**Global Bioheroes: clinical research and new vaccines for health security**

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**Notes on contributor**

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**Abstract**

In the pursuit of ‘global health security’, some governments advocate deployment of pharmaceuticals to combat deadly infectious diseases wherever they emerge. Following the Ebola outbreak in West Africa, attention has turned to other emerging diseases and future pharmaceutical solutions. There is growing support for enabling faster clinical research to make new vaccines available sooner. Research on experimental vaccines must ordinarily be consistent with ethical principles designed to protect human research participants. However, where a target disease is framed in security terms, it could be argued that an extraordinary response is required: exposing research participants to more risk in order to accelerate research and enable more lives to be saved pharmaceutically. This article assesses two scenarios of security-oriented research. The scenario envisaged by the Coalition for Epidemic Preparedness Innovations (CEPI) is the propelling of vaccine research through to the stage of human safety-testing before a natural outbreak of the relevant disease. Efficacy and effectiveness tests are then able to be conducted once an outbreak begins. In a hypothetical second scenario, pre-outbreak vaccine research undertaken for the sake of health security would also include efficacy-testing. This would involve the exposure to pathogenic microorganisms of healthy volunteers (‘global bioheroes’) from around the world.

**Keywords:** Coalition for Epidemic Preparedness Innovations (CEPI), Ebola, health security, research ethics, vaccines

‘We are real heroes in this country …’

Participant in an Ebola vaccine clinical trial, Sierra Leone, 2015

(Tengbeh et al. 2018: 39)

**Introduction**

This article is offered as a provocation in response to recent claims that scientific researchers should pursue new vaccines against emerging infectious diseases as a matter of global health security. Traditionally, security claims have been used to create political space and establish moral permission to do extraordinary things. So, if the scientific pursuit of new vaccines is to be regarded as a security issue, to what extraordinary lengths might we go when conducting clinical research? This question is prompted by the launch in early 2017 of a new organization: the Coalition for Epidemic Preparedness Innovations (CEPI). With support and funding from several governments, international organizations, philanthropic foundations, and pharmaceutical companies, CEPI’s core mission is to finance and coordinate the accelerated development of vaccines against certain emerging infectious diseases. CEPI’s first president, John-Arne Røttingen, argued in 2017 that financial contributions from governments around the world are ‘a premium they need to pay for global health security’ (Cohen 2017). And the Coalition’s website states that making new vaccines available sooner, to prevent and contain epidemics, will ‘contribute to the health security the world needs’ (CEPI 2018a). Prominent figures in the field of global health policy had been advocating the establishment of an organization like CEPI (Plotkin et al. 2015), mainly because the large-scale Ebola outbreak in West Africa had powerfully demonstrated the human and societal damage a deadly virus can cause in the absence of an effective vaccine. In 2014, the World Health Organization (WHO) declared that outbreak to be a public health emergency, and the United Nations Security Council described the spread of Ebola in West Africa and beyond as a threat to international peace and security. The essential problem, framed in both health and security terms, was that a dreaded disease was spreading out of control. Non-pharmaceutical approaches to disease-control had had to be used, which were sometimes disruptive and damaging in themselves, although the Ebola outbreak was eventually brought under control in this way. If an effective vaccine had been available at the time, the damage would probably have been far less. Thus one lesson drawn from this experience was that, when emerging diseases like Ebola present a health and security problem, the best solution is a pharmaceutical one.

In health policy discourse the concept of ‘global health security’ has become particularly associated with deadly infectious diseases. The practice of securing global health has mainly involved the development of strong worldwide capacities for detecting and responding to disease outbreaks which could cause a transnational contagion crisis. The goal has not been to secure the health of all people against all disease risks, but rather to ‘minimize vulnerability to acute public health events that endanger the collective health of populations living across geographical regions and international boundaries’ (WHO 2007: 5). Some scholars have criticised this vision of global health security on ethical grounds for being too narrow in scope and leading to the unjust neglect of many health burdens (McInnes and Lee 2006; Davies 2008; Rushton 2011). Others have argued that framing infectious diseases in security terms might lead toward individual injustices, especially where ruthless governments curtail human rights for disease-control purposes (Elbe 2006; Selgelid and Enemark 2008). Here, though, ethical concern has tended to focus on how the pursuit of global health security by non-pharmaceutical means (e.g. mass quarantine, social distancing, and border controls) could, for better or worse, go ‘beyond rules that would otherwise bind’ (Buzan et al. 1998: 5). There has been relatively little normative consideration of pharmaceutical strategies in the context of disease securitization, yet the experience of clinical research (involving human subjects) conducted during the West African Ebola crisis shows there is now a greater need for this.

