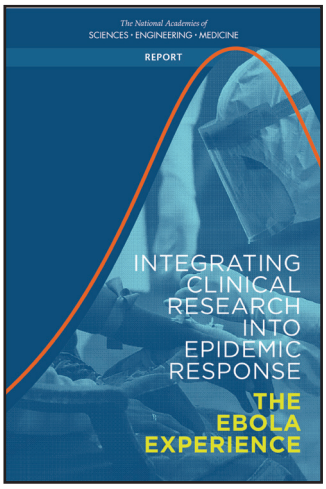
Report
HIGHLIGHTS

April 2017

Integrating Clinical Research into Epidemic Response

The Ebola Experience



The 2014 Ebola epidemic in western Africa was the longest and deadliest Ebola outbreak in history, resulting in 28,616 cases and 11,310 deaths. At the time, little was known about how to best manage patients to improve survival. There were no approved medicines to treat or prevent Ebola, only a few potentially useful agents with limited study. Given the nature of the disease and its high mortality rate, it was not feasible to perform clinical trials to investigate safety or efficacy until a natural outbreak of sufficient size and duration took place. The 2014–2015 Ebola epidemic presented such a situation.

With support from the Office of the Assistant Secretary for Preparedness and Response, the National Institute of Allergy and Infectious Disease, and the U.S. Food and Drug Administration, the National Academies of Sciences, Engineering, and Medicine convened a committee to analyze the clinical trials that were conducted during the epidemic. The resulting report, *Integrating Clinical Research into Epidemic Response: The Ebola Experience,* assesses the value of the trials and makes recommendations about how the conduct of trials could be improved in the context of a future international emerging or re-emerging infectious disease event.

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ASSESSMENT OF THE EBOLA CLINICAL TRIALS

The clinical trials that took place during the 2014–2015 Ebola epidemic were conducted in an atmosphere and on a timeline entirely different from most clinical trials. Trial teams faced immense logistical obstacles, including limited health and health research infrastructure, fear, rumors, lack of trust, and supply chain hurdles. They should be praised for addressing and overcoming them in the face of pressing need.

Yet given the resources, time, and effort put into these trials, they were not as successful as they could have been. None of the therapeutic trials were able to reach definitive conclusions about efficacy. Some of the inconclusive trials may have actually set back the search for safe and effective therapeutics. The results of the vaccine trials were more fruitful. There are two Ebola vaccine candidates that current data suggest may be safe and immunogenic, and one that is most likely protective, though more testing is needed.

Planning and conducting clinical research during the Ebola epidemic also required confronting a number of ethical issues. Stakeholders debated whether it was ethical to conduct clinical trials at all in the midst of a public health emergency. Researchers disagreed on how clinical trials should be designed during the Ebola epidemic, weighing the process of randomization, or comparing one or more groups receiving the medications being studied to a group only receiving standard medical care, against ethical concerns around depriving any patients of potential benefit from medications being studied in these circumstances.

The committee concludes that the randomized controlled trial (RCT) was an ethical and appropriate design to use, even in the context of the Ebola epidemic, stating that RCTs are the most reliable way to identify the relative benefits and risks of products being studied. Except when rare circumstances are applicable, every effort should be made to implement RCTs during epidemics. Randomization can take many forms (e.g., individual randomization, cluster randomization, adaptive trial designs), and trial teams conducting research during future epidemics will need to assess the specific context in order to determine the best trial design.

THE COMMITTEE'S RECOMMENDATIONS

The mobilization of a rapid and robust research response during the next epidemic will depend not just on what happens during the epidemic, but on what happens before or between epidemics. The committee's recommendations stem from the Ebola experience but apply to the conduct of clinical trials during epidemics more broadly. To this end, the recommendations focus on three main areas: strengthening capacity, engaging communities, and facilitating international coordination and collaboration. The figure below incorporates these recommendations into a visual representation of an idealized timeline of activities necessary to launch a clinical trial within the course of outbreak.

To read the full text of the recommendations, please visit nationalacademies.org/EpidemicClinicalTrials.

