Investigational Vaccine Implementation in Emerging Outbreaks: A Case of Marburg Virus in Rwanda

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Forward:

Pharmaceuticals such as vaccines and therapeutics are critical tools used to combat emerging infectious disease outbreaks. As seen during COVID-19 and many other historic epidemics, they can be essential in mitigating the severity of disease and the number of lives lost. However, with many diseases, effective vaccines or therapies do not exist or have not been thoroughly evaluated by the time they are needed. The distribution of investigational products in outbreak settings raises questions that require communities to balance research ethics with clinical care for individual patients. The Rwandan Marburg virus outbreak in 2024 provides an excellent case study of the ethical tensions policy-makers face when determining whether and how to use experimental products during epidemics. This paper analyzes the Rwandan Ministry of Health's decision to distribute an investigational Marburg vaccine outside of a randomized controlled trial. Ultimately, this ethical analysis underscores the necessity for adaptable public health responses that respect local contexts and prioritize community perspectives.

Introduction:

In late September of 2024, Rwanda announced its first outbreak of Marburg virus disease (MVD), a highly lethal hemorrhagic fever closely related to Ebola. Within a few weeks, the outbreak became the third largest ever, with a recorded 66 cases and fifteen deaths.[1] Outbreaks of filoviruses such as Marburg virus that historically have had high mortality rates incite international attention and alarm. While most outbreaks are self-limited and have small caseloads, this can quickly change, as seen in the 2014-2016 Ebola epidemic in West Africa. Infection control measures, strong contact tracing, and expansive testing are all important for curbing spread.[2] Thanks to an intense public health effort by the Rwandan Ministry of Health, the outbreak

was brought under control in under three months with one of the lowest case fatality rates for an outbreak of this size.[3] The last known case tested negative on November 8th, 2024 and the outbreak was declared over in December of 2024.[4]

Rwanda's strong response included quickly coordinating the delivery of over 2,700 investigational vaccines. Developed by the Sabin Vaccine Institute, the vaccine candidate had not yet been evaluated for efficacy, but was undergoing Phase II clinical trials.[5] Initially, Rwanda announced a plan to distribute Sabin's vaccine to healthcare workers through a phase III randomized controlled trial, data from which would help determine the vaccine's efficacy. Two days later, they changed course, opting instead to vaccinate as many frontline healthcare workers as possible outside of a randomized setting. Although they would be able to collect safety and immunogenicity data, they would not be able to evaluate the vaccine's efficacy with that approach.[6]

Rwanda's choice highlights a difficult ethical question policymakers must address when deploying investigational vaccines in emerging outbreak settings: should randomized controlled trials be conducted or are other distribution methods ethically superior? This debate was controversial during the West African Ebola epidemic and forced communities to wrestle with balancing the public good with care for individual patients.

This paper will examine the ethics of Rwanda's decision about how to distribute the Sabin vaccine during the 2024 Marburg outbreak. Using lessons from the 2014-2016 West African Ebola epidemic, I argue that Rwanda's choice to forgo randomization has strong ethical backing rooted in the principles of risk-benefit analysis, community engagement, and justice. Additionally, their decision showcases the importance of a flexible approach to public health decision-making and highlights a critical lesson for emerging infectious disease responses everywhere: context matters.

Ethical Emergency Use of Investigational Products:

The first question policymakers had to address in the Marburg outbreak was whether or not to provide access to experimental vaccines. As was the case with the Ebola epidemic in 2014, there are currently no approved vaccines for Marburg virus. Out of the products in development, Sabin's vaccine is the only one that has been tested in humans. A phase I trial revealed a favorable safety profile in 2022 and the vaccine is currently undergoing phase II trials in Uganda and Kenya.[7] No safety concerns have been reported to date.[8]

Typically, interventions must undergo rigorous safety testing and often lengthy regulatory licensing processes before they are available to the public. However, not using potentially beneficial investigational products also presents ethical issues, especially with highly lethal and transmissible pathogens like Marburg and Ebola.

