ANNUAL REVIEWS

Annual Review of Virology

Ethics of Conducting Clinical Research in an Outbreak Setting

Kathryn M. Edwards[1] and Sonali Kochhar[2,3]

[1]Division of Pediatric Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA; email: Kathryn.edwards@vumc.org

[2]Global Healthcare Consulting, New Delhi 110024, India

[3]Department of Global Health, University of Washington, Seattle, Washington 98104, USA

Annu. Rev. Virol. 2020. 7:475–94

First published as a Review in Advance on March 25, 2020

The *Annual Review of Virology* is online at virology.annualreviews.org

https://doi.org/10.1146/annurev-virology-013120-013123

Keywords

ethics, clinical research, outbreak, epidemic, Ebola, pregnant women, coronavirus

Abstract

The conduct of clinical trials during the West Africa Ebola outbreak in 2014 highlighted many ethical challenges. How these challenges were addressed, what clinical studies were conducted during that outbreak, and the lessons learned for dealing with future outbreaks were the subject of a National Academy of Medicine committee report titled *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. This report suggested improvements for research during subsequent emerging or re-emerging outbreaks and is summarized in this review. We also discuss the current Ebola outbreak in the Democratic Republic of the Congo and highlight how the dialogue has changed and how successful clinical trials have been implemented. We conclude with a description of productive efforts to include pregnant women and children in therapeutic and vaccine trials during outbreaks that are currently ongoing.

1. INTRODUCTION

The Ebola outbreak in West Africa in 2014 resulted in 28,616 cases and 11,310 deaths (1, 2). At the onset of the outbreak there was little knowledge of how to manage the infected patients and how to prevent transmission to family members and health care workers. There were no licensed vaccines or therapeutics. Preclinical Ebola trials had been conducted with only a few agents in nonhuman primates (3, 4). The potential to conduct clinical trials within the evolving clinical setting was hotly debated. How the debate emerged, what clinical trials were ultimately successfully conducted, and what new information was gained formed the basis of a National Academy of Medicine (NAM) committee report commissioned by the US Assistant Secretary of Preparedness and Response, the National Institute of Allergy and Infectious Disease (NIAID), and the Food and Drug Administration (FDA). The resulting report, *Integrating Clinical Research into Epidemic Response: The Ebola Experience* (2), made recommendations about the conduct of future clinical trials and suggested improvements for subsequent outbreaks. One of the authors of this manuscript was a member of that committee (K.M.E.).

In this review, we summarize findings of the NAM report. We then turn to the current Ebola outbreak in the Democratic Republic of the Congo (DRC) and highlight the lessons learned in combating this new outbreak. Finally, the exclusion of pregnant women and children from the therapeutic and vaccine trials in the West African Ebola outbreak in 2014 was problematic. One of us has been involved in ongoing efforts to address these exclusions (S.K.), and we conclude with a description of these efforts.

2. THE WEST AFRICAN EBOLA OUTBREAK IN 2014: THE NATIONAL ACADEMY OF MEDICINE REPORT

2.1. Ethical Concerns

Many international thought leaders (5), including members of the World Health Organization (WHO) Ethics Working Group (6), stated that there was an ethical obligation to conduct research during the Ebola epidemic (5–8). However, some health care workers providing bedside care in the Ebola treatment units believed that it was impossible to deliver optimal clinical care and conduct meaningful research (2). Although outbreaks stress the medical infrastructure, particularly in countries with few existing resources, they are often the only period available with adequate numbers of infected patients to conduct meaningful clinical trials of therapeutics and vaccines. Another problematic aspect of the dialogue surrounding clinical trials during the West Africa Ebola outbreak was the very high case fatality rate. Assignment to the placebo control group was often perceived as a death sentence. This concern was further complicated by the fact that several international health care providers contracted Ebola in Africa and were promptly evacuated to medical care facilities in the United States and Europe where they received unlicensed therapeutic agents through compassionate clearance and were not subjected to enrollment into randomized clinical trials (9). Their survival rates were higher than those seen in Ebola virus–infected patients in Africa, and this improved survival led to further concern in the African communities that were affected by the disease. An impassioned call was made to provide these therapeutic agents to the thousands of African patients, not just the international workers who were infected (10).

The inclusion of placebos in the clinical trials was also highly controversial. Because of the very high death rate, many suggested that all subjects enrolled should receive experimental treatments and none should be assigned to the placebo group (7). Some thought that historical controls (11) could be chosen from a similar group of subjects treated in the past and compared with those being currently treated with the new intervention. However, this approach did not prove reasonable, as the prognosis varied depending on the treatment site and the time when patients were treated. It

was also not possible to ensure that all important prognostic variables, including those not measured or unknown, were balanced across the intervention groups. New diagnostic methods were continually evolving, which allowed earlier detection of disease, and supportive care improved as the outbreak progressed. A paper in the *New England Journal of Medicine* published in 2014 by Schieffelin et al. (12) reported an overall 74% mortality in 106 patients treated in Sierra Leone with a mortality rate of 94% seen in those over 45 years of age. In contrast, Ansumana et al. in 2015 (13) reported on 581 patients also treated in Sierra Leone who had an overall mortality of 31%, with a decrease in the mortality rate from 48% to 23% in the few months between September and December 2014. Finally, Uyeki et al. (14) reported that the overall mortality rate in the 27 international workers who acquired Ebola in Africa and were treated in the United States and Europe was 18.5%. Thus, these studies provided a compelling rationale for the use of contemporaneous controls from the same study setting in the study design to appropriately judge the effect of the intervention.

Based on earlier conclusions reached about the ethics of conducting research on the treatment of human immunodeficiency virus (HIV) (15), seven core scientific and ethical requirements were identified by the NAM committee report (2) that were recommended to guide clinical research conducted during epidemics. These are scientific and social value, respect for persons, community engagement, concern for participant welfare and interests, a favorable risk-benefit balance, justice in the distribution of benefits and burdens, and post-trial access to the tested agents that had been proven effective (16–22). The integration of these seven core requirements is illustrated in **Figure 1** and highlights how clinical trials should optimally be initiated prior to the peak of the epidemic.

2.1.1. Scientific and social value. A clinical study's value depends on the quality of the scientific information produced and the relevance of the information to addressing public health and

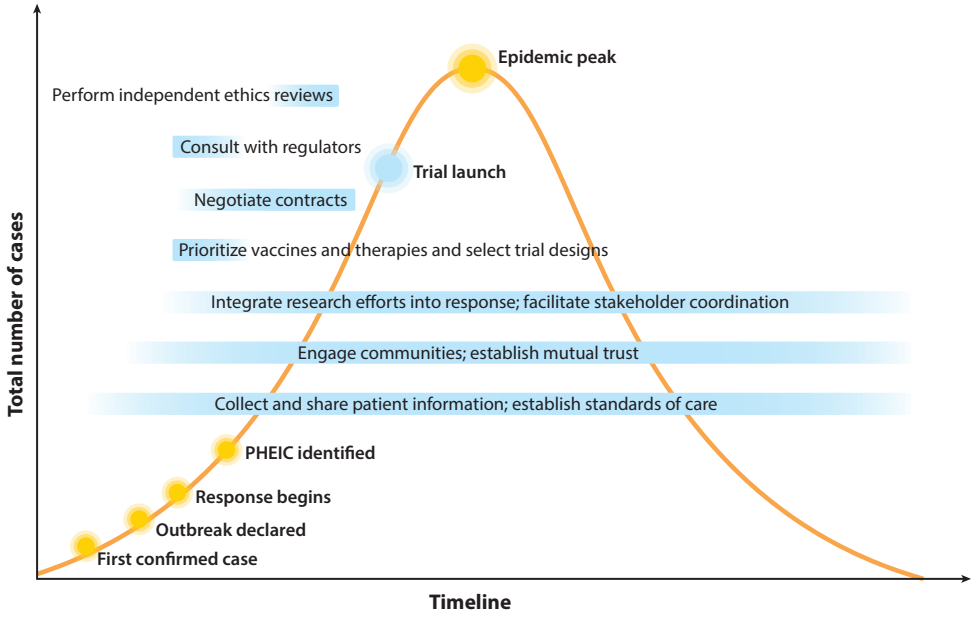

Figure 1

A timeline for launching critical components for clinical trials in an epidemic. Abbreviation: PHEIC, Public Health Emergency of International Concern. Figure adapted with permission from Reference 2.

clinical issues (22). The knowledge gained must justify the risks to the subjects and the costs associated with the trials (16, 18, 22). Clinical trials conducted during outbreaks should generate data that are reliable to guide public health practices and meet regulatory standards so that interventions found to be safe and effective can be approved and registered for use in future outbreaks (22).