In the face of emerging infectious disease risks, some of which are framed in security terms, there is a strong political preference for using protective vaccines and therapeutic drugs (if they are available). This is because non-pharmaceutical approaches to disease control are often disruptive and unpopular (Eckholm 2003; Onishi 2014). The swift deployment of pharmaceutical resources wherever they are needed to prevent or treat a deadly disease is widely regarded as better, and the availability of ‘medical countermeasures’ is now frequently characterised as a critical component of ‘global health security’ (Marinissen et al. 2014). This is evidence of an increasing ‘pharmaceuticalization’ of security-oriented approaches to disease-control (Elbe et al. 2014). When it comes to existing pharmaceutical resources, access and availability are dependent upon worldwide production, purchasing and distribution practices. But when new vaccines or drugs are needed to tackle emergent infectious diseases, a key issue is whether or how clinical research could be conducted to demonstrate a new pharmaceutical’s safety and effectiveness. Securitization, as a political move, could serve to accelerate that research, but such a move might entail risks as well as benefits. If securitization can create an ‘exceptional political space to break key norms and rules governing the development and approval of drugs and vaccines’ (Roemer-Mahler and Elbe 2016: 499), what might this mean in practice? How, if at all, should invoking the idea of ‘health security’ change the way clinical trials are conducted? Is the change to be achieved by CEPI sufficient, or should the pursuit of health security involve greater acceleration of research?

This article addresses these questions by first considering ethical requirements in clinical research and their relevance during the 2014-16 Ebola crisis. The discussion then shifts to an assessment of CEPI’s approach to accelerating vaccine research. Finally, the article proposes an alternative approach (a Global Bioheroes programme) whereby health security and global solidarity are justifications for exposing clinical research volunteers to a greater degree of risk.[[1]](#endnote-1)

**Experimental pharmaceuticals and human research ethics**

Medical scientists usually investigate experimental drugs and vaccines by engaging in sequential phases of clinical research. Before the commencement of clinical trials, a new pharmaceutical will have been laboratory-tested in animals to generate preliminary data on its efficacy and toxicity. If these pre-clinical tests are successful enough to warrant development of that pharmaceutical for possible human use, three phases of clinical trials may then follow. In Phase I the purpose is to establish the safety and required dosage of the investigational drug or vaccine. The study usually takes several months, involving a small number (20 – 100) of healthy volunteers. If the pharmaceutical is found to be safe enough to warrant further investigation, a clinical trial proceeds to Phase II. Here the purpose is to test for efficacy, and research involving up to several hundred people with the relevant disease takes up to two years. If sufficient efficacy is shown under the highly-controlled circumstances of a Phase II trial, the research can move on to a larger-scale investigation into how effective the pharmaceutical is under real-world conditions. In Phase III (effectiveness) research, up to 3,000 volunteers who have the disease participate in a study lasting up to four years (National Library of Medicine 2017; FDA 2018). Ordinarily, it is only after passing successfully through Phases I-III that a pharmaceutical is approved by a regulatory authority for use in the general population, and most clinical research is not fully successful. For drug development programs aimed at an infectious disease, the average likelihood of progressing all the way from Phase I research to approval by the US Food and Drug Administration (FDA) is 19.1 percent. That likelihood increases at each subsequent phase: 27.5 percent from Phase II, and 64.5 percent from Phase III (BIO 2016). Such statistics are important to recall whenever researchers assert that a particular ‘promising’ pharmaceutical has the potential to save lives.

When trialling a new pharmaceutical with a view to using it for disease-control purposes, it is usually scientifically necessary to expose human subjects to a degree of risk. Clinical trial participants may need to run the risk, for example, that a candidate drug is unsafe in humans, or that a candidate vaccine is not protective against a disease. This means that ethical concerns can arise as researchers seek to advance scientific knowledge while also protecting the interests of human subjects. Principles of human research ethics are intended to guide the process of balancing these two imperatives. The principles that are generally applicable to clinical research today are derived largely from the post-war criminal trials of physicians who had conducted atrocious medical experiments in Nazi German concentration camps during World War Two. These experiments lacked scientific merit, and the non-consenting human subjects were usually killed afterwards (Craig and Desai 2015). On the basis of judicial findings at the Nuremburg trials, the Nuremburg Code emerged to establish that voluntary, informed consent is an indispensable condition of any research involving humans. The Code also includes a requirement for research to have social value (‘The experiment should be such as to yield fruitful results for the good of society’), and for the risk-benefit ratio to be favourable (‘The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment’) (Nuremburg Code 1949). These and other principles were later developed in the World Medical Association’s Declaration of Helsinki (WMA 1964), and today they are among seven ethical principles that are generally applicable to clinical research: Social Value, Scientific Validity, Fair Subject Selection, Favourable Risk-Benefit Ratio, Independent Review, Informed Consent, and Respect for the Enrolled Subject (NIH 2017). Researchers’ widespread adherence to these principles means that clinical trials of experimental pharmaceuticals tend to take longer today than they might have done during the pre-Nuremburg era, and this is generally accepted as a desirable trade-off between scientific and ethical interests. However, the ordinarily slow pace of progress toward new drugs and vaccines against infectious diseases became a source of great concern in 2014 when Ebola was spreading out of control in West Africa.

