Ethical Rationale for the Ebola "Ring Vaccination" Trial Design

The 2014 Ebola virus epidemic is the largest and most severe ever recorded. With no approved vaccines or specific treatments for Ebola, clinical trials were launched within months of the epidemic in an unprecedented show of global partnership. One of these trials used a highly innovative "ring vaccination" design. The design was chosen for operational, scientific, and ethical reasons—in particular, it was regarded as ethically superior to individually randomized placebo-controlled trials.

We scrutinize the ethical rationale for the ring vaccination design. We argue that the ring vaccination design is ethical but fundamentally equivalent to placebo-controlled designs with respect to withholding a potentially effective intervention from the control group.

We discuss the implications for the ongoing ring vaccination trial and future research. (*Am J Public Health*. 2016;106:432–435. doi:10.2105/AJPH.2015.302996)

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The *Ebola ça Suffit* (Ebola, this is enough) trial of a novel Ebola virus vaccine, which is currently being conducted in Guinea,[1,2] is remarkable for several reasons. First, the trial was launched within months during one of the worst public health crises in decades.[3,4] An international group of investigators and sponsors forged agreement about controversial issues such as trial design, overcame tremendous operational challenges, and established partnerships with local communities without whom the trial would have never happened. This is a major achievement. Second, the first trial results are impressive. According to a recent interim analysis, the vaccine protects individuals at risk for contracting Ebola with an estimated effectiveness of 75%.[2] Third, the trial is the first to use a "ring vaccination" design that involves tracing and vaccinating the contacts of Ebola patients. This highly innovative trial design, based on a method of eradicating smallpox, evaluates both the ring vaccination approach and vaccine effectiveness.[1]

Ethical considerations played a critical role in choosing the ring vaccination design,[1] yet so far they have not been adequately discussed. We argue that the ring vaccination design is ethical but for different reasons than those put forward by the *Ebola ça Suffit* sponsors, the trial investigators, and some commentators. Moreover, the prevailing ethical confusion about the trial design raises concern that its broad acceptance rests on false beliefs and expectations.

EBOLA ÇA SUFFIT TRIAL

In its first phase, the *Ebola ça Suffit* trial used a cluster randomized controlled design that was modeled on a ring vaccination approach.[1,2] Ring vaccination is an infection control measure that involves vaccinating a cluster of individuals at high risk for infection on the basis of their social or geographic connection to a known case. This creates a protective "ring" or cluster of immune individuals around newly diagnosed cases, thereby preventing further spread of infection.[5]

The *Ebola ça Suffit* trial modified the ring vaccination approach in 2 important ways. First, it used an unproven vaccine instead of a proven effective one—*Ebola ça Suffit* was launched after the vaccine had completed phase I testing.[6,7] Second, clusters of individuals at high risk for infection were randomly assigned to either immediate or delayed vaccination.[1,2] Half of the clusters were vaccinated as soon as the contacts of a person newly diagnosed with Ebola and the contacts of those contacts were identified. The other half received the vaccine 21 days later. This delay reflected Ebola's incubation period and created a control for the intervention clusters receiving immediate vaccination. Vaccine effectiveness could then be evaluated by comparing the incidence of Ebola between clusters randomly assigned to immediate vaccination and those assigned to delayed vaccination.[1,2] Following the impressive interim results, *Ebola ça Suffit* has now entered a second phase and is being continued as an observational ring vaccination trial, in which all clusters of individuals at increased risk for infection are immediately vaccinated.[8] In this article, we focus on the first phase of *Ebola ça Suffit*, which randomly assigned clusters of individuals to immediate or delayed vaccination.

RING VACCINATION DESIGN

The ring vaccination design was adopted for operational, scientific, and ethical reasons. Meeting the trial's scientific objectives was a major challenge

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because of the waning epidemic and limited health infrastructure in Guinea. The incidence of Ebola in the general population was decreasing,[9] and small outbreaks occurred suddenly in different regions. In this situation, the ring vaccination design had important advantages.[1]

Operationally, the design allowed investigators to track the epidemic and run the trial until disease elimination, enabling them to recruit relatively high numbers of participants in the circumstances. It was also advantageous that all eligible participants within a cluster could be vaccinated and assessed around the same time in the same location and that the trial could go dormant during interepidemic periods.