In previous filovirus outbreaks, those in favor of deploying investigational agents have argued that outbreaks present a narrow opportunity to gather efficacy data, as that can often only happen in the context of an outbreak. If beneficial, novel vaccines can also mitigate the spread of disease and inspire hope during a crisis.[9] Those opposed to using investigational products have argued that "experimenting" on the population during an outbreak can increase community mistrust in the health system and hinder other important public health efforts.[10] Deploying experimental agents can also drive attention and resources away from proven infection control tactics that benefit everyone.[11]

During the Ebola epidemic in 2014, the World Health Organization (WHO) convened medical ethicists to discuss the issue of whether or not to use investigational products in outbreak settings. The panel unanimously agreed that their use was justifiable – even "ethically imperative" – so long as a set of ethical requirements were met.[12]

These ethical requirements were formalized by the National Academy of Medicine in 2017 based on lessons from the Ebola epidemic and established principles from the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki.[13] The framework consists of seven principles:

1) *Scientific and social value*: Information gathered through the use of investigational products in emergencies must be of sufficient scientific quality and social value to help decision-making.
2) *Respect for persons:* Individuals and communities participating in research must consent and be provided with reliable and understandable information about the risks and benefits of participating.
3) *Community engagement*: Communities must be involved in discussions about clinical trial design, potential risks and benefits, and individual versus societal good.
4) *Concern for participant welfare and interests:* Risks to participants and communities must be minimized and every effort should be made to increase benefits.
5) *Favorable risk-benefit balance:* Equipoise, a state of uncertainty in the medical community about the prophylactic merits of an investigational product, must be present to justify the risks to research participants.
6) *Justice in the distribution of benefits and burdens:* Benefits and burdens of research must be fairly distributed across the population.
7) *Post-trial access:* If an investigational product is shown to be effective and safe, communities who hosted and participated in the research must have post-trial access to the product. The responsibility of the cost of that access should be determined in advance.

There is now broad consensus that investigational vaccines can and should be used in emergent situations if these principles are met.[13(p61)] There is less consensus about how to deploy them.

Rwanda's Options for Distribution:

Rwanda had two principal options for delivering the Sabin vaccine: 1) deploy it under a phase III randomized controlled trial (RCT), the gold-standard method of determining a vaccine's efficacy or 2) deliver it outside of a randomized setting.

In Option 1, vaccines would be distributed under a phase III trial protocol that used a cluster-randomized, stepped-wedge design. In the design, contacts of cases and contacts of contacts would be vaccinated immediately or after a delay of three weeks. This "ring vaccination" approach was a novel design employed during the successful *Ebola ça Suffit* trial during the 2014-2016 Ebola outbreak. Data from that trial led to the approval of the first Ebola vaccine.[14] After the outbreak, the World Health Organization developed similar trial protocols that could be put in place for other emerging outbreaks. One such pre-designed protocol is what Rwanda initially planned to use.

In Option 2, vaccines would be distributed under a phase II, rapid-response, open-label trial. The highest-risk populations would receive the vaccine first, starting with healthcare workers, and there would be no control group. Researchers would then monitor side effects and take blood samples to gather immunogenicity data.[6] Vaccine efficacy could not be evaluated with this method. Option 2 was the ultimate choice of the Rwandan officials.

Applying the Ethical Framework:

Using the requirements outlined by the National Academy of Medicine, I analyze the ethical implications of both options Rwanda considered for vaccine distribution. I argue their ultimate choice to forgo randomization is ethically sound, especially regarding the principles of risk-benefit analysis, community engagement, and justice in distribution.

Concern for Participant Welfare and Interests

The ethical principle of concern for participant welfare states that risks to participants and communities participating in a trial must be minimized and every effort should be made to increase benefits. A commonly cited concern with RCTs is that they deprive the control group of a potentially beneficial agent. As Donald Henderson, a trial consultant for *Ebola ça Suffit,* said, "How can you possibly make it available to some and not to others?"[15] Not only does a control group cause visceral feelings of unfairness, but it also conflicts with a research promise to maximize the benefits to participants as much as possible.

The delayed vaccination design of *Ebola ça Suffit* and the proposed Marburg vaccine trial aimed to address this issue. Everyone in the trial would receive the investigational vaccine within three weeks. However, while delayed vaccination may be easier for communities to accept, it is ethically similar to a placebo-controlled trial. If the core concern is withholding potential benefits from the control group, those in the "delayed" clusters still do not have access to the intervention while they are at the highest risk of infection.[16] Rwanda's decision more successfully showed concern for participant welfare and interests by delivering the vaccine to those at highest-risk of contracting the disease, without relegating a control group to delayed vaccination.

Justice in Distribution

The ethical principle of justice in distribution compels trials to fairly distribute the benefits and burdens of research across the population. Defenders of randomization argue that it is more ethical under this principle because of the limited supply of investigational products. Since only a finite number of people would have access to the vaccine, randomization offers a more unbiased distribution method than other distribution frameworks, such as sickest-first or first-come-first-served.[17] Although product supply has been an issue in other epidemics, Rwanda's outbreak was small enough that product availability was not yet a concern. Before the outbreak began, Sabin only had around 850 doses available, but they quickly scaled up and delivered another thousand doses within a week.[18]

Moreover, random distribution is not always the preferred or most equitable allocation method, as seen in the COVID-19 vaccination strategy.[19] Distributing to higher risk populations can be a more ethical and more equitable approach. The non-randomized option allowed Rwanda to have flexibility about who to vaccinate first (in this case, health care workers), which would not have been possible under a phase III trial design.