2.1.2. Respect for persons. Clinical research during an outbreak must demonstrate respect for the trial participants and communities where the research is conducted. This respect includes providing understandable, relevant, and reliable information to potential study participants about the need for the research, the choices available to them, the risks and benefits of each option, and what will happen if they choose or decline to participate in the research (16–22). Individuals, or their proxies, must provide informed consent to participate in the research based on their full understanding of what is being proposed (16–22).

2.1.3. Community engagement. In outbreaks, there is great uncertainty and there are increased levels of stress and discord. During such times, communication channels must be open and messages clear. Information about the clinical research must be carefully articulated and include clinical trial design, risks and benefits of research participation, how randomization will be managed, the existing standard of care available without participation in the study, and whether a placebo control arm will be included. Although there are challenges, it is critical to engage communities early in the dialogue about the study design to enable informed decision-making (22).

2.1.4. Concern for participant welfare and interests. The risk to the clinical trial participants must be limited to what is necessary for sound scientific research but must not cause unnecessary risks (21, 22). In addition to concerns about study risks, other potential risks include harm due to confidentiality breaches and the stigma associated with participation (20). Researchers must always optimize the benefits to the trial participants (22–24).

2.1.5. Favorable risk-benefit balance. Research must be designed to maximize the benefits while minimizing the potential harm to study participants (17, 22, 23). Research should be conducted only when there is a state of equipoise (25) in which there is true uncertainty that one of the interventions is superior to the others. In a state of equipoise, it is ethical to allow participants to be randomly allocated to receive one or more of these interventions and to observe, measure, and document the outcome. Randomized clinical trials that increase the prospect of obtaining information that will help to resolve this uncertainty are likely to have significant scientific and social value.

2.1.6. Justice in the distribution of benefits and burdens. Both the risks and the benefits of research during an outbreak must be distributed fairly. Research should not focus on the health needs of some groups while neglecting the needs of others. During outbreaks, research subjects are particularly vulnerable to exploitation due to disease, marginalization, or deprivation, but they also have unique health needs that can be studied only in the epidemic situation. Conducting clinical research in outbreaks helps to effectively and safely address the current health needs and those in future outbreaks.

2.1.7. Post-trial access. If an investigational agent is shown to be safe and effective, then there is an ethical obligation to provide post-trial access of the product to the communities that participated in the clinical studies (22, 23). Before the study begins it should be determined who will bear the cost of delivering successful treatments: the research sponsor, the manufacturer,

the participants, the host nation, or some other entity. For the West Africa Ebola epidemic of 2014–2015, the US Assistant Secretary for Preparedness and Response at the Department of Health and Human Services had given a commitment for providing access to any investigational product found to be safe and effective (2).

2.2. Summary of Therapeutic Research Conducted in the 2014 Ebola Outbreak

After extensive discussion of clinical trial design for therapeutic trials associated with the outbreak, the WHO Ethics and Scientific and Technical Advisory Committees convened and reached several conclusions. The WHO Ethics Working Group stated that single-arm studies that used nonrandomized historical control data have "a high risk of bias and may lack internal validity" (26). However, they softened their recommendations and stated, "In principle, so long as standard requirements for human research ethics are met, all scientifically recognized methodologies and study designs should be considered as ethically acceptable—whether they are placebo-controlled randomized trials or trials that don't involve randomization to control groups" (26). The WHO Scientific and Technical Advisory Committee on Ebola Experimental Interventions met 1 month later and stated that "it was likely that for anti-Ebola treatments that did not have large effects, randomized concurrently controlled trials may be needed" (27).

Ultimately, formal clinical trials were conducted on five investigational therapeutic agents in the three countries most affected by the epidemic. **Table 1** provides a summary of those trials. In general, the results of the therapeutic studies were disappointing, and none of them concluded that there was definitive therapeutic benefit. The epidemic was waning at the onset of the trials, making it impossible to enroll the sample sizes needed to reach definitive endpoints. In addition, because the trials were designed as single-arm trials with historical controls, conclusive evidence of effectiveness could not be obtained. Only ZMapp (an experimental combination of three chimeric monoclonal antibodies directed against Ebola virus) showed promise as a possible effective treatment, but there were insufficient data to determine with certainty whether it was a better treatment than supportive care alone (28). Thus, in summary, the overall yield of the therapeutic trials was described as "scientifically thin" in a special report in *Science* (29).

2.3. Summary of the Vaccine Trials Conducted in the 2014 Ebola Outbreak

The vaccine trials conducted during the West African Ebola outbreak progressed more rapidly than the therapeutic trials because several of the vaccine candidates had already been tested in preclinical studies in nonhuman primates (30, 31). Regulators worked closely with the vaccine investigators to expedite the studies. For example, a first-in-human phase 1 trial was approved by regulators in the United Kingdom within only 4 working days. The design of the vaccine trials was

Table 1 Summary of therapeutic trials conducted during the West African Ebola outbreak

Study product	Trial location(s)	Design	Timeline	Result(s)
Convalescent sera	Guinea	Nonrandomized, open label	February 2015	No improvement
Favipiravir	Guinea	Nonrandomized, open label	December 2014	Inconclusive
Brincidofovir	Liberia	Single arm	January 2015	Study stopped
TKM-130803	Sierra Leone	Single arm	March 2015	Ineffective
ZMapp	Liberia, Guinea, Sierra Leone, United States	Randomized, open label; control group was standard of care	March 2015	Possibly effective; inconclusive results

also controversial. In September 2014 the WHO organized a meeting to discuss the clinical trials for candidate Ebola vaccines. Two of the available experimental vaccines, the GlaxoSmithKline chimpanzee adenovirus 3 (CHAd3) vaccine and the Newlink recombinant vesicular stomatitis virus (rVSV) vaccine, were the only vaccine candidates that met the WHO criteria for study: "availability of good manufacturing practice grade vials after lot release for clinical trials, and 100% efficacy that had been documented in nonhuman primates with acceptable preclinical safety" (32, p. 6).

The ethical concerns surrounding the vaccine trials were slightly different than those of the therapeutic trials. Vaccine recipients were not already infected with Ebola and not in immediate danger of death. There were also safety concerns associated with vaccine administration to healthy subjects, but some commented that they were smaller than the risks of not providing the investigational agent (33). One ethicist stated, "[I]t is not so clear that when not infected [a person] would or should be willing to accept an unknown risk from an unlicensed preventive vaccine, given that other measures such as good quality protective equipment, if properly used, may reduce the risk of infection to an acceptable level" (34, p. 108). There was also concern that the vaccine might make an individual feel that they were protected from infection and they would forego safety precautions and the use of personal protective equipment while caring for Ebola patients. This concept of risk compensation behavior had been proposed with HIV prevention strategies (35). Finally, it was thought possible that vaccines could enhance disease severity if the vaccine recipient was infected with the natural circulating pathogen. Such disease enhancement, with several deaths, had been reported in young children who received a formalin-inactivated respiratory syncytial virus (RSV) vaccine and were subsequently infected with natural RSV several decades ago (36).

Like with the therapeutic studies, selecting the control arm for the Ebola vaccine trials proved to be one of the most controversial issues. There were three main control options: a placebo control, an active non-Ebola vaccine control, or delayed vaccination with the experimental vaccine (37). The placebo control was considered by some to be unethical because it did not provide protection to the research participants (38). Many argued that using an active non-Ebola vaccine control would be preferable. Another stated, "An RCT may yield results faster, but if it's simply unacceptable for trial participants, a stepped-wedge design is preferable" (39, p. 290). A stepped-wedge trial design had benefits because it provided an intervention to all participants over time, either as individuals or in clusters. It also enabled all participants to receive the intervention by the conclusion of the trial, although administration of the vaccine was delayed for some. Although the stepped-wedge design had limitations, including the inability to evaluate the safety of the vaccine over a longer period, it became an attractive trial design (39).