**Clinical trials during an Ebola outbreak**

By the time that Ebola outbreak ended in early 2016, there had been around 29,000 reported cases (including over 11,000 deaths), mainly in Guinea, Liberia, and Sierra Leone (WHO 2016a). The outbreak would probably have ended sooner had an Ebola vaccine been available when it started. By the middle of 2014, non-pharmaceutical containment measures were failing, and the idea emerged that the situation was desperate enough to warrant the use of untested pharmaceuticals in West Africa (Farrar et al. 2014). There was some opposition to this idea, mainly on the grounds that such use would risk worsening the crisis. For example, one representative of the humanitarian organization Médecins Sans Frontières argued it would be counterproductive to bring in ‘unlicensed things to experiment on [local] people’ who were ‘already distrustful of the teams trying to stamp out the outbreak’ (Enserink 2014a). However, the case for an extraordinary pharmaceutical intervention was later boosted by the WHO’s declaration on 8 August that Ebola in West Africa was a public health emergency of international concern. Three days later, the WHO convened a 12-member panel to consider the ethical implications of using experimental drugs and vaccines to help bring the outbreak under control. The panel recommended unanimously that in ‘the particular circumstances of this outbreak … it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention’ (WHO 2014a). The provision of such interventions had to be accompanied by an effort to gather good scientific data on their effects and guided by the principles of human research ethics (WHO 2014b: 7).

In early September 2014 the WHO assembled around 150 scientists, ethicists and regulatory officials to identify and prioritize the most promising pharmaceuticals for use in clinical trials. At that meeting WHO assistant director-general Marie-Paule Kieny observed: ‘Right now the epidemic is out of control. The situation is drastic and calls for drastic measures’ (Maurice 2014: e45). It soon became apparent, however, that there was little scope to halt Ebola transmission and treat Ebola victims by pharmaceutical means. The emergency response to Ebola eventually included the use of therapeutic anti-Ebola drugs that had not undergone any safety testing in humans, but very few doses of these were available for treatment and research purposes. More promising was the proposal to clinically trial some candidate vaccines to prevent Ebola infection, but these were only going to be useful for disease-control if they could be proven to work before the outbreak in West Africa ended. International consortia were hurriedly formed to accelerate trials of two existing candidate Ebola vaccines: cAd3-EBOZ, developed by GlaxoSmithKline (GSK) and the US National Institutes of Health; and rVSV-EBOV, developed by the Public Health Agency of Canada. Both vaccines had entered Phase I (safety) trials by the end of September 2014, after which it was hoped that the ongoing Ebola outbreak in West Africa would present an opportunity to conduct Phase II (efficacy) and Phase III (effectiveness) trials (Cohen 2014: 1441).

By the time later-phase clinical trials were ready to start in late 2014, the Ebola outbreak was subsiding and doubts arose about whether there would be a sufficient number of people available to participate in the research (as actual or potential victims of disease). In October, GSK announced that its Ebola vaccine would ‘come too late’ for the current epidemic (Cox 2014), and in November a scientist working on rVSV-EBOV warned: ‘We can't necessarily assume that the vaccine will have a dramatic effect on the future development of the current epidemic’ (Hackenbroch et al. 2014). By late January 2015 it appeared that non-pharmaceutical prevention and infection-control measures had indeed turned the tide on Ebola, with the WHO reporting fewer than 100 new confirmed cases in the three worst-affected countries (WHO 2015a). The circumstances upon which the WHO’s ethics panel had earlier based its recommendation for deploying unlicensed pharmaceuticals in West Africa no longer existed. The threat that Ebola had seemed to pose to global health security had lessened—an outbreak out of control had become an outbreak about to end—so the urgency and justification of an extraordinary pharmaceutical intervention (using untested drugs and vaccines to address an immediate disease-control challenge) fell away. Thereafter, the race to stop Ebola in West Africa became a race merely to avoid missing a research opportunity for developing new pharmaceuticals that might be used anywhere sometime in the future. Ultimately, most clinical trials running in 2015 did not outpace Ebola’s decline, but by July of that year a trial of the rVSV-ZEBOV vaccine in Guinea had achieved research success: evidence of efficacy. Published results showed that, among nearly 6,000 at-risk people who received the experimental vaccine, all were free of Ebola virus 10 days later. In an unvaccinated ‘control’ group of the same size, 23 people later developed Ebola (Henao-Restrepo et al. 2017).