Scientifically, the design included concurrent control clusters that were needed for drawing robust conclusions from the collected data.[10] In view of temporal changes in background conditions, it would have been extremely difficult to address confounding factors if designs with historical controls had been used—for example, varying infection rates or varying public health measures, such as safe burial practices and other measures to reduce disease transmission. Moreover, by targeting individuals at high risk for infection, the ring vaccination design increased the trial's statistical power.[1] Finally, although this is still debated,[11] the design might have allowed investigators to evaluate not only vaccine effectiveness but also vaccine efficacy and indirect vaccination effects (i.e., the degree to which unvaccinated individuals are protected in clusters at different levels of vaccine coverage).

In addition to these operational and scientific advantages, the ring vaccination design was chosen for its alleged ethical superiority over alternative designs. Specifically, an individually randomized placebo-controlled trial

> was deemed unacceptable . . . because of national and international concerns about leaving vulnerable individuals unprotected against EVD [Ebola virus disease] when a potentially effective vaccine was available.[1]

As Donald Henderson, a key figure in smallpox eradication and trial consultant, put it: a placebo-controlled trial

> did not seem to be a great idea. . . . It's the business of saying "You are getting the drug" and "You are not getting the drug." . . . How can you possibly make it available to some and not to others?[12]

The ring vaccination design was widely seen as a defensible alternative to conducting a placebo-controlled trial because it "allows all consenting contacts . . . to be vaccinated within the context of the trial."[13] In the words of Jeremy Farrar, director of the Wellcome Trust research charity that cofunded the trial,

> To substitute a potentially life-saving vaccine for an inert substance, given the circumstances [the known mortality of Ebola and the lack of other options for prevention or treatment], would not have been ethical—but a comparison still needed to be made. So half of the volunteer participants were vaccinated immediately, and the other half after a three-week delay.[14]

ETHICAL JUSTIFICATION FOR RING VACCINATION DESIGN

The stated ethical justification for the ring vaccination design currently rests almost exclusively on the fact that it avoids the use of a placebo control. However, this not only overlooks important ethical considerations but also bases the *Ebola ça Suffit* trial on spurious ethical grounds.

A key ethical requirement for research is that it must use rigorous scientific methods to address socially valuable questions.[15] First and foremost, the design was ethically justified because it offered a feasible approach to evaluating a novel vaccine under extremely difficult circumstances. It is unacceptable to expose study participants to risks, and use limited resources, when trials are unlikely to yield robust data. The operational and scientific advantages of a ring vaccination design therefore had major ethical import.

This is not to say that a ring vaccination design has no limitations.[1,2] For example, it is complex to analyze and subject to the same biases as other cluster randomized trials, such as imbalances in important variables at the cluster level. Also, an effective vaccine may not have been identified because it was unsuitable for a ring vaccination approach or because the trial was inadequately powered to detect its effects. Moreover, depending on the circumstances and the given scientific questions, epidemiologists and statisticians may find other trial designs equally or more appropriate.[16]

Second, the ring vaccination design was not ethically defensible because it avoided using a placebo control. Indeed, it was ethically similar to placebo-controlled trials in that it withheld a potentially beneficial vaccine from some participants for a certain time. The key ethical concern about placebo-controlled trials is not the administration of a placebo; ingesting a sugar pill or receiving a saline injection involves few if any risks. The concern is that a proven effective or promising investigational intervention is withheld from the control group.[17] The ring vaccination design equally withheld a potentially beneficial vaccine from the delayed vaccination clusters. If the vaccine was effective, participants in these clusters would have been at increased risk for contracting Ebola. Indeed, this is precisely what the trial aimed to show to confirm the vaccine's effectiveness—and what the interim results indicated.[2] Thus, if placebo-controlled trials are unethical in an epidemic of a life-threatening disease because they withhold a potentially effective vaccine, then so are trials that use a ring vaccination design.

However, withholding the Ebola vaccine from the control cluster for the sake of a scientifically sound evaluation of its effectiveness was ethically justified. The vaccine was investigational and thus may have proven to be ineffective or even harmful; only 22% of the investigational vaccines beginning phase II, and 50% beginning phase III, make it to commercial launch under ordinary circumstances.[18] Moreover, all participants in the *Ebola ça Suffit* trial received infection prevention advice and information on how to contact the study team at all times in case of Ebola-like symptoms. All participants were monitored for such symptoms by daily home visits by the Guinean Ebola response team (routine contact tracing of communities for 21 days after identification of an Ebola case), and the study team conducted home visits postvaccination to monitor for serious adverse events, including Ebola virus disease. Participants also had access to free medical checkups and care at a private clinic or the nearest Ebola Treatment Unit for any acute illness during the study period. Any serious adverse

event occurring among participants were reported to the Independent Data and Safety Monitoring Board within 24 hours.[2,10,19] Finally, investigators did not expect that the study vaccine would have a postexposure prophylactic effect.[1] These considerations suggest, against concerns to the contrary,[20] that delayed vaccination in the control cluster did not expose participants to undue risks of harm.