Four phase 2/3 clinical vaccine trials were conducted in West Africa during the outbreak. They are summarized in **Table 2**. Like the therapeutic trials, the vaccine trials began as the outbreak waned but yielded more useful results. The Guinea ring-vaccination study (Ebola ça Suffit) evaluated the rVSV vaccine using an open-label, cluster-randomized ring-vaccination trial, in which suspected cases of Ebola virus disease (EVD) in Guinea were ascertained by Ebola surveillance teams, and efficacy for prevention of subsequent disease was demonstrated. This trial was the only vaccine trial that yielded efficacy data. However, because all participants were immunized by day 84 of the study and because no sera were collected during the trial, long-term safety or efficacy and immunological correlates of protection could not be determined (40). The results of the Partnership for Research on Ebola Virus in Liberia (PREVAIL) trial, a randomized, placebo-controlled trial that included both CHAd3 and rVSV, provided long-term serologic and safety data, but because vaccine efficacy could not be determined, the trial could not provide correlates of protection (41). The Centers for Disease Control and Prevention (CDC)-coordinated Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) employed the rVSV Ebola vaccine

Table 2 Summary of vaccines studied in the West African Ebola outbreak

Vaccine	Phase	Location	Trial start	Number of participants	Result(s)
VSV-EBOV: Guinea ring trial (120)	3	Guinea	April 1, 2015	7,284	Effectiveness of vaccine demonstrated
VSV-EBOV: CDC STRIVE (121)	3	Sierra Leone	April 9, 2015	8,673	Unable to demonstrate efficacy; safety and immunogenicity shown
VSV-EBOV/ChAd3: PREVAIL I (122)	2	Liberia	February 2, 2015	1,500	Unable to demonstrate efficacy; safety and immunogenicity shown
EBOVAC-Salone: Ad26.ZEBOV and MVA-BN-Filo (43)	Stage 3	Sierra Leone	October 8, 2015	1,023	No data on safety and immunogenicity available

Abbreviations: CDC, Centers for Disease Control and Prevention; ChAd3, chimpanzee adenovirus type-3; EBOV, Ebola virus; PREVAIL, Partnership for Research on Ebola Virus in Liberia; STRIVE, Sierra Leone Trial to Introduce a Vaccine against Ebola; VSV, vesicular stomatitis virus.

in a randomized, unblinded phase 2/3 trial with phased vaccine introduction, no placebo, and concurrent evaluation of vaccine safety and efficacy (42). Overall, the vaccine was safe without significant vaccine-related adverse events. The EBOVAC-Salone study (43) was implemented in Sierra Leone to assess the safety and immunogenicity of the adenovirus-vectored Ebola vaccine with a boost with a vaccinia vector against Ebola and Marburg (Ad26.ZEBOV/MVA-BN-Filo prime-boost regimen). The study recruited participants both during and after the outbreak, but no data are published that describe the safety or immunogenicity of the vaccine.

2.4. Recommendations of the National Academy of Medicine Committee for Future Outbreaks

The NAM committee acknowledged that future epidemics of Ebola or other emerging pathogens would occur and that planning for these outbreaks was needed during the interepidemic periods. Three specific areas were targeted for preparation: strengthening capacity, engaging communities, and facilitating international coordination and collaboration. It was also acknowledged that adequate funds would be needed to accomplish initiatives in these areas. For diseases such as Ebola, where human challenge studies cannot safely be done, outbreaks are the only way to evaluate the efficacy of therapeutics and vaccines. Also, because no serologic correlates of protection (44) were established during the initial Ebola vaccine trials, measurement of antibody levels could not be translated into vaccine effectiveness.

2.4.1. Strengthening capacity. The three countries most affected by the Ebola outbreak, Guinea, Liberia, and Sierra Leone, were among the poorest countries in the world. According to the United Nations Human Development Index, Guinea ranked 179, Liberia ranked 175, and Sierra Leone ranked 183 of 187 countries ranked (45). The committee identified six major capacity issues that markedly hindered the research response: (1) lack of clinical experience with Ebola; (2) weak surveillance and laboratory capacity; (3) poor medical infrastructure and few trained health care workers; (4) small pool of clinical research experts and very limited prior experience in the conduct of clinical research; (5) inexperienced in-country ethics review boards that lacked the resources, experience, training, and information management systems; and (6) lack of experience and expertise in completing the various and complex legal and bureaucratic steps for clinical trial conduct (48). The committee concluded that all of these inadequacies should be addressed in preparation for future outbreaks.

2.4.2. Community engagement. Rumors abounded at the onset of the outbreak about the source of Ebola virus and the role of developed countries in causing the outbreak (45, 46). Because of these rumors, there was initial distrust of local and national governments and international scientists who came to assist with the outbreak. Initial planning was mostly top-down with little community input or respect for community traditions or religion, particularly around burying the dead. With time, communications improved, local communities became more involved, and international researchers engaged community leaders (47, 48). The NAM report strongly supported early input of social scientists to facilitate community engagement in subsequent outbreaks. It also stressed that community leaders should participate from the onset in response planning, public health management, and research conduct. Such collaboration would be markedly enhanced if during the interepidemic periods meaningful interactions between the community and the public health sector could be established. The report also suggested that partnerships that were established during the outbreak should be maintained and strengthened afterward (49).

2.5. Facilitating International Coordination and Collaboration

The NAM report highlighted that the discovery process for new therapeutic agents and vaccines and the infrastructure for trial conduct would be best accomplished through an international collaborative effort consisting of stakeholders from governments, foundations, pharmaceutical companies, academia, humanitarian organizations, and the WHO. It also suggested that this collaborative international effort should prioritize pathogens to target for research; develop generic clinical trial templates during the interepidemic periods that could be adapted rapidly for phase 1, 2, and 3 clinical trials; develop systems to prioritize available vaccine and therapeutic agents for evaluation during the outbreaks; and establish expertise in trial monitoring to ensure transparency and accountability.

2.6. Expert Advisory Panels Formed

Several initiatives were forged after the 2014 West African outbreak to prepare for subsequent outbreaks. In addition, two (50) Ebola expert advisory panels called for a new global financing mechanism to invest 1 billion USD annually and recommended a strong convening and normative role for the WHO (51, 52). In addition, the WHO prioritized diseases and pathogens with epidemic potential (53) and developed a research and development (R&D) blueprint to coordinate its own and other stakeholders' work (54). The WHO Blueprint for Action was developed to address the challenges of evaluating unlicensed vaccines during outbreaks (55). The focus of this initiative was to develop guidelines for the conduct of trials of vaccine candidates within the context of the "scientific, ethical, and logistic issues arising during public health emergencies" (56). The participants in this initiative acknowledged that each outbreak with unique pathogens posed different challenges. They also noted that if multiple candidates were available for study, there should be a prioritization of the best candidates and trial sites. The necessity to integrate research into the comprehensive public health response without jeopardizing clinical care was also stressed. Finally, they reiterated that communities have to be involved in the study conduct.

The Blueprint for Action report was also unique in that it proposed several alternative study designs, in addition to the more standard double-blind, placebo-controlled, individually randomized vaccine trials. Clinical study endpoints were discussed, and laboratory-confirmed disease was supported as the optimal way to evaluate the efficacy of the vaccine. Serologic studies of vaccine recipients were also supported because the establishment of serologic correlates of protection could be used subsequently to predict vaccine effectiveness. Randomization was proposed as a

critical part of trial design, and the inclusion in each study of a comprehensive data monitoring plan was proposed.

The WHO also established a group to address the ethical framework of the use of unlicensed products during an outbreak. The group, known as Monitored Emergency Use of Unregistered Interventions (MEURI) (57), proposed several criteria for which patients might access investigational therapeutic agents on an emergency basis outside of clinical trials. The products considered for use were those that had shown promising safety and efficacy in the laboratory and in relevant animal models but had not been evaluated in clinical trials. This was a positive step given the controversy this engendered during the West African outbreak. The criteria needed for access to investigational agents were as follows:

1. There is no proven effective treatment.
2. It is not possible to initiate clinical studies immediately.
3. There are existing preliminary data that support the efficacy and safety of the product, and an appropriately qualified scientific advisory committee has deemed the product has a favorable risk-benefit ratio.
4. The relevant country authorities and an appropriately qualified ethics committee have approved the study.
5. Adequate resources are available to ensure that risks are minimized.
6. Informed consent was obtained.
7. The emergency use of the intervention is closely monitored, and the results of the intervention are shared in a timely manner with the wider medical and scientific community.

2.7. Coalition for Epidemic Preparedness Innovations

Another innovative and highly productive group to support vaccine development, the Coalition for Epidemic Preparedness Innovations (CEPI), was formed in 2017 (58–61). This group is a partnership launched between public, private, philanthropic, and civil society organizations to develop vaccines for future epidemics and ensure equitable access to the vaccines for people during epidemics. CEPI aims to advance vaccines against prioritized diseases through proof-of-concept and clinical-safety testing and stockpiling of the investigational vaccine candidates before epidemics begin; funding innovative and new platform technologies to accelerate the development and manufacture of vaccines against previously unknown pathogens; and supporting and coordinating activities to improve the collective responses to epidemics, strengthen capacity in at-risk countries, and advance the regulatory science for vaccine development (62). CEPI is currently funding vaccine candidates against its priority pathogens [Middle East respiratory syndrome coronavirus (MERS-CoV), Nipah virus, Lassa fever virus, chikungunya virus, and Rift Valley fever virus] and vaccine platforms against unknown pathogens (referred to as Disease X). To assess the effectiveness of the vaccine platforms, additional vaccine candidates are being developed (including influenza virus, Marburg virus, rabies virus, RSV, and yellow fever virus) (63).