It is nevertheless important to emphasise, firstly, that this clinical research success was unrelated to the successful containment of the outbreak. Ebola in West Africa was not defeated pharmaceutically. Secondly, evidence of vaccine efficacy was achieved in difficult research circumstances which themselves raised ethical concerns. The WHO Research Ethics Review Committee, which reviewed many clinical research proposals during the Ebola outbreak, identified a number of difficulties from a human research ethics perspective. These included: uncertainty about whether studies could be completed as planned (and thus whether they should be commenced); the uncertain balance of benefits and risks associated with particular investigational drugs and vaccines; and a local ‘target population’ ill-equipped to understand the implications of participating in clinical trials (Aliro et al. 2017). Committee members reported that research participants were ‘invariably seriously ill, at risk of infection, or facing stigmatization and its consequences, afraid, vulnerable, and unclear about the objectives, benefits and risks of study participation and the distinction between research and medical practice’ (Aliro et al. 2017). In such circumstances, some humanitarian organizations were sceptical of research efforts that seemed unlikely to succeed but distracted from efforts to provide medical care to as many people as possible (Keusch et al. 2017: 6). And some ethicists argued that pharmaceutical experimentation during the Ebola outbreak should not displace non-pharmaceutical containment measures that had a proven record of controlling infectious outbreaks (Rid and Emanuel 2014: 1896; Dawson 2015).

Guinea, Liberia and Sierra Leone are low-income countries with poor health infrastructure and weak governance, and Ebola response efforts there occurred in the face of much local distrust toward international healthcare providers. In this setting, individuals’ economic vulnerability had the potential to hinder adherence to the cardinal research ethics principle of informed consent. For example, in Liberia there was concern that compensation being offered to Ebola drug research participants ($300 for 10 hospital visits) might be too high in a country where many people earn less than $5 a day (Onishi and Fink 2015). If so, there was a risk of consent being coerced rather than genuinely volunteered. Also, in impoverished West Africa the available medical care was far from the best in the world. During the rVSV-ZEBOV trial in rural Guinea, for example, it was difficult to monitor any adverse effects of the vaccine and provide follow-up care because village residents sometimes did not have proper addresses (Shuchman 2015: 1934). When the vaccine trial was extended to Sierra Leone, there was some uncertainty about what risks research participants were consenting to undertake. One participant claimed:

We hadn’t been told before we had the vaccine that we would suffer from anything. We were only told afterwards that this would be the case. The people who gave us the vaccines came from Guinea. They were French and couldn’t speak with us very clearly so they never told us what to expect (Holt 2016).

Notwithstanding the ethical concerns that had arisen in West Africa, Marie-Paule Kieny described the rVSV-ZEBOV vaccine trial’s success as a ‘turning point’ in the history of research and development (R&D) and a demonstration that ‘the urgency of saving lives can accelerate R&D’ (WHO 2015c). Afterwards, the experience of accelerated mid-outbreak clinical research on Ebola pharmaceuticals was hailed as a model for future efforts to tackle emerging infectious diseases, despite that fact that West Africa had received no immediate disease-control benefit from that research. Even so, a key lesson had been learned: that efficacy trials for candidate Ebola vaccines could have started sooner if safety trials had already been conducted. A candidate Ebola vaccine had been rapidly and successfully tested in the midst of an outbreak, but that vaccine did not help to end that outbreak. In future, it seemed, more pre-outbreak research was needed to move vaccines further along the development pipeline, so CEPI was founded to achieve this ‘health security’ goal.

**CEPI: vaccine research for global health security**

CEPI aims to ‘contribute to the health security the world needs’ by accelerating clinical research on new vaccines to control emerging infectious diseases (CEPI 2018a). The Coalition was founded on the proposition that a repeat of the Ebola crisis had to be averted, and that this could be achieved by having safety-tested vaccines ready to be efficacy-tested as soon as a disease outbreak begins. The anticipated public-health benefit is that, if stockpiled doses of a candidate vaccine were quickly proven to be efficacious, there might then be time to administer them on an emergency basis to prevent infection and save lives. Ordinarily, there is little commercial incentives for pharmaceutical companies to engage in activities of this kind. Therefore, as of early 2018 CEPI had sought and received financial backing ($620 million) from the governments of Australia, Belgium, Canada, Germany, Japan and Norway, as well as the Wellcome Trust and the Bill & Melinda Gates Foundation (Withers 2018). The allocation of public funding for such a purpose followed a precedent set in the United States where Project Bioshield the Biomedical Advanced Research and Development Authority were established in to incentivise companies to develop, produce and sell novel pharmaceuticals for diseases of bioterrorism concern. Indeed, the very existence in 2014 of several candidate Ebola drugs and vaccines was a direct result of over $600 million in US Government investment therein for biodefense reasons since 2003 (Boddie 2015: 6).

CEPI’s approach to securing global health pharmaceutically is closely aligned with the WHO’s Blueprint for R&D Preparedness. The overall goal of the Blueprint is to reduce delays between the identification of a disease outbreak and the deployment of effective medical interventions to save lives and minimize socioeconomic disruption. It prioritizes emerging pathogens (for which no pharmaceuticals exist) that are deemed likely to cause severe outbreaks in the near future, and for each targeted disease it provides a profile of the kinds of vaccines and treatments that are needed (WHO 2018a). The Blueprint list currently includes 10 known diseases: Crimean-Congo haemorrhagic fever, Ebola, Marburg, Lassa fever, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever, and Zika (WHO 2018b). CEPI’s task is to award grants to pharmaceutical companies to develop vaccines for these diseases (in animal trials and early-phase clinical trials) and then stockpile them as an emergency preparedness measure. One of its main objectives for the period 2017 – 2021 is to advance ‘at least four vaccine candidates against two to three priority pathogens to proof-of-concept …, to enable clinical efficacy testing in the initial stages of a potential outbreak’ (CEPI 2018b).