Risk-Benefit Profile

The points above surrounding justice and concern for participant welfare are only relevant under the assumption that the investigational vaccine will be beneficial, or at least not harmful. Proponents of RCTs argue that there is a real possibility that investigational products will cause harm. For example, the United States administered an experimental H1N1 vaccine to people in New Jersey in 1976. The feared epidemic did not manifest and more than fifty people were diagnosed with Guillain-Barré Syndrome after vaccination.[20] True equipoise exists with Sabin's vaccine, therefore they argue randomization with a control group is the most ethical choice.

However, the idea of equipoise often breaks down in emergencies and with highly lethal diseases. When mortality rates for a disease can reach over 50%, people are much more willing to tolerate a higher risk profile in a product if the potential benefit is preventing infection. The risks of the vaccine can pale in comparison to the risk of death from Marburg. As Adebamowo et al argued in a perspective piece about RCTs for Ebola, "Ethical arguments are not the same for all levels of risk."[21]

Additionally, the Sabin vaccine underwent initial safety testing in phase I and phase II trials. Although not rigorous enough for approval, data from those trials provide good evidence the vaccine is relatively safe, especially when compared to Marburg infection.[22]

Scientific and Social Value

The strongest argument in favor of RCTs is that randomization has the highest likelihood of producing scientifically valid results. Ethical principles of research state it is unacceptable to use limited resources and expose communities to potential harm if trials do not reveal robust and relevant data for decision-making. Since other study designs can yield inconclusive or confounded results, randomized controlled trials are the only ethical choice.[16] This argument is especially poignant in the wake of the Ebola epidemic. Out of 13 vaccine and treatment trials conducted during the epidemic, only one yielded a conclusive result. This was in part due to non-randomized study designs that "lacked scientific rigor," according to a *Science* special report.[6]

It is broadly recognized that randomized controlled trials are the gold-standard scientific method for evaluating pharmaceuticals. In ideal settings, they are the best way to test efficacy. However, outbreaks like Marburg are anything but ideal. Emergencies stress health systems, even highly functioning ones like Rwanda's. The intense resources and time required to create controlled conditions that yield valid results may negatively impact clinical care. They can also be impractical to implement, as MSF wrote during discussions about RCTs for Ebola: "It is unclear that any capacity exists to impose controlled conditions during a raging epidemic."[21]

Additionally, efficacy is also not the only way of providing social value. While efficacy data is preferred, the distribution method Rwanda chose allows them to collect valuable immunogenicity and safety data about the vaccine that can inform its use in future outbreaks.

Community Engagement

One of the many lessons from Ebola was the necessity of involving communities in discussions about deployment of investigational agents. Failure to do so can result in mistrust that undermines the entire public health response. Even if conditions are amenable to a randomized controlled trial, if a community does not approve of the design, it can be considered unethical.[13]

On the whole, randomized controlled trials during outbreaks appear to be unacceptable to many communities. A survey of public health research stakeholders at an African CDC conference found less than a quarter of respondents considered it ethical to conduct placebo-controlled randomized trials during infectious disease outbreaks with high fatalities.[23] During the Ebola epidemic, Médecins Sans Frontières consistently reported that randomized, placebo-controlled trials would not be acceptable to the communities to whom they provided care.[24,25] In Rwanda, policymakers changed course after initially approving the RCT protocol because of local concerns. While one could argue effective dialogue with communities could mitigate concerns, in an emergency setting, these conversations are often not possible. Ultimately, the ethical problems of going against local perspectives and sewing distrust in health systems far outweigh the benefits of RCTs.

Conclusion:

An analysis of Rwanda's decision-making reveals that the public health response to emerging outbreaks requires a flexible approach. While randomized controlled trials are the best choice for scientific validity, the ethical principles of justice, risk-benefit analysis, and community engagement may supersede gold-standard methodology. Rwanda took the ethical course of action by deciding to forgo a randomized trial for the Sabin vaccine. By listening to its population, they fostered more trust in their health system while also collecting socially valuable data about safety. Context matters when making difficult decisions about public health. Without community buy-in, any intervention is unlikely to succeed.

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