3. THE EBOLA OUTBREAK IN THE DEMOCRATIC REPUBLIC OF THE CONGO

The world's second largest Ebola epidemic on record was declared on August 1, 2018, in the North Kivu and Ituri provinces of the DRC. Since then, cases also have been reported in South Kivu (64, 65). Widespread violence in the provinces, resulting from conflicts among numerous armed groups, has limited access to infected patients, and a strike of area health care due to nonpayment of salaries likely resulted in a delayed response. However, since the West Africa Ebola outbreak

in 2014, there have been substantial improvements in medical management, including better supportive care, accessible Ebola treatment centers, new treatments, and an effective vaccine. Yet, the case fatality rate remains at 66%, the number of cases continues to increase 18 months into the epidemic, and people are dying at home or in general health care centers. There is widespread community mistrust, and violent attacks on health workers and Ebola responders have occurred. There is also resentment over security forces surrounding the response (64–67).

The WHO MEURI panel supported the conduct of a comparative trial in the DRC with four therapeutic agents: ZMapp (a monoclonal antibody cocktail), remdesivir (GS-5734) (an antiviral drug), REGN3470-3471-3479 (a monoclonal antibody cocktail), and mAb114 (a monoclonal antibody) in very early stages of development. The results from this trial were reported on December 12, 2019, in the *New England Journal of Medicine* (68). The investigational therapies were compared in patients of any age who had a positive reverse transcriptase–polymerase chain reaction result for Ebola virus RNA and provided informed consent. The enrolled patients received standard of care and were randomly assigned in a 1:1:1:1 ratio to intravenous administration of one of the four agents. Those receiving REGN-EB3 were added later in the study and compared only with those receiving ZMapp who were enrolled contemporaneously (the ZMapp subgroup). The primary endpoint was death at 28 days. A total of 681 patients were enrolled from November 20, 2018, to August 9, 2019, when the Data Safety Monitoring Board assessed the interim outcome data and recommended that all subsequent patients be assigned to either the mAb114 or REGN-EB3 groups. Mortality data at 28 days showed that 61 of 174 patients (35.1%) in the mAb114 group had died, as compared with 84 of 169 (49.7%) in the ZMapp group ($P = 0.007$) and 52 of 155 (33.5%) in the REGN-EB3 group, as compared with 79 of 154 (51.3%) in the ZMapp subgroup ($P = 0.002$). Both a shorter duration of symptoms before admission and lower baseline values for viral load, serum creatinine, and aminotransferase levels correlated with improved survival. It was reassuring that ethical and scientifically sound research could be conducted during an Ebola outbreak in the DRC through the enrollment of an adequate number of subjects to provide the power to differentiate the benefits of the different agents. These findings are important, as the benefit of ZMapp could not be definitively determined in the West African Ebola outbreak due to study design and inadequate numbers of subjects recruited (69).

4. THE ETHICS OF ENROLLING PREGNANT WOMEN AND CHILDREN IN RESEARCH DURING OUTBREAKS

Compared to the general population, pregnant women are often at greater risk for significant morbidity and mortality from epidemic diseases, including Ebola, Lassa fever, and influenza (70). Other epidemics in pregnant women, such as Zika and measles, have also had tragic consequences for their offspring (71, 72). During the recent Ebola outbreaks, maternal mortality rates between 89% and 93% with 100% fetal or neonatal mortality have been reported (73). Because of concern for transmission of Ebola through blood and body fluids, caregivers have also been reported to be hesitant to attend deliveries or assist with complicated miscarriages, further increasing maternal and neonatal mortality (74).

Historically, pregnant women and children (75) have been excluded from most clinical trials because they have been considered members of vulnerable populations. It has been stated that they would be more vulnerable to the adverse effects of study interventions than nonpregnant adults. However, the data to support such exclusions are sparse. It has also been stated that pregnant women and children are more prone to coercion or undue influence, but again the data to support these statements are lacking. Because of such concerns, guidelines have been proposed to provide safeguards for pregnant women and children (76, 77). However, in their attempts to protect

pregnant women and children, these guidelines have contributed to an increased reluctance to test products in these populations, which has led to a paucity of information about the safety and efficacy of approved therapeutics and vaccines in both pregnant women and their infants (78, 79). In the early days of the HIV epidemic, when no effective treatments existed, prohibiting pregnant women and children from clinical trials deprived them of what might have been their only opportunity to receive potentially effective treatments. At that time, one author concluded that many patients were being "protected to death" (80, p. 2). However, over the last several decades, the momentum has shifted to actively including pregnant women and children in clinical trials, and more recently, vaccines specifically targeted for pregnant women have been developed (81).

Pregnant women are capable of making decisions about their own medical care, but the experimental products they receive have the potential to cross the placenta and adversely affect the fetus (82). Although clinical trials in pregnant women have revealed some differences in drug pharmacokinetics (83), vaccine responses in pregnant and nonpregnant women have been generally comparable (84). Because of the reluctance to enroll pregnant women in clinical trials, observational studies and post-licensure analyses of large linked databases provide the bulk of safety information concerning immunization during pregnancy (85). Provided with the potential risks and benefits of the experimental product and available evidence for safety, pregnant women are capable of judging their participation in a clinical trial, just as they decide about their routine care. A 1994 Institute of Medicine report titled *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* stated, "Pregnant women should be presumed to be eligible for participation in biomedical research" (78, p. 59). In spite of this encouragement, disappointingly Shields & Lyerly (86) reported in 2013 that nearly 95% of phase 4 studies that potentially could have included pregnant women chose to exclude them. This led some to conclude, "As with other traditionally excluded populations, progress will not happen until we shift the burden of justification from inclusion to exclusion" (82, p. 9).

In 2017 the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) was revised, and it removed pregnant women as a population that was "potentially vulnerable to coercion or undue influence" (87, p. 4). The subsequent US 21st Century Cures Act established a Task Force on Research Specific to Pregnant Women and Lactating Women whose duty was to provide safe and effective therapies for pregnant and lactating women (88).

But despite the increased efforts to include pregnant women in clinical trials, their inclusion has been slow to be implemented. Since the beginning of the current Ebola outbreak in the DRC, there have been more than 3,351 Ebola cases, including more than 2,217 deaths reported (89). The WHO estimates that 56% of the cases are women and 28% are children less than 18 years old (89). More than 236,000 people have been vaccinated with the rVSV-ZEBOV vaccine in the DRC during the current outbreak. Overall, since 2015, the Ebola vaccine has been administered to more than 16,000 volunteers. Pregnant women were excluded from receiving the vaccine in West Africa, as there was thought to be insufficient evidence of vaccine safety. This decision led to anger that women were being put at unnecessary risk because of their exclusion (73, 90, 91).

To further progress in the immunization of pregnant women, a multiyear Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) project funded by the Wellcome Trust was established to develop consensus-driven, actionable ethics guidance on equitably including the interests of pregnant women and their offspring in vaccine R&D during epidemics. In 2017, guidance specific to the Zika crisis was developed (92). In 2018, a working group was formed to develop a roadmap to ensure that the needs of pregnant women and their offspring were responsibly and ethically included in the development and deployment of vaccines during epidemics (93). One of the authors of this review (S.K.) is a member of that group. As a part of this process, 22 recommendations were developed to address public health emergency

preparedness, vaccine R&D, and vaccine delivery during epidemics. These recommendations were aimed at national and international policy makers, regulatory bodies, ethics committees, oversight bodies, researchers, funders, vaccine manufacturers, and community advisory bodies. Targeted recommendations regarding clinical research were also formulated and included these:

- Suitability for use in pregnancy should be a strong consideration in the development and investment decisions for vaccines against emerging pathogens.
- When pathogens pose a risk of severe harm to pregnant women or their offspring and the most promising vaccine candidates are contraindicated for routine use in pregnancy, alternative vaccine candidates for pregnant women should be developed.
- Nonclinical studies that are a prerequisite for clinical trials in pregnant women, such as developmental toxicology studies, should be initiated early in the clinical development of promising vaccine candidates.
- Studies to assess immune responses to vaccines in pregnancy should be conducted before or between outbreaks whenever scientifically, ethically, and legally possible.
- Clinical development plans for investigational vaccines against emerging and re-emerging pathogens should include studies designed to evaluate vaccines in pregnancy. Pregnant women should have opportunities to enroll in vaccine studies conducted during epidemics whenever the prospect of benefit outweighs the risks to pregnant women, their offspring, or both.
- Vaccine studies that include women of childbearing potential should systematically collect data on immunogenicity and pregnancy-specific indicators of safety in participants who are unknowingly pregnant at the time of exposure or become pregnant within a relevant window following vaccination.
- Women participating in vaccine trials who become aware of a pregnancy during the trial should be guaranteed the opportunity, through a robust reconsent process, to remain in the trial and complete the vaccine schedule when the prospect of direct benefit from completing the schedule outweighs the risks of receiving subsequent doses.
- When a pregnant woman of legal standing consents to enroll or continue in a vaccine trial, her voluntary and informed consent should allow participation.
- Whenever possible, the perspectives of pregnant women should be considered in designing and implementing vaccine studies in which pregnant women are enrolled or in which women enrolled may become pregnant.