The anticipated health benefit of CEPI is clear. Safety-testing a candidate vaccine prior to an outbreak obviates the need to spend time doing this during an outbreak. And accelerating vaccine development in this way has the potential therefore to make vaccines available more quickly to people who need them. Even so, the CEPI approach is unlikely to avoid some of the research challenges (practical and ethical) that arose during the West Africa Ebola outbreak. As a pharmaceutical contribution to global health security, it faces at least five potential problems. First, when clinical research is conducted in the midst of a health crisis, there is a risk that this will be a damaging distraction from ongoing disease-control efforts. The value of CEPI-funded research would need to be sufficient to justify allocating scarce resources (including medical personnel) to vaccine efficacy trials rather than to activities that could alleviate a disease crisis more directly (see: Keusch et al. 2017: 54; WHO 2016b: 32). If the candidate vaccine turned out not to be efficacious, such that no one could benefit from taking it, this could provoke accusations that the clinical trial was an unjust, wasteful ‘long-shot’ intervention (see Caplan 2015: e16).

The second potential problem with the CEPI approach is that it perpetuates the controversial practice of ‘off-shoring’ human research risk. Pharmaceutical companies based in wealthy countries often conduct research elsewhere because they want to develop new pharmaceuticals more quickly and cheaply. This can bring the benefit of improved research capacity in poorer parts of the world. But the rapid growth, over the last two decades, in the number and scale of clinical trials conducted in poorer countries has sometimes given rise to ethical concerns (Jack 2008). In settings where research is conducted without adequate local oversight, there can be a higher risk that research subjects will be exploited, and the deliberate choosing of such settings is known as ‘ethics dumping’ (Nordling 2018). Moreover, the standard of medical monitoring and care available to off-shore subjects tends to be lower than that available in researchers’ home countries, and there can also be differences in the availability of proven effective treatments for the disease being researched (Emanuel et al. 2004: 930). This distinction is especially important when a clinical trial involves randomly administering to half the participant cohort a placebo ‘control’ rather than the experimental pharmaceutical. Under the CEPI plan for mid-outbreak efficacy testing, it will probably be mainly poor people in poorer, epidemic-prone parts of the world who are exposed to the health risk of receiving a placebo or a possibly non-efficacious candidate vaccine.

The health risk to individuals participating in CEPI-funded research is counter-balanced to some degree by the potential public-health benefit of establishing a new vaccine’s efficacy. However, a third potential problem is the practical difficulty of attaining that benefit in a research environment not conducive to good science. Establishing controlled conditions could be difficult in the chaotic context of a raging epidemic, or else a disease outbreak might turn out to be too small or too short, in which case the results of a clinical trial might be unreliable. Moreover, from an ethical perspective, the challenging circumstance of an outbreak might be a problem if research participants are unable to be provided with necessary care while a clinical trial proceeds. As experience with mid-outbreak Ebola vaccine trials in West Africa showed, it can be hard to afford the required respect to research participants where there are practical obstacles to keeping them sufficiently informed and continuing to check their wellbeing. It is easy enough to recommend that principles of human research ethics must be upheld even in an infectious disease emergency (see WHO 2009), but in practice the conditions of that emergency can make it difficult to uphold those principles.

The most important principle of human research ethics is the requirement for free and informed consent, but here the CEPI approach to vaccine research might give rise to a fourth problem. During an infectious disease outbreak, when researchers are testing the efficacy of a candidate vaccine, it might be difficult to be confident that consenting research participants have freely volunteered and been fully informed of the risks. If the outbreak occurs in a part of the world where there is mistrust of government and local health systems, the pressure of an emergency situation might exacerbate that mistrust. This in turn could complicate the process of communicating information to prospective research participants about the practical details of a clinical trial and about scientific concepts such as randomization, control groups and standard of care (Keusch et al. 2017: 55-56). The meaning of such concepts can be difficult to convey even in wealthy settings with highly educated populations (London et al. 2012: 291), so it seems likely that this challenge would be even greater when researchers approach an impoverished, less educated population. And where a population is also fearful of an ongoing disease emergency, the ethical risk is that research participants’ consent is circumstantially coerced; perhaps by their feeling desperate for the health protection they think a clinical trial might provide, or by feeling ‘powerless to decline an invitation to participate’ (WHO 2016b: 32-33). Experience from the West Africa Ebola outbreak suggests strongly that such problems could likewise arise when CEPI-funded researchers attempt to conduct vaccine efficacy trials ethically in the midst of a dreaded disease outbreak.

