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Controlling Ebola Trials

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There are currently no therapeutic agents that have been shown to be effective against Ebola virus disease (EVD). A number of experimental therapies are in the early stages of testing in humans. The larger studies that seek to demonstrate efficacy will, almost inevitably, have to be carried out in the West African countries currently suffering from the epidemic. The scientifically and ethically optimal design of these studies is a matter of heated debate, which has largely focused on whether randomized controlled trial designs should be used.

In "Selecting the Right Tool for the Job," Caplan, Plunkett, and Levin (2015) argue that the most pressing question regarding experimental treatments for EVD is not whether an experimental therapy is better than nothing, but which of the current candidate therapies is the most promising. They therefore reject randomized controlled trials that would compare, for example, supportive care and placebo against supportive care and an experimental therapy, in order to test for a statistically significant effect of the experimental therapy. Instead, they write:

> The wisest use of limited resources is to eschew the null hypothesis and instead to refocus on alternative trial designs that can demonstrate which intervention among those available is most likely to provide benefit to those suffering from Ebola in desperate circumstances.

As an alternative, Caplan and colleagues propose an adaptive trial design without a concurrent control group. This design would sequentially allocate research participants to each of the experimental therapies to be tested. The cure rate for each therapy would be tallied and therapies eliminated once their cure rates lagged behind the leader by some fixed number. The treatment that remains once the rest have been eliminated is the best. Although it is not explicitly stated, we are led to infer that this winning treatment should then be rapidly incorporated into the standard of care for patients with EVD in West Africa.

Caplan and colleagues' approach might make sense were it true that the most important question really is which of the existing experimental therapies is most promising. However, this would only be the case if one of the following were true. First would be if there were a high *ex ante* probability that at least one of the experimental therapies for EVD would have substantial efficacy. In that case, we might be sufficiently confident that patients with EVD really would benefit from the therapy selected through the adaptive trial design Caplan and colleagues propose, despite the lack of a control arm. Second, their approach might make sense if there were no other ways in which the limited resources expended on distributing experimental therapies could be used to combat Ebola. In that case, as long as providing an experimental therapy was not expected to be actively harmful, there would be no loss from providing the apparently best option to EVD patients.

In fact, neither of these is the case. First, the probability that any particular new drug going into human testing will turn out to be safe and effective is relatively low (Hay et al. 2014). We therefore cannot rely on the assumption that at least one of the current experimental therapies will turn out to be substantially effective.

Second, there are multiple alternative uses of the limited health care resources that would be expended on supplying the winning treatment to patients (Rid and Emanuel 2014). For example, it is widely thought that EVD

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patient outcomes would be dramatically improved by improvements in health care infrastructure to allow better supportive care, including appropriate use of intravenal fluid replacement, and training of more health care workers to provide the acute care patients need (Chertow et al. 2014; Lamontagne et al. 2014). Instead of spending money on manufacturing drugs of uncertain efficacy and using the limited health care infrastructure and personnel to distribute them, policymakers could focus their resources on increasing access to this supportive care. Alternatively, it might be that the best use of limited resources is in the improvement of infection control measures and the accompanying infrastructure for that (Whitty et al. 2014). Again, this priority would compete for the resources needed to manufacture and provide the drugs.

Consider, then, the real choices facing policymakers with limited resources for combating Ebola. Should they invest in new drug therapies, in more field hospitals, in upgrading infrastructure for better basic supportive care, in contact tracing and patient isolation? How much should they focus on each of these, given current limits on personnel, infrastructure, and funds?

Among other factors, the answers to these questions depend on the relative costs and benefits of the different options. An informed answer therefore requires that we have good information about the likely effectiveness of novel therapies. Without such information we cannot compare the value of new treatment interventions to alternative allocations of resources that might provide even greater benefits to current and future EVD patients in West Africa. Whatever trial designs are chosen, therefore, they must be capable of testing whether the experimental therapy is effective at all against EVD.

DISCLAIMER

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