Finally, the PREVENT document expressed a vision statement that was particularly compelling and paradigm shifting and included three tenets: Pregnant women are not unjustifiably excluded from participating in vaccine studies, pregnant women and their offspring benefit from advances in vaccine technologies and are not left behind as new vaccine products are developed, and pregnant women have access to safe and effective vaccines to protect them and their offspring against emerging and reemerging pathogenic threats.

The PREVENT guidance recommendations were presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, an independent advisory body of the WHO, in the fourth quarter of 2018 (94). In February 2019, SAGE reversed their earlier decision to exclude pregnant women in vaccine studies and recommended that due to the severity of the epidemic, pregnant women, breastfeeding women, and infants under 1 year of age in the DRC could be vaccinated against Ebola virus. Recommendations to include pregnant women and children were also made in the ring-vaccination campaigns of contacts and contacts of contacts and geographically targeted vaccinations to prevent people at high risk from contracting the disease. SAGE also recommended that clinical trials of one or more of three other candidate Ebola vaccines be

conducted in the neighboring areas of the affected provinces and that pregnant and breastfeeding women should be included. In addition, all vaccinated pregnant women should be closely monitored for adverse events and EVD until the birth of their infants.

In June 2019, 4 months after SAGE began the process to amend the protocol to include pregnant women, the DRC Ministry of Health announced that the National Ethics Committee at the School of Public Health at the University of Kinshasa had approved an amendment to the vaccination protocol permitting administration of the rVSV-ZEBOV vaccine to pregnant women beyond their first trimester of pregnancy and to lactating women if they were identified as case contacts. Children over 6 years of age were also allowed to be vaccinated. Unfortunately, it took over 4 years from the beginning of the West African Ebola outbreak and over 10 months after the current DRC Ebola epidemic for pregnant women and children to be given the vaccine (95).

On December 19, 2019, the FDA approved Ervebo (rVSV-ZEBOV), the first vaccine for the prevention of EVD, caused by Zaire ebolavirus in individuals 18 years of age and older. The European Commission licensed the vaccine on November 11, 2019, and the vaccine has been prequalified by the WHO, a process that could speed approval in African countries (96). It is hoped that the lessons learned from including pregnant and lactating women in clinical research for Ebola vaccines will provide guidance for the clinical development of other vaccines for epidemics.

5. INCLUSION OF CHILDREN

Children have also been classified as vulnerable subjects for research because of their inability to protect themselves and their need to depend on an adult's (typically a parent's) legal standing, their limited capacity to protect their interests and provide protection and care, their lack of decision-making autonomy, and the real or perceived influence of authority figures on their decisions. Harm due to clinical research might have a long-term effect on the child's development and growth (97–99). Ethical issues have arisen in the past when hospitalized children or children living in orphanages have been subjected to clinical trials without disclosure of the risks and benefits (100). Valid ethical concerns stemming from these situations halted much clinical research in children. Because of limited studies, drug doses in children were often calculated based on pharmacokinetic data extrapolated from adults while not considering the marked age-related differences in metabolism and excretion. There was reluctance by pharmaceutical companies to conduct clinical research in children, especially because the pediatric drug market was considerably smaller.

However, children need to be involved in clinical research to improve and maintain pediatric care standards. Children are also particularly vulnerable to rapidly spreading infectious diseases due to their lack of preexisting immunity, smaller size, and risk of contagion from family members (101). For this reason, countries in Europe and the United States enacted several legal provisions "to encourage, entice or compel pharmaceutical companies to undertake pediatric trials" (100, p. 90).

In federally funded pediatric clinical research studies, there are four categories of research that are permitted, with different degrees of regulatory oversight, permissions from parents, and assent from the child. The four categories are research that is not greater than minimal risk; research with the prospect of direct benefit to the child that is at least as favorable as existing therapy and that justifies the risk; research that is slightly higher than minimal risk but holding out no potential benefit to the child where the research is likely to produce information of vital importance regarding the disorder being evaluated; and research that is not otherwise approvable (typically because it poses more substantial risk and holds out no prospect of direct benefit) but that the Secretary of Health and Human Services concludes, following consultation with experts, provides "a reasonable

opportunity to further understanding that could prevent or alleviate a serious problem affecting the health or welfare of children" (102, p. 1). International regulatory guidance documents have similar criteria to protect children participating in clinical research and ethically including them by limiting harm, differentiating risk, and considering the complex characteristics of children (103, 104).

In the Ebola outbreak in the DRC, 28% of the confirmed infections are reported in children less than 18 years of age, with 9% of the infections in children between 1 and 4 years of age and 6% in children under 1 year of age. The case fatality ratio in children is very high, nearly 80% in children aged 1–4 years and 70% in children under 1 year of age. The recently reported results of the therapeutic trial of four investigational therapies in the DRC (68) included patients of all ages who had a positive Ebola virus reverse transcriptase–polymerase chain reaction assay. Although most enrolled patients were 18 years or older, 12.8% were 6 to 17 years of age, 12.8% were 5 years of age or younger, and 0.7% were neonates (≤7 days old). A total of 55.6% of the enrolled patients were female, and 6.1% were pregnant at the time of enrollment. In addition, two investigational Ebola vaccines have been evaluated in children in the DRC, rVSV-ZEBOV vaccine in children >6 months and Ad26.ZEBOV/MVA-BN-Filo vaccine in children >1 year (105).

6. CORONAVIRUS EPIDEMIC

During the preparation of this review, a cluster of 27 cases of pneumonia of unknown etiology was reported from Wuhan City, Hubei Province, China, on December 31, 2019 (106), with a common link to Wuhan's Seafood Wholesale Market. On January 9, 2020, a novel coronavirus (SARS-CoV-2) was identified by the China CDC as the causative agent (107, 108). Coronaviruses are a large family of viruses, including severe acute respiratory syndrome (SARS-CoV) and MERS-CoV, that can lead to severe respiratory illnesses. The SARS-CoV-2 strain is genetically related to SARS-CoV and may interact with the same receptors. Based on the rapid global spread of cases, the WHO declared the epidemic a Public Health Emergency of International Concern (109). The WHO R&D Blueprint for Action has been activated to accelerate the development of diagnostics, vaccines, and therapeutics for coronavirus disease 2019 (COVID-19) (110). In line with CEPI's mandate to accelerate the development and manufacture of vaccines against previously unknown pathogens with a 16-week goal from identification of antigen to vaccine candidate release for clinical trials (62), CEPI has announced the initiation of four programs to develop vaccines against COVID-19. The candidates will use the rapid response platform supported by CEPI for vaccine development. Platform technologies employ systems that use the same basic components as a backbone and insert new genetic or protein sequences to adapt for use against different pathogens (111). The platform technologies now in use for development of MERS-CoV vaccines include a DNA vaccine (phase 1 trials are expected to commence in April 2020 in the United States and in parallel in China) and a molecular-clamp vaccine (which involves synthesis of viral surface proteins that attach to host cells during infection and clamp them into shape to allow immune recognition of the native antigen). Two messenger RNA (mRNA) vaccine candidates against COVID-19 also are being developed. mRNA-1273 is an mRNA vaccine that encodes for a prefusion stabilized form of the spike (S) protein, which is responsible for binding host cell receptors and initiating infection. The vaccine is being developed in collaboration with the NIAID. The phase 1 clinical trial was initiated in the United States in March 2020. A pandemic vaccine adjuvant will be available to enhance efficacy of a COVID-19 vaccine (112). A call has also been launched by CEPI for organizations with large manufacturing capabilities for vaccine candidates to advance an effective vaccine against the disease and transfer their vaccine platform to a global network of large-scale manufacturing (112). Other vaccine candidates under development (113) include a recombinant subunit vaccine based on the COVID-19 trimeric S protein (S-Trimer), a linear DNA vaccine, a

live attenuated recombinant measles virus (rMV) vectored vaccine, an infectious bronchitis virus (IBV) vaccine modified to treat COVID-19, a modified horsepox vaccine, and an oral recombinant vaccine in tablet formulation.