The fifth and most serious potential problem with the CEPI approach to vaccine development is that it involves too little pre-outbreak research. Arguably, CEPI will not propel an experimental vaccine far enough down the development pathway toward timely usefulness. Rather, the Coalition’s plan is for efficacy testing to be undertaken only once an outbreak of the relevant disease is underway, and this carries the risk that a vaccine will bring no disease-control benefit. Advocates for the establishment of a global vaccine development fund had referred to the 2014 Ebola outbreak when they made their case, which was based on the supposed connection between time saved by doing pre-outbreak vaccine research and lives saved by being able to vaccinate people at the start of an epidemic (Plotkin et al. 2015: 300). Too many people had died in West Africa, they argued, because the commencement of efficacy testing had to wait until candidate Ebola vaccines had been safety-tested (see Hoyt and Hatchett 2016: 384). However, it is important to see this argument for what it is: a judgment made in hindsight. Even if many doses of a safety-tested Ebola vaccine had existed in 2014, it might not have turned out to be efficacious in humans, in which case many people in West Africa would have died anyway. CEPI is designed to have Phase I (safety) clinical trials successfully completed prior to the moment when a disease outbreak presents an opportunity for Phase II (efficacy) testing. But any hope that that vaccine will be successful in an efficacy trial needs to be tempered by a realisation that many ‘promising’ pharmaceuticals do not retain their potential and thus never enter into clinical use. Sometimes, due to biological differences, a vaccine that is proven efficacious in laboratory-based animal studies might not show any benefit when tested in humans (Editorial 2018; Yasinski 2018). Thus, if there is too much optimism that a CEPI-funded candidate vaccine *will* be proven efficacious during an outbreak, there is a risk of public disappointment in the event that that vaccine does not work. This in turn could jeopardising public confidence in the value of future research efforts and pharmaceutical interventions.

CEPI’s pre-emptive pharmaceutical approach to emerging infectious diseases—settling initially for animal efficacy only and stockpiling candidate vaccines that are merely safe—appears to reflect an unwillingness to undertake pre-outbreak efficacy research involving healthy volunteers. Such research would certainly be more risky for human participants, but it would also allow greater certainty about the disease-control benefit to be derived from a new vaccine. Arguably, if the control of emerging infectious disease is to be taken seriously as a matter of ‘health security’ (CEPI 2018a), there is a security-based justification for conducting a riskier form of pre-outbreak research: deliberate infection of healthy volunteers to test the efficacy of candidate vaccines. A precedent for doing this is Operation Whitecoat.

**Human challenge studies: Operation Whitecoat and US national security**

During the early Cold War period, the US Government feared that the Soviet Union was developing biological warfare capabilities that threatened US national security. In this context, between 1954 and 1973, around 2,300 young American men entering military service as conscientious objectors participated in Operation Whitecoat as medical research volunteers. At the US Army’s biodefense facility at Fort Detrick, Maryland, almost all Whitecoat volunteers were Seventh Day Adventists trained as medics who, for religious reasons, refused to fight (Pittman 2005: 183). They were willing instead to risk their health for their country by participating in research on the prevention and treatment of infectious diseases. The objectives of Whitecoat experiments included ‘development of vaccines against biological weapons and endemic disease threats’ (Pittman 2005: 183). These experiments were more ambitious than those envisaged by CEPI, because the US Army’s clinical research on human efficacy involved deliberately causing a disease rather than waiting for its natural occurrence. Over two decades, the group of Whitecoat volunteers participated in 135 clinical studies involving exposure to live pathogens and receipt of investigational vaccines (Pittman 2005: 183). Most exposures were to *Coxiella burnetii* (Q fever) bacteria, and there were also exposures to pathogens that cause sand fly fever, tularaemia, and Venezuelan equine encephalitis (Pittman 2005: 184-185). No participant died or suffered long-term injury during Operation Whitecoat (Pittman 2005: 183), and the research led to effective vaccines and treatments for several deadly diseases. For example, Whitecoat testing in the 1960s showed that most human volunteers vaccinated with LVA (a tularaemia vaccine) were protected against disease symptoms following ‘aerosol challenge’ with a virulent strain of tularaemia bacteria (Twine et al. 2010).

In contrast to clinical Ebola research conducted in West Africa in 2015, Whitecoat research did not take place in the midst of a naturally-occurring disease outbreak, so it did not draw resources away from any immediate disease-control efforts. All Whitecoat research was conducted in the United States, so there was no off-shoring of research participation risks. And the research environment for efficacy-testing was highly controllable and science-friendly, with research participants able to receive state-of-the-art medical care when needed. Even so, the clear ethical downside to Operation Whitecoat was that the deliberate infection of human subjects endangered their health. Many volunteers apparently thought the risk of efficacy-testing was nevertheless worth taking in return for a potential security benefit: US citizens could be better protected against Soviet biological weapons. And it is important to note that individuals’ decisions to participate in Operation Whitecoat experiments appear to have been well-informed and genuinely voluntarily. Prospective research participants were asked to give consent at several stages—once before they joined the program, and then twice in respect of each individual experiment (Zitner 2001)—and around 20% of the men invited to join declined (Stephenson and Anderson 2007: 567). Volunteers for specific studies were briefed and allowed to ask questions, and anyone expressing interest was then interviewed individually. Depending on the level of risk involved in an experiment, participants were not allowed to sign a consent document until the expiry of a waiting period ranging from 24 hours to four weeks, during which time they were encouraged to consult with family members (Stephenson and Anderson 2007: 565-66).

