VIEWPOINT

Evaluating Novel Therapies During the Ebola Epidemic

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Viewpoint

The Ebola hemorrhagic fever outbreak in West Africa poses acute and novel challenges for health policy and research ethics. Faced with an exceptionally virulent infectious agent, limited resources, and danger to health workers, local and international authorities struggle to deploy proven public health techniques that can limit the spread of the disease.[1] In the midst of the crisis, experimental interventions that have never been evaluated in human trials have captured professional and public attention. The prospect of first-in-human use of these interventions during an uncontrolled epidemic raises at least 4 pressing ethical questions. First, is there a role for "compassionate use" of agents in the absence of human safety, efficacy, or dosing data? Second, given the critical scarcity of these agents, which patients should receive priority access? Third, what trial designs should be used to study these agents? Fourth, how should efforts to evaluate experimental agents coexist with established clinical and public health interventions to treat patients and to minimize spread?

Two fundamental principles should guide responses to these questions. Decisions must aim to prevent the maximum number of deaths during the current outbreak. Equally important, policy makers must seek to optimize knowledge gained for use in confronting future Ebola epidemics.

Experimental Interventions for Ebola

A small biotechnology company, Mapp Biopharmaceutical, has conducted preclinical testing of ZMapp, a passive immunotherapy that combines 3 humanized monoclonal antibodies produced in *Nicotinia* plants. A recent trial of this product, administered up to 5 days after experimental inoculation of macaque monkeys with a virulent Ebola strain, suggests impressive efficacy at preventing lethal disease.[2] Based on these data, 6 health workers and a priest have received doses of ZMapp, and media reports suggest that at least some of these patients benefited from the product. However, the absolute scarcity of the product—the available supply is depleted, and scaling production will take months—limits broader access. Other novel agents under development may also have a role and may be more amenable to rapid scale-up of production.[3]

Prompted by the controversy surrounding this immunotherapy product and other novel agents, the World Health Organization (WHO) convened an expert panel on August 11, 2014, to advise on its role. The panel "concluded unanimously that it would be acceptable on both ethical and evidential grounds to use as potential treatments or for prevention unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans, provided that certain conditions are met."[4]

Avoid Compassionate Use

The vernacular term "compassionate use" refers to the use of an unapproved agent, outside the context of a scientific protocol, with the goal of benefiting an individual patient with a serious, usually life-threatening condition. In the face of a disease such as Ebola, with a case-fatality rate greater than 50%, the inclination to administer promising but unproven new agents in a compassionate-use manner is understandable. Compassionate use is theoretically compatible with learning; as the WHO advisory panel noted, "physicians overseeing [the administration of unproven new agents] have a moral obligation to collect and share all scientifically relevant data generated…in order to establish the safety and efficacy of the interventions."[4]

Allowing considerations of rescue rather than scientific hypotheses to drive use of novel agents, however, risks compromising the acquisition of knowledge needed to clarify their role in the next epidemic and ultimately to maximize benefits for patients. In addition, particularly in the first-in-human setting, a compassionate use approach will not necessarily prevent more deaths than would administration of the drug in a well-designed clinical trial. Moreover, when the novel agent is scarce, clinicians and health system authorities will need to confront the difficult question of who among the many deserving patients should receive access regardless of whether a compassionate use or clinical trial framework is adopted. For these reasons, policy makers should advocate for clinical trials organized around appropriate scientific questions, rather than endorsing compassionate use.

Emphasize Patient Benefit and Scientific Gain in Decisions About Access

In the short term, production of ZMapp and other novel agents will be insufficient to provide these therapies to all patients who might benefit. As a result, clinicians and health authorities will inevitably need to ration the available supplies. In the context of clinical trials, decisions about eligibility criteria should incorporate judgments about 2 factors: which patient groups are most likely to benefit from receiving the agent and which are most likely to generate scientific insights that will inform its evidence-based use in the next epidemic. The inclination to conduct initial trials among critically ill Ebola patients, rather than among patients with less advanced disease, will be strong. However, in the macaque trials that ought to inform design of the first-in-human studies, ZMapp was effective when adminis-

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tered within 5 days after experimental inoculation. Extrapolating from this preclinical experience—and acknowledging that evidence about the efficacy of this form of immunotherapy when administered late in the course of infection is lacking—both patient-benefit and scientific rationales suggest limiting eligibility in the initial trials to patients with early rather than advanced disease. Furthermore, in situations of extreme scarcity of therapy, considerations of consent, reciprocity, and logistics might justify prioritizing health care workers and others on the front lines of the Ebola epidemic for access to trials.

Use Randomization in Study Design

Given the urgent circumstances, individuals and organizations involved in planning clinical trials may consider administering the experimental agent to a consecutive series of patients and then attempt to evaluate its safety and efficacy in light of what is known about the natural history of the disease. This would be a mistake. Investigators should instead move directly to randomized trials that compare best supportive care plus an experimental agent with best supportive care alone. Without a concurrent randomized control group, individuals who receive the drug will differ systematically from the untreated individuals with whom they are compared. Study participants may be sicker or less ill, younger or older, or identified at an earlier or later stage of disease than those in historical—or even contemporary—comparison groups. These differences will confound efforts to reach valid inferences about the safety and efficacy of the drug.

Objections to the use of randomization in the midst of a devastating epidemic will center on ethical and scientific concerns. Scientific questions will focus on whether dose-finding and feasibility considerations require a pilot single-treatment group, uncontrolled trial. Yet even these preliminary questions are best answered in the context of a randomized control group. Furthermore, it is possible that early hints of either efficacy or serious toxicity in an uncontrolled trial, even if difficult to interpret given inevitable selection biases, will derail the possibility of conducting a subsequent randomized trial.

Some will argue that it is unethical to randomize patients with a disease that has a 55% to 60% short-term case fatality rate to a control group when an intervention that holds any promise for reducing their likelihood of death is available. This objection does not consider that, given the scarcity of the drug, a finite number of patients will receive access regardless of what study design is used. It also fails to acknowledge that alternative means for prioritizing access, such as first-come first-served and sickest first, are themselves ethically unsatisfactory.[5] Especially in the setting of absolute scarcity of the novel agent, where nothing ethically is lost by allocating access through a lottery,[6] randomization should begin with the very first trials.[7]

Protect Clinical and Public Health Infrastructures

Perhaps most important in confronting the present epidemic, efforts to evaluate novel agents risk diverting attention and human and material assets from proven therapeutic and public health measures.[4] Well-motivated initiatives directed at promising new therapies must not jeopardize existing health infrastructures. Rather, local and international health authorities must ensure that the resources needed to conduct clinical trials represent dedicated additional capacity. Without attention to this issue, efforts to study novel agents may ironically increase, not reduce, the death toll from this epidemic.

Moving Forward

Scientifically and ethically justified use of scarce new agents in the midst of the Ebola epidemic, or any other epidemic for which novel agents hold promise, requires reflection on the understandable desire to rescue imminently dying patients. Clinicians, investigators, and policy makers must deploy novel agents in ways that address pressing scientific questions, prioritize research in populations that will be most scientifically informative as well as most likely to benefit, ensure valid answers through the use of supportive care controls, and protect critical clinical and public health resources from diversion to longer-term aims. By doing so, they can maximize lives saved in the present epidemic and ensure knowledge gains for the next.

ARTICLE INFORMATION

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