Therapeutics under development for COVID-19 include remdesivir (a nucleotide analog prodrug that was found to be ineffective for Ebola) and chloroquine, both of which inhibit 2019-nCoV infection in vitro (114). Remdesivir is in phase 3 clinical trials in the United States (led by the NIAID) and in Asia. Other therapeutics (113, 115, 116) being tested for 2019-nCoV include leronlimab (a CCR5 antagonist that has been tested in phase 2 clinical trials for HIV), galidesivir [a nucleoside RNA polymerase inhibitor that disrupts viral replication and is currently in advanced development under the FDA Animal Efficacy Rule (also known as the Animal Rule) to combat multiple potential viral threats], favilavir (an antiviral), brilacidin (a defensin mimetic), regeneron (a combination of neutralizing monoclonal antibodies REGN3048 and REGN3051, which is in phase 1 trials), and a combination of HIV protease inhibitors lopinavir and ritonavir.

In summary, although formidable challenges remain for the conduct of clinical trials of vaccines and therapeutics during epidemic situations, definite progress has been made since the West Africa Ebola outbreak in 2014. The WHO and international consortia, including CEPI, have established advisory bodies with expertise in ethics, clinical design, communication, pharmacovigilance, and implementation both to assist in the conduct of studies during the outbreak and also importantly to plan for the next potential outbreak with developing therapeutics and vaccines during the interepidemic periods. Finally, the progress made in including pregnant women and children in clinical trials has been substitutive. The approaches to clinical research in outbreak settings developed for Ebola virus have moved the field forward (117–119) and will improve the responses to SARS-CoV-2 and future epidemics. However, many challenges remain including poverty, lack of surveillance systems, inadequate health care delivery systems, and fear and misinformation in the countries impacted. It is hoped that in the years ahead these challenges can also be addressed.

DISCLOSURE STATEMENT

K.M.E. is an advisor for BioNet, IBM, and Merck. She is also on the Data Safety and Monitoring Boards for Sanafi, X-4 Pharma, Sequirus, Moderna, and Pfizer.

LITERATURE CITED

1. CDC (Cent. Dis. Control Prev.). 2019. 2014 Ebola outbreak in West Africa epidemic curves. *Centers for Disease Control and Prevention*. **https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/cumulative-cases-graphs.html**
2. Natl. Acad. Sci. Eng. Med. 2017. *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. Washington, DC: Natl. Acad. Press
3. Qiu X, Wong G, Audet J, Bello A, Fernando L, et al. 2014. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature* 514(7520):47–53
4. Dye JM, Herbert AS, Kuehne AI, Barth JF, Muhammad MA, et al. 2012. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. *PNAS* 109(13):5034–39
5. Rid A, Emanuel EJ. 2014. Ethical considerations of experimental interventions in the Ebola outbreak. *Lancet* 384(9957):1896–99
6. Alirol E, Kuesel AC, Guraiib MM, de la Fuente-Núñez V, Saxena A, et al. 2017. Ethics review of studies during public health emergencies—the experience of the WHO ethics review committee during the Ebola virus disease epidemic. *BMC Med. Ethics* 18(1):43
7. WHO (World Health Organ.). 2014. Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD). *World Health Organization*, Aug. 12. **https://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/**
8. Enserink M. 2014. Infectious diseases. Ebola drugs still stuck in lab. *Science* 345(6195):364–65

9. Enserink M. 2014. How two U.S. patients changed the debate about using untested Ebola. *Science*, Aug. 7. **https://www.sciencemag.org/news/2014/08/how-two-us-patients-changed-debate-about-using-untested-ebola-drugs**
10. Largent EA. 2016. Ebola and FDA: reviewing the response to the 2014 outbreak, to find lessons for the future. *J. Law Biosci.* 3(3):489–537
11. Fleming TR, Ellenberg SS. 2016. Evaluating interventions for Ebola: the need for randomized trials. *Clin. Trials* 13(1):6–9
12. Schieffelin JS, Shaffer JG, Goba A, Gbakie M, Gire SK, et al. 2014. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N. Engl. J. Med.* 371(22):2092–100
13. Ansumana R, Jacobsen KH, Sahr F, Idris M, Bangura H, et al. 2015. Ebola in Freetown area, Sierra Leone—a case study of 581 patients. *N. Engl. J. Med.* 372(6):587–88
14. Uyeki TM, Mehta AK, Davey RT Jr., Liddell AM, Wolf T, et al. 2016. Clinical management of Ebola virus disease in the United States and Europe. *N. Engl. J. Med.* 374(7):636–46
15. Wainberg MA, Kippax S, Bras M, Sow PS. 2014. HIV and Ebola: similarities and differences. *J. Int. AIDS Soc.* 17:19896
16. Nuremberg Code. 1949. In *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10*, Vol. 2, pp. 181–82. Washington, DC: USGPO
17. US Dep. Health Educ. Welf. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: US Dep. Health Hum. Serv. **https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html**
18. Counc. Eur. 1997. *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine*. Eur. Treaty Ser. No. 164, Counc. Eur., Strasbourg, Fr. **https://rm.coe.int/168007cf98**
19. UNESCO (UN Educ. Sci. Cult. Organ.). 2005. *Universal Declaration on Bioethics and Human Rights*. Paris: UNESCO
20. US Dep. Health Hum. Serv. 2009. *Federal Policy for the Protection of Human Subjects*, 82 Fed. Reg. 7149, Jan. 19. **https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html**
21. World Med. Assoc. 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 310(20):2191–94
22. WHO (World Health Organ.), CIOMS (Counc. Int. Organ. Med. Sci.). 2016. *International Ethical Guidelines for Health-Related Research Involving Humans*. Geneva, Switz.: Counc. Int. Med. Sci.
23. UNESCO (UN Educ. Sci. Cult. Organ.). 2006. *Bioethics Committees at Work: Procedures and Policies*. Paris: UNESCO
24. Bingley K. 2019. *Partnerships Review: Research for Health in Humanitarian Crises*. London: Elrha
25. Freedman B. 1987. Equipoise and the ethics of clinical research. *N. Engl. J. Med.* 317(3):141–45
26. WHO (World Health Organ.). 2014. *Ethical issues related to study design for trials on therapeutics for Ebola virus disease*, WHO Ethics Working Group Meet. Oct. 20–21, WHO, Geneva, Switz. **https://apps.who.int/iris/bitstream/handle/10665/137509/WHO_HIS_KER_GHE_14.2_eng.pdf;jsessionid=681D67F58F1CADBC0B5A630203417C13?sequence=1**
27. WHO (World Health Organ.). 2014. WHO Meeting of the Scientific and Technical Advisory Committee on Ebola Experimental Interventions—Briefing note. *World Health Organization*, Nov. 13. **https://www.who.int/medicines/ebola-treatment/scientific_tech_meeting/en/**
28. NIAID (Natl. Inst. Allergy Infect. Dis.). 2016. *Experimental Ebola drug ZMapp may benefit patients, but insufficient data to be certain, study finds*. News Release, Feb. 23. **https://www.niaid.nih.gov/news-events/experimental-ebola-drug-zmapp-may-benefit-patients-insufficient-data-be-certain-study**
29. Cohen J, Enserink M. 2016. Infectious disease. As Ebola epidemic draws to a close, a thin scientific harvest. *Science* 351(6268):12–13
30. Sullivan NJ, Sanchez A, Rollin PE, Yang ZY, Nabel GJ. 2000. Development of a preventive vaccine for Ebola virus infection in primates. *Nature* 408(6812):605–9
31. Mire CE, Geisbert JB, Marzi A, Agans KN, Feldmann H, et al. 2013. Vesicular stomatitis virus-based vaccines protect nonhuman primates against Bundibugyo ebolavirus. *PLOS Negl. Trop. Dis.* 7(12):e2600