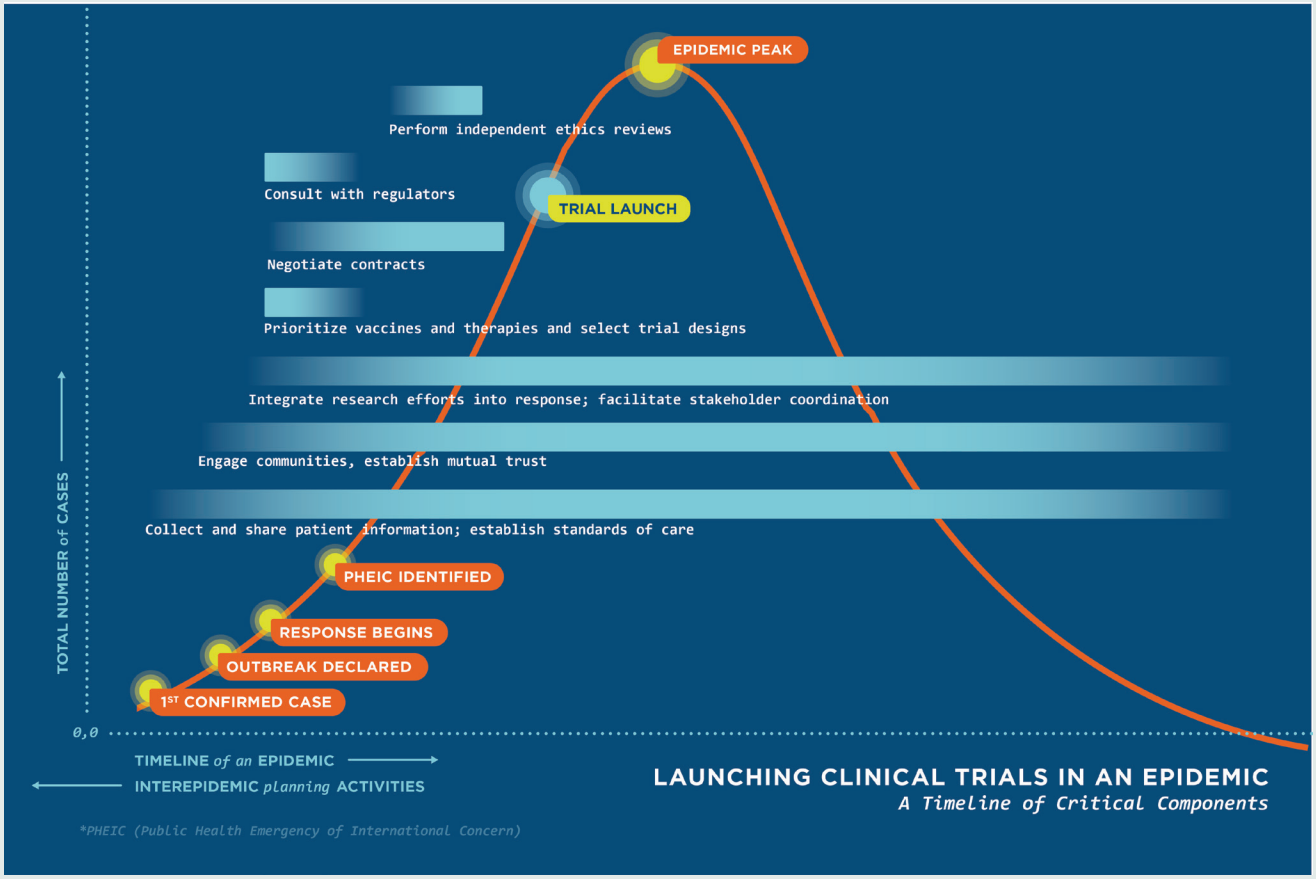

Figure **The seven key components identified here, if done in an efficient, coordinated, and timely manner, would enable trials to be launched before reaching the peak of the epidemic.**

Preparation now will enable moving forward with sound clinical trials that have the best chance of identifying new vaccines and therapies that will improve our ability to respond to infectious disease outbreaks and provide care for future populations.

Strengthening capacity

The three countries most affected by the Ebola epidemic—Guinea, Liberia, and Sierra Leone—were ill equipped to respond to or support clinical research during an epidemic. Lack of clinical experience with Ebola and poor surveillance and laboratory capacity hindered attempts to control the outbreak.

Collection of patient-level data, which provides critical clues to better patient management, also was a challenge, due to poor health infrastructure and a shortage of health care personnel. Stakeholders must work collaboratively to improve capacity to collect and share data before an epidemic begins. At the start of an outbreak, developed nations and research funders should provide resources to enable data collection.

Building capacity for research cannot—and should not—be separated from building health systems capacity in general; to be most effective, clinical research needs to be embedded within the health care system. Funders and development agencies should provide resources and assistance for the development of core capacities in low- and middle-income countries. Stakeholders also should work with these countries to help them develop capacity to quickly negotiate legal agreements, complete ethics reviews, and develop clinical trial templates to better respond in an epidemic. Research systems should be incorporated into these countries' emergency preparedness and response systems.

Engaging communities

During the Ebola epidemic, there was a great deal of fear, mistrust, and misunderstanding between the affected communities and the response and research staff. Communication and community engagement improved over the course of the epidemic, resulting in an improved acceptance of and participation in infection control and research efforts.

The committee found that the success of clinical research is dependent on the community's understanding of, engagement in, and sense of involvement and respect in the process of planning and conducting research. For this reason, community engagement should be prioritized during epidemic responses and should involve people trained in social and communication sciences. Engagement should be a continuous and evolving effort that begins at the outset of the epidemic.

Facilitating international coordination and collaboration

Emerging infectious disease outbreaks can quickly become globalized, calling for a global solution. Better coordination of international research efforts taking place sooner could have led to a safe and effective medicine that might have been deployed during the epidemic—and at the outset of the next one.

A coalition of stakeholders should work during the inter-epidemic period to: advise on and invest in priority pathogens to target for research and development, develop generic clinical trial design templates, and identify teams of clinical research experts who could be deployed to assist with research during an outbreak. This international coalition could also discuss and agree on methods to address administrative requirements that would rapidly become high priority during an outbreak, such as the location and management of a central data repository.

Coordination of international research efforts must continue after an outbreak begins. To that end, the international coalition of stakeholders should convene an independent rapid research response workgroup with the expertise to appraise and prioritize products for trial, determine which trial designs are best suited for the circumstances, and monitor and evaluate the trials. This workgroup would include national leadership and community representatives from affected countries and ensure that resources are allocated efficiently and effectively, that the goals of the response and research activities are clear and agreed upon, and that community engagement and communication strategies are aligned.

CONCLUSION

Careful inter-epidemic planning and execution through a well-coordinated and collaborative effort from national, international, and local representatives can help ensure that the global community is prepared to answer challenging questions through the conduct of research. Considerable, sustainable investments will be required to achieve this, though the options are to invest now or pay later, when an outbreak strikes. Preparation now will enable moving forward with sound clinical trials that have the best chance of identifying new vaccines and therapies that will improve our ability to respond to infectious disease outbreaks and provide care for future populations.

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