In the post-Whitecoat era, ethical sensibilities have shifted, and today it is a widely-held view that the human efficacy of a new vaccine against a dangerous disease may only be studied during a natural outbreak. With regard to Ebola in particular, some authors have observed that pre-outbreak clinical trials to determine a pharmaceutical’s efficacy in humans would be ethically infeasible because of that disease’s high mortality rate (Stephenson and Anderson 2007: 560; Keusch et al. 2017: 1). And yet, arguably, the conduct of pre-outbreak efficacy testing of vaccines would only extend the humanitarian, security-oriented logic used by CEPI advocates who claim that pre-outbreak safety-testing is justified: more time saved in developing a vaccine can mean more lives saved by making it available sooner. Against the claim that it would be unethical to expose clinical research participants to a high level of risk, it could be argued that it is unethical *not* to conduct vaccine efficacy trials before an emerging infectious disease causes a crisis. To refrain from such research is to run the more serious risk that a candidate vaccine being efficacy-tested during an outbreak will not help to end it, and that risk would be borne by many more people.

**Global Bioheroes: a solidarist approach to health security**

Accelerated vaccine development for the sake of ‘health security’ could and perhaps should go further than CEPI would take it. If securitization in this and other spheres of activity involves extraordinary measures going ‘beyond rules that would otherwise bind’ (Buzan et al. 1998: 5), the relevant ‘rule’ here is the common ethical objection to placing research participants at high risk. Going beyond this objection would open the door to pre-outbreak efficacy testing in humans of candidate vaccines against emerging infectious diseases, but the absolute ethical requirement of free and informed consent could and should still be observed. One option might be to follow the Whitecoat precedent directly by calling for research volunteers from among military personnel. Julian Savulescu has argued, for example, that soldiers should be allowed to ‘trade risk on the battlefield with risk in the laboratory’ in order to produce vaccines and ‘ultimately maintain national security’ (Savulescu 2015: 99). In the context of an ongoing war involving both bioterrorism and physical violence, soldiers’ participation in high-risk medical experiments would be equally as justified as their participation in lethally risky combat (Savulescu 2015: 100). However, in the pursuit of *global* health security, this option might be difficult to justify because in many part of the world military service is coerced rather than voluntary.

To promote pre-outbreak clinical research on the human efficacy of new vaccines, a better approach might be based not on service but on an ethos of solidarity. Such a research programme for securing global health pharmaceutically could be called ‘Global Bioheroes’, and it would involve civilian volunteers from around the world. Each individual biohero would courageously confront biological danger in the form of clinical research risk; hazarding and perhaps sacrificing their health in enacted solidarity with disease-threatened people worldwide. A familiar notion of a hero in a security context is the soldier who, in solidarity with fellow members of a society in need of protection, risks their body in combat against a threatening enemy. A biohero helping to fight a virus would similarly combine bodily risk-taking and a spirit of solidarity, but for the sake of health security rather than victory in war. And whereas wars have often been fought for causes of dubious worth, a person volunteering instead to defeat global disease threats as a research participant might find that form of heroism easier to justify.

Appeals to solidarity are not uncommon in matters of global health policy. On 8 August 2014, when WHO director-general Margaret Chan requested more resources to deal with the Ebola outbreak in West Africa, she described her request as ‘an urgent call for international solidarity’ (Enserink 2014b: 719). And in July 2015 a panel of experts appointed by the WHO to assess the West Africa Ebola experience reported: ‘We have learned lessons of solidarity. … in an increasingly globalized world, a disease threat in one country is a threat to us all. Shared vulnerability means shared responsibility’ (WHO 2015b). According to Dawson and Verweij (2012: 1), calling for solidarity can mean asking people to set aside their short-term individual interests in favour of longer-term collective benefits through the use of rhetoric such as ‘we can beat this together’, and they provide the example of voluntary social distancing to help limit the spread of disease during a pandemic. More generally, being in solidarity with other people can mean acting on their behalf based on recognition of similarity (West-Oram and Buyx 2017: 213), and it can involve a commitment to action that potentially brings risk and harmful consequences to oneself (Jennings and Dawson 2015: 35). Perhaps, therefore, solidarity in the face of globally-shared disease risks could manifest as multiple individual commitments worldwide to share the personal risk associated with developing pharmaceutical solutions more quickly.

Already, in research conducted in wealthy countries, some volunteers freely consent to risk their own health in human challenge studies so that other people elsewhere might benefit from new pharmaceuticals. There is limited empirical data on what motivates clinical research participation in general, but one recent study has reported that motivations range from financial need to a desire to contribute to the health of others (Stunkel and Grady 2011). In 1974, after the US Army had closed Operation Whitecoat, a vaccine testing centre in Maryland began recruiting volunteers to participate in human challenge studies conducted in isolated rooms at a university hospital. Volunteers received compensation equal to that received for performing jury duty and they were required to pass a written test proving they understood the risks. Experiments included ‘challenging’ (infecting) research participants with influenza or cholera in order to test drugs and vaccines (Cohen 2016: 884). Since that time, and although the higher risk to research participants has sometimes been controversial, human challenge studies have gradually become more prevalent in the United States and beyond. As of 2016, volunteers in various studies were reportedly being deliberately infected with malaria, influenza, shigella, dengue, norovirus, tuberculosis, rhinovirus, *Escherichia coli*, typhoid, giardia or campylobacter (Cohen 2016: 883). This activity clearly entails a risk that healthy people might suffer harm and, if the disease being researched is contagious, potentially spread infection to others. However, advocates of human challenge studies argue that this risk is outweighed by the benefit of their ‘enormous potential … to accelerate vaccine development’ (Feasey and Levine 2017: 2419).

Conducting vaccine efficacy trials involving participants exposed to naturally-occurring infection is slower and more expensive, whereas human challenge studies can save time and money by speedily establishing whether a candidate vaccine should be abandoned or pursued further. For example, in a recent clinical trial conducted in the Netherlands, researchers aimed to speed up vaccine development by deliberately infecting 17 volunteers with tiny worms that cause schistosomiasis, a disease that kills thousands of people each year. The advantage of conducting a ‘controlled infection study’, according to the researchers, was that it avoided the huge expense, complexity and time commitment associated with field-trialling a vaccine (Kupferschmidt 2018). In the United Kingdom in 2017, more than 100 residents of Oxford voluntarily swallowed *Salmonella typhi* bacteria to test a new vaccine against typhoid fever, a disease that annually kills almost 200,000 people. This study, funded by the Gates Foundation, quickly showed that the vaccine was 87 percent effective, leading the foundation’s director of diarrheal diseases to declare that ‘challenge tests are a great way to short-circuit the process of proving it works’ (McNeil 2017).

A Global Bioheroes programme could similarly save time (and potentially save many lives) by promoting human challenge studies on infectious diseases listed in the WHO’s Blueprint for R&D Preparedness. The basic proposition here is that healthy volunteers from around the world would be scientifically exposed to potentially deadly viruses in order to test the efficacy of candidate vaccines. Already, with regard to one Blueprint disease (Zika), some bioethicists have suggested that laboratory-based challenge studies might become justifiable if natural Zika incidence became so sporadic that field-based vaccine efficacy trials would be impractical (Baumgaertner 2018). Ideally, Global Bioheroes research would take place in an isolated, high-containment, state-of-the-art research facility in a resource-rich setting conducive to good science. In a randomised clinical trial, volunteers would have a 50 percent chance of not receiving a vaccine (that might be efficacious) and instead only receiving a placebo and the best supportive medical care in the world. Some Blueprint diseases are more deadly than others, but that might allow efficacy research to involve a relatively small number of volunteers. A high mortality rate means that, if a candidate vaccine is efficacious, this should be easy to prove even in small-scale trials, perhaps involving as few as 100 people (see Hayden 2014: 178). If candidate vaccines were tested all the way through Phase II (efficacy) prior to the occurrence of a natural disease outbreak, effectiveness (phase III) testing could then take place in the field. And at that stage, in comparison to the CEPI (safety-testing only) scenario, there would be a higher likelihood that at-risk people receiving the candidate vaccine would be protected from infection and that this in turn would have a significant inhibitory effect on the progress of the outbreak.

Just as it would have been good to have had a safety-tested Ebola vaccine available to West Africans in mid-2014, it would have been better if a vaccine had existed that had already been proven efficacious. But if one lesson from the Ebola experience is that a lack of prior investment in research holds back disease prevention in a crisis (Plotkin et al. 2015: 297), it is also worth acknowledging that habitual risk-aversion in clinical research can do that too. Ethically, the downside of Global Bioheroes is that research participants in pre-outbreak vaccine efficacy trials would experience greater risk than they would in CEPI-style safety trials. However, that fact alone does not necessarily mean that the overall risk-benefit ratio is unacceptable. The ethical upside is that Global Bioheroes would be better than CEPI according to CEPI’s own humanitarian logic: the higher the state of pharmaceutical readiness, the higher the likelihood of saving lives pharmaceutically. Add to this a CEPI-style invocation of ‘health security’, and the benefit (to be weighed against risk) of Global Bioheroes appears to increase. That security-based argument would need to be made powerfully and persuasively, however, to ensure public confidence that a higher-than-usual degree of risk to research volunteers was warranted