a team from among the present students. However, this does not correspond to the situation that sponsors and investigators are facing. They already have a team—namely, supportive care in the form of fluid replacement, broad-spectrum antibiotics, malaria treatment, and antipyretics that considerably reduce mortality (Beeching, Fenech, and Houlihan 2014). Indeed, a recent report from Freetown, Sierra Leone, documented a mortality rate of 31% under supportive care (Ansuman et al. 2014).

The existing team is not winning each and every game, and there is considerable uncertainty about its average performance—the documented mortality rate under various supportive regimen fluctuates between 31% and 77% in the affected countries (Ansuman et al. 2014; Bah et al. 2015; Schieffelin et al. 2014; WHO Ebola Response Team 2014; WHO Ebola Response Team 2015), and evidence from high-income countries (HICs) suggests that mortality might be further reduced by replacing larger fluid volumes (Kreuels et al. 2014; Lyon et al. 2014; Parra, Salmerón, and Velasco 2014). However, the existing team is clearly not an all-out loser. It would therefore be irrational to give up on this team entirely and assemble a new team from a pool of players whose performance, crucially, is more uncertain than the performance of the existing team.

Furthermore, schoolyard captains typically know the baseball skills of their fellow students based on prior observation of their skill in playing basketball. By contrast, sponsors and investigators have little knowledge about the safety and efficacy of experimental Ebola treatments, given that they are in the earliest stages of testing. To mirror the task of sponsors and investigators, then, the baseball analogy needs to be modified such that schoolyard captains already have a team whose performance is moderate and variable. Furthermore, the captains’ task is to determine whether they should replace any team members from a new pool of students whose baseball talents are largely unknown.

THE RIGHT TOOL FOR THE JOB

Once properly construed, the baseball analogy shows that the goal of research in this epidemic is to test the null hypothesis and RCTs with a concurrent control group are in fact “the right tool for the job.” The best way for captains to determine whether they should make any replacements is to test new candidates against current team members—in other words, to test the null hypothesis that the new candidates are no better than the existing team. Of course, it may be more efficient to test several candidates against the existing team, as RCTs with multiple study arms do, or to modify the testing in other ways to enhance its efficiency. But the comparison to current team members—the inclusion of a concurrent control group in an RCT—is essential for making valid decisions for or against new candidates. By contrast, the alternative RSTs advocated by the authors test new candidates head-to-head and therefore cannot exclude that the winner among them is no better than current team members or, crucially, performs more poorly than they do. Given that both the performance of the existing team and the talent of the new candidates are uncertain, the latter is a real possibility.
There are two situations in which RSTs may be justified in the amended schoolyard baseball scenario. First, RSTs could be justified if the existing team were clearly terrible—for example, if it had lost all games in a series of 20 or more. In this case, the captain would lose little, if anything, if she abandoned this team outright and simply constituted a new one. Yet as discussed earlier, supportive care—although far from perfect—is not an all-out loser. RSTs are therefore not justified on these grounds in the current epidemic. The authors may disagree because they claim at one point in the article that supportive care is “ineffective.” But the data already described here leave little doubt that this claim is false.

Second, RSTs could be appropriate if the schoolyard captains had good reason to believe that Babe Ruth was in the pool of new candidates. His performance would be so much better than everyone else’s that he could be identified independent of whether he is being compared to the existing team or other players. The authors seem to assume this kind of situation, since they recommend RSTs as a way of identifying “truly superior treatment.” Unfortunately, such superior treatments—players like Babe Ruth—are exceedingly rare. Under ordinary circumstances, only 10% of investigational agents considered sufficiently promising to enter Phase I safety trials make it to commercial launch (Hay et al. 2014)—and of these, only a minority are “truly superior.” Given the fast-tracking of trials, success rates may be even lower for experimental Ebola treatments. Moreover, treatments are not being selected based on their clinical promise alone, but also based on their timely availability. Indeed, a recent WHO Scientific Advisory Committee cautioned against testing interventions with “weak supporting data” simply because they are more readily available than more promising agents (WHO 2014b). In the vast majority of cases, then, RSTs should not be conducted in the current epidemic in the hope of identifying a “truly superior treatment.”

In summary, the authors’ main argument for why research during an epidemic should aim to quickly identify the “winning treatment,” and why RSTs should be conducted instead of RCTs in this epidemic, does not stand. Consequently, their efforts to demonstrate that RSTs require fewer participants and less time have little import. If such trials do not answer the relevant question, namely, whether the experimental treatments add something to supportive care, their other advantages matter little. In negotiating different trial designs, it is essential to emphasize that RCTs are, in the vast majority of cases, the “right tool for the job” in this epidemic.

ACKNOWLEDGMENTS

Franklin Miller and Joseph Millum offered helpful comments on an earlier version of this commentary. I have also benefited from discussions with Steven Joffe and Ezekiel Emanuel.

FUNDING

The work was funded by the People Programme (Marie Curie Actions) of the European Union’s Seventh Framework Programme (FP7/2007-2013) under REA grant agreement 301816.

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Placing and Evaluating Unproven Interventions Within a Clinical Ethical Taxonomy of Treatments for Ebola Virus Disease

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The target article by Shah, Wendler, and Danis (2015) ends with a call “to determine when it is ethically obligatory, rather than just permissible, to offer unproven interventions to patients.” In the following commentary we attempt to assist in this process by outlining a clinical ethical taxonomy of interventions/treatments in Ebola virus disease (EVD) and discussing how the placement of proven and unproven treatments within this taxonomy affects whether or not they are ethically permissible, obligatory, or impermissible. We also identify an additional constraint that may counsel against providing unproven interventions—the need to ensure sustained excellent infection control. In addition, we describe how patients with potential EVD may form a unique subtype of individuals in regards to the ethics of their care, apart from individuals with and without EVD, when providing proven and unproven therapies.

The following taxonomy categorizes treatments based primarily on their degree of clinical effectiveness and outlines the implications for ethical decision making and clinical practice (Table 1). Although the vast majority of current EVD care is in the resource-limited setting, Ebola is a worldwide health threat and this taxonomy is applicable to all health care settings. The provided examples are chosen for convenience and illustrative purposes and are not intended to be exhaustive.

In our taxonomy, interventions already approved for other indications or otherwise available are category B-2. Although we agree that there are some unique features to the use of experimental interventions not needed for use in a research trial, in our taxonomy we do not consider them different than experimental interventions (category B-1) because of their clinical similarity and the additional objections raised by Shah and colleagues to their use. Health care professionals are only ethically obligated to provide treatments in category A. The obligation is dependent on the following: availability of resources, that its provision does not prevent use of a more effective treatment, that it can be provided with sustained and excellent infection control, and that doing so does not put the organization, mission, other patients, or the public at unacceptable risk. Treatments in category B-1 and B-2 are permissible to offer outside of research, but offering them within the context of a research trial is preferable. If treatments are delivered outside of research it should be the result of a preplanned, transparent, and equitable process with clinically and ethically justifiable stopping points. When allocating scarce resources, priority should go to category A treatments, followed by treatments in category B-1 and B-2 that are part of research, followed by treatments in B-1 and B-2 not done as research. It is important to note that many treatments that may be reflexively provided in resource-rich care settings are in category B, not A.

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