32. WHO (World Health Organ.). 2015. *Report of the SAGE Working Group on Ebola Vaccines and Vaccination with Provisional Recommendations for Vaccination September 30, 2015*. Geneva, Switz.: World Health Organ.
33. Sridhar S. 2015. Clinical development of Ebola vaccines. *Ther. Adv. Vaccines* 3(5–6):125–38
34. Dawson AJ. 2015. Ebola: what it tells us about medical ethics. *J. Med. Ethics* 41(1):107–10
35. Underhill K. 2013. Study designs for identifying risk compensation behavior among users of biomedical HIV prevention technologies: balancing methodological rigor and research ethics. *Soc. Sci. Med.* 94:115–23
36. Openshaw PJ, Tregoning JS. 2005. Immune responses and disease enhancement during respiratory syncytial virus infection. *Clin. Microbiol. Rev.* 18(3):541–55
37. Nason M. 2016. Statistics and logistics: design of Ebola vaccine trials in West Africa. *Clin. Trials* 13(1):87–91
38. Cohen J, Kupferschmidt K. 2014. Tough choices ahead in Ebola vaccine trials. *Science*, Oct. 17. **https://www.sciencemag.org/news/2014/10/tough-choices-ahead-ebola-vaccine-trials**
39. Cohen J, Kupferschmidt K. 2014. Infectious diseases. Ebola vaccine trials raise ethical issues. *Science* 346(6207):289–90
40. Henao-Restrepo AM, Preziosi MP, Wood D, Moorthy V, Kieny MP. 2016. On a path to accelerate access to Ebola vaccines: the WHO's research and development efforts during the 2014–2016 Ebola epidemic in West Africa. *Curr. Opin. Virol.* 17:138–44
41. Davey RT. 2016. *PREVAIL I: a randomized controlled safety and immunogenicity trial of two different vaccines against Ebola virus*. Paper presented at the 8th International Symposium on Filoviruses, Antwerp, Belgium, Sept. 12–15
42. Samai M, Seward JF, Goldstein ST, Mahon BE, Lisk DR, et al. 2018. The Sierra Leone trial to introduce a vaccine against Ebola: an evaluation of rVSVΔG-ZEBOV-GP vaccine tolerability and safety during the West Africa Ebola outbreak. *J. Infect. Dis.* 217(Suppl. 1):S6–15
43. Mooney T, Smout E, Leigh B, Greenwood B, Enria L, et al. 2018. EBOVAC-Salone: lessons learned from implementing an Ebola vaccine trial in an Ebola-affected country. *Clin. Trials* 15(5):436–43
44. Plotkin SA. 2010. Correlates of protection induced by vaccination. *Clin. Vaccine Immunol.* 17(7):1055–65
45. Iaccino L. 2014. Ebola "caused by Red Cross" and other conspiracy theories. *International Business Times*, Oct. 16. **http://www.ibtimes.co.uk/ebola-caused-by-red-cross-other-conspiracy-theories-1469896**
46. Feuer A. 2014. The Ebola conspiracy theories. *NY Times*, Oct. 18. **https://www.nytimes.com/2014/10/19/sunday-review/the-ebola-conspiracy-theories.html?_r=2**
47. UNDP (UN Dev. Programme). 2014. *Human Development Report 2014: Sustaining Human Progress: Reducing Vulnerabilities and Building Resilience*. New York: UN Dev. Programme
48. Natl. Acad. Sci. Eng. Med. 2017. Strengthening capacity for response and research. In *Integrating Clinical Research into Epidemic Response: The Ebola Experience*, pp. 155–97. Washington, DC: Natl. Acad. Press
49. Natl. Acad. Sci. Eng. Med. 2017. Engaging communities in research and response. In *Integrating Clinical Research into Epidemic Response: The Ebola Experience*, pp. 199–222. Washington, DC: Natl. Acad. Press
50. WHO (World Health Organ.). 2015. Key events in the WHO response to the Ebola outbreak. *World Health Organization*, accessed Dec. 27, 2019. **https://www.who.int/csr/disease/ebola/one-year-report/who-response/en/**
51. Brende B, Farrar J, Gashumba D, Moedas C, Mundel T, et al. 2017. CEPI—a new global R&D organisation for epidemic preparedness and response. *Lancet* 389(10066):233–35
52. Gostin LO, Tomori O, Wibulpolprasert S, Jha AK, Frenk J, et al. 2016. Toward a common secure future: four global commissions in the wake of Ebola. *PLOS Med.* 13(5):e1002042
53. WHO (World Health Organ.). 2019. Prioritizing diseases for research and development in emergency contexts. *World Health Organization*, accessed Dec. 26, 2019. **https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-context**
54. WHO (World Health Organ.). 2016. *An R&D Blueprint for Action to Prevent Epidemics*. Geneva, Switz.: World Health Organ. **https://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf?ua=1**

55. Moon S, Sridhar D, Pate MA, Jha AK, Clinton C, et al. 2015. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. *Lancet* 386(10009):2204–21
56. Dean NE, Gsell PS, Brookmeyer R, De Gruttola V, Donnelly CA, et al. 2019. Design of vaccine efficacy trials during public health emergencies. *Sci. Transl. Med.* 11(499):eaat0360
57. WHO (World Health Organ.). 2016. Emergency use of unproven interventions outside of research. In *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*, pp. 35–37. Geneva, Switz.: World Health Organ.
58. Bloom DE, Cadarette D. 2019. Infectious disease threats in the twenty-first century: strengthening the global response. *Front. Immunol.* 10:549
59. Roberts RB. 2017. CEPI—a global partnership. *Germs* 7(1):8–9
60. Plotkin SA. 2017. Vaccines for epidemic infections and the role of CEPI. *Hum. Vaccines Immunother.* 13(12):2755–62
61. Gouglas D, Christodoulou M, Plotkin SA, Hatchett R. 2019. CEPI: driving progress towards epidemic preparedness and response. *Epidemiol. Rev.* 41(1):28–33
62. CEPI (Coalit. Epidemic Prep. Innov.). 2020. Why we exist. *Coalition for Epidemic Preparedness Innovations*, accessed Jan. 9, 2020. **https://cepi.net/about/whyweexist/**
63. CEPI (Coalit. Epidemic Prep. Innov.). 2020. Support CEPI. *Coalition for Epidemic Preparedness Innovations*, accessed Jan. 9, 2020. **https://cepi.net/get_involved/support-cepi/**
64. Ilunga Kalenga O, Moeti M, Sparrow A, Nguyen VK, Lucey D, et al. 2019. The ongoing Ebola epidemic in the Democratic Republic of Congo, 2018–2019. *N. Engl. J. Med.* 381(4):373–83
65. Aruna A, Mbala P, Minikulu L, Mukadi D, Bulemfu D, et al. 2019. Ebola virus disease outbreak—Democratic Republic of the Congo, August 2018–November 2019. *MMWR Morb. Mortal. Wkly. Rep.* 68(50):1162–65
66. MSF. 2020. DRC Ebola outbreak. Crisis update—January 2020. *MSF*, accessed Jan. 22, 2020. **https://www.msf.org/drc-ebola-outbreak-crisis-update**
67. WHO (World Health Organ.). 2020. Ebola in the Democratic Republic of the Congo: health emergency update. *World Health Organization*, accessed Jan. 22, 2020. **https://www.who.int/emergencies/diseases/ebola/drc-2019**
68. Mulangu S, Dodd LE, Davey RT Jr., Tshiani Mbaya O, Proschan M, et al. 2019. A randomized, controlled trial of Ebola virus disease therapeutics. *N. Engl. J. Med.* 381(24):2293–303
69. PREVAIL II Writing Group for the Multi-National PREVAIL II Study Team. 2016. A randomized, controlled trial of ZMapp for Ebola virus infection. *N. Engl. J. Med.* 375(15):1448–56
70. Kochhar S, Edwards KM, Ropero Alvarez AM, Moro PL, Ortiz JR. 2019. Introduction of new vaccines for immunization in pregnancy—programmatic, regulatory, safety and ethical considerations. *Vaccine* 37(25):3267–77
71. Grazel R, Harris-Haman P. 2018. Zika virus infection: a vector-borne threat to pregnant women and infants. *Adv. Neonatal Care* 18(5):350–59
72. Moss WJ. 2017. Measles. *Lancet* 390(10111):2490–502
73. Gomes MF, de la Fuente-Núñez V, Saxena A, Kuesel AC. 2017. Protected to death: systematic exclusion of pregnant women from Ebola virus disease trials. *Reprod. Health* 14(Suppl. 3):172
74. Hayden EC. 2015. Maternal health: Ebola's lasting legacy. *Nature* 519(7541):24–26
75. Malvy D, Sissoko D, Camara AM. 2017. Integrating clinical research into epidemic response: the field perspective in the Ebola experience. *Med. Sci.* 33(10):891–97
76. US Dep. Health Hum. Serv. 2018. *Federal Policy for the Protection of Human Subjects ('Common Rule')*. 45 CFR 46, July 19. **https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML**
77. Goldkind SF, Sahin L, Gallauresi B. 2010. Enrolling pregnant women in research—lessons from the H1N1 influenza pandemic. *N. Engl. J. Med.* 362(24):2241–43
78. Mastroianni AC, Faden R, Federman D, eds. 1994. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. I. Washington, DC: Natl. Acad. Press
79. Field MJ, Behrman RE, eds. 2004. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: Natl. Acad. Press