More fundamentally, investigators' principal obligation is to conduct scientifically valid and socially valuable research.[15] Investigators should also enhance potential benefits for participants, but only to the extent that this is consistent with designs that produce robust data.[21,22] Based on the preclinical and phase I data,[6,7,23] it was not possible to predict the Ebola vaccine's outstanding effectiveness that is now emerging. Judged ex ante, and as stated in the *Ebola ça Suffit* study protocol,[10] not including a concurrent control group or cluster would have imperiled the scientific validity of whichever design was chosen for larger follow-up trials. At the same time, the ring vaccination design that was used enhanced the potential benefits to participants by eventually providing all of them with the study vaccine and minimizing the time without vaccination in the control cluster, to an extent that may have been difficult to achieve with other designs. For example, providing the control group in a placebo-controlled trial with the vaccine 3 weeks after they received a placebo likely would have required an impracticably large sample size. This was a clear advantage of the ring vaccination design, because the study population was at increased risk for contracting Ebola.

In summary, the *Ebola ça Suffit* trial was ethically justifiable and may have been ethically preferable to a placebo-controlled trial, because its design enhanced potential benefits for participants while safeguarding the scientific validity of the trial under extremely difficult circumstances. This conclusion holds even though the design involved withholding a potentially effective vaccine from some participants, just like in a placebo-controlled trial.

AVOIDING ETHICAL CONFUSION

The confusion around why the *Ebola ça Suffit* trial was ethically acceptable raises its own concerns. Sponsors, investigators, and commentators tended to portray the trial as an ethically preferable alternative to a placebo-controlled trial without clearly acknowledging or downplaying the fact that it, too, withheld the study vaccine for a period of time. Moreover, commentators frequently conflated the ring vaccination method of public health practice with the fundamentally different method of public health research used by *Ebola ça Suffit*. For example, Seth Berkley, the chief executive of the Vaccine Alliance Gavi, wrote that "we must not lose sight of the fact that this is not just a research exercise; it is a public health intervention."[24] Similarly, *The Washington Post* erroneously explained that "the ring method is not a true clinical trial but a strategy for eradicating a disease."[12] Commentators have argued that *Ebola ça Suffit* "demonstrates how the goals of clinical research, public health and individual well-being can all be integrated."[25] This raises concern that many, including investigators, trial participants, and commentators, may be in the grip of something akin to the "therapeutic misconception"[26]—confusing a proven effective public health practice with a scientific experiment evaluating an investigational vaccine.

This lack of clarity about the study method suggests that broad acceptance of the ring vaccination design may have rested on, or was supported by, false beliefs and expectations and that public trust in the *Ebola ça Suffit* trial may have been fragile. Although the design and conduct of this trial were exemplary, it does not serve transparency and community trust and partnership to portray the study as if it were a public health intervention comparable to the effort to eradicate smallpox. On the contrary, *Ebola ça Suffit* was a randomized controlled trial in which the control cluster received the investigational vaccine after a delay. Assuming that the investigational vaccine would prove effective, this predictably and intentionally increased the risk of infection in the control cluster. This delayed vaccination strategy was ethically justified to evaluate the effectiveness of the vaccine while enhancing potential benefits to participants.

The success of the *Ebola ça Suffit* trial might be seen to suggest that placebo-controlled trials are no longer necessary for evaluating investigational vaccines for Ebola or other comparable conditions, or perhaps never were. This can lead to difficulties when evaluating trial designs in other circumstances, especially those in which placebo-controlled trials could be overall preferable. We have shown that the *Ebola ça Suffit* trial raises essentially the same ethical concern as a placebo-controlled trial because it, too, exposed participants in the control group to an increased risk of infection by withholding a potentially effective vaccine for a period of time. As the ring vaccination design undoubtedly will become more popular, it is essential to be clear about how it compares ethically to traditional placebo-controlled trials. AJPH

CONTRIBUTORS

A. Rid wrote the first draft. F. G. Miller revised the article critically for important intellectual content. Both authors conceptualized the idea for the article, approved of the final version, and agree to be accountable for all aspects of the work.

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HUMAN PARTICIPANT PROTECTION

No protocol approval was necessary because the research did not involve human participants.

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