80. Hentoff N. 1996. Breakthrough for HIV-positive babies. *NY Times*, Aug. 15. **https://www.washingtonpost.com/archive/opinions/1996/08/05/breakthrough-for-hiv-positive-babies/a3be3f8c-e9d3-4f1b-bcd7-eb457c581d59/?utm_term%20=%20.b504cd1631fd**
81. Kochhar S, Bonhoeffer J, Jones CE, Muñoz FM, Honrado A, et al. 2017. Immunization in pregnancy clinical research in low- and middle-income countries—study design, regulatory and safety considerations. *Vaccine* 35(48, Part A):6575–81
82. Lyerly AD, Little MO, Faden R. 2008. The second wave: toward responsible inclusion of pregnant women in research. *Int. J. Fem. Approaches Bioeth*. 1(2):5–22
83. Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, et al. 2016. Pregnancy-associated changes in pharmacokinetics: a systematic review. *PLOS Med*. 13(11):e1002160
84. Kay AW, Blish CA. 2015. Immunogenicity and clinical efficacy of influenza vaccination in pregnancy. *Front. Immunol.* 6:289
85. Fulton TR, Narayanan D, Bonhoeffer J, Ortiz JR, Lambach P, et al. 2015. A systematic review of adverse events following immunization during pregnancy and the newborn period. *Vaccine* 33(47):6453–65
86. Shields KE, Lyerly AD. 2013. Exclusion of pregnant women from industry-sponsored clinical trials. *Obstet. Gynecol.* 122(5):1077–81
87. Buchanan L. 2017. *Brief overview of the revised Common Rule and subpart B—pregnant women, 2017*. PowerPoint, Off. Hum. Res. Prot., Rockville, MD. **https://www.nichd.nih.gov/sites/default/files/2017-11/4-OverviewNew_Rule_SubpartB.pdf**
88. Task Force on Research Specific to Pregnant Women and Lactating Women. 2018. *Report to Secretary, Health and Human Services Congress 2018*. Rep., Natl. Inst. Health, Washington, DC. **https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf**
89. WHO (World Health Organ.). 2019. *Ebola virus disease—Democratic Republic of the Congo*. News Release, Dec. 19. **https://www.who.int/csr/don/19-december-2019-ebola-drc/en/**
90. Haddad LB, Jamieson DJ, Rasmussen SA. 2018. Pregnant women and the Ebola crisis. *N. Engl. J. Med.* 379(26):2492–93
91. Schwartz DA. 2018. Clinical trials and administration of Zika virus vaccine in pregnant women: lessons (that should have been) learned from excluding immunization with the Ebola vaccine during pregnancy and lactation. *Vaccines* 6(4):81
92. Faden RR, Krubiner CB, Lyerly AD, Little MO, August A, et al. 2017. Ethics, pregnancy, and ZIKV vaccine research & development. *Vaccine* 35(49):6819–22
93. Krubiner CB, Faden RR, Karron RA, Little MO, Lyerly AD, et al. 2019. Pregnant women & vaccines against emerging epidemic threats: ethics guidance for preparedness, research, and response. *Vaccine*. In press. **https://doi.org/10.1016/j.vaccine.2019.01.011**
94. WHO (World Health Organ.). 2019. SAGE interim recommendations on vaccination against Ebola Virus Disease (EVD). *World Health Organization*. **https://www.who.int/immunization/interim_ebola_recommendations_feb_2019.pdf**
95. Schwartz DA. 2019. Maternal and infant death and the rVSV-ZEBOV vaccine through three recent Ebola virus epidemics—West Africa, DRC Équateur and DRC Kivu: 4 years of excluding pregnant and lactating women and their infants from immunization. *Curr. Trop. Med. Rep.* 6:213–22
96. US FDA (US Food Drug Admin.). 2020. Ebola preparedness and response updates from FDA. *US Food and Drug Administration*, accessed Dec 23, 2019. **https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/ebola-preparedness-and-response-updates-fda**
97. Welch MJ, Lally R, Miller JE, Pittman S, Brodsky L, et al. 2015. The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials. *Clin. Trials* 12(5):503–10
98. Kipnis K. 2003. Seven vulnerabilities in the pediatric research subject. *Theor. Med. Bioeth.* 24(2):107–20
99. Kelly B, Mackay-Lyons MJ. 2010. Ethics of involving children in health-related research: applying a decision-making framework to a clinical trial. *Physiother. Can.* 62(4):338–46
100. Bavdekar SB. 2013. Pediatric clinical trials. *Perspect. Clin. Res.* 4(1):89–99
101. AAP (Am. Acad. Pediatr.). 2002. *The Youngest Victims: Disaster Preparedness to Meet Children's Needs*. Elk Grove Village, IL: Am. Acad. Pediatr. **https://www.aap.org/en-us/Documents/disasters_youngest_victims_disaster_preparedness.pdf**

102. US Dep. Health Hum. Serv. 2005. *Children as Research Subjects and the HHS "407" Process*. Washington, DC: US Dep. Health Hum. Serv. **https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-407-review-process/index.html**
103. Nuffield Counc. Bioethics. 2015. *Children and Clinical Research: Ethical Issues*. London: Nuffield Counc. Bioethics. **https://www.nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf**
104. Med. Res. Counc. 2004. *MRC Ethics Guide: Medical Research Involving Children*. London: Med. Res. Counc. **https://mrc.ukri.org/documents/pdf/medical-research-involving-children/**
105. WHO (World Health Organ.). 2019. Safety of Ebola virus vaccines. *World Health Organization*, July 12. **https://www10.who.int/vaccine_safety/committee/topics/ebola/Jul_2019/en/**
106. WHO (World Health Organ.). 2020. *Pneumonia of unknown cause—China*. News Release, Jan. 5. **https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/**
107. Wuhan City Health Comm. 2019. Wuhan Municipal Health and Health Commission's briefing on the current pneumonia epidemic situation in our city 2019. *Wuhan City Health Committee*, accessed Feb. 7, 2020. **http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989**
108. Ting Q. 2020. Experts claim that a new coronavirus is identified in Wuhan 2020. *Xinhua*, accessed Feb. 7, 2020. **http://www.xinhuanet.com/2020-01/09/c_1125438971.htm**
109. WHO (World Health Organ.). 2020. Statement on the second meeting of the International Health Regulations 2005 Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). *World Health Organization*, accessed on Feb. 6, 2020. **https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)**
110. WHO (World Health Organ.). 2020. Novel coronavirus R&D. *World Health Organization*, accessed Feb. 7, 2020. **https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/**
111. Rauch S, Jasny E, Schmidt KE, Petsch B. 2018. New vaccine technologies to combat outbreak situations. *Front. Immunol.* 9:1963
112. CEPI (Coalit. Epidemic Prep. Innov.). 2020. 2019-nCoV vaccine. *Coalition for Epidemic Preparedness Innovations*, accessed Feb. 7, 2020. **https://cepi.net/?s=2019-nCoV**
113. Duddu P. 2020. Novel coronavirus: major vaccines/drugs in the pipeline. *Clinical Trials Arena*, Feb. 24, accessed Feb. 24, 2020. **https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/**
114. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 30:269–71
115. Li H, Wang YM, Xu JY, Cao B. 2020. Potential antiviral therapeutics for 2019 Novel Coronavirus. *Zhonghua Jie He He Hu Xi Za Zhi*. 43:E002
116. Lu H. 2020. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci. Trends* 14(1):69–71
117. Shrivastava SR, Shrivastava PS, Ramasamy J. 2015. Lessons learnt from the 2014 Ebola outbreak in West-Africa. *J. Res. Med. Sci.* 20(1):107–8
118. Honorine S. 2017. Five lessons learned from the West Africa Ebola outbreak. *MSF UK*. **https://www.msf.org.uk/article/five-lessons-learned-west-africa-ebola-outbreak**
119. Oleribe OO, Salako BL, Ka MM, Akpalu A, McConnochie M, et al. 2015. Ebola virus disease epidemic in West Africa: lessons learned and issues arising from West African countries. *Clin. Med.* 15(1):54–57
120. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, et al. 2017. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 389(10068):505–18
121. Widdowson MA, Schrag SJ, Carter RJ, Carr W, Legardy-Williams J, et al. 2016. Implementing an Ebola vaccine study—Sierra Leone. *MMWR Suppl.* 65(3):98–106
122. Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, et al. 2017. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N. Engl. J. Med.* 377(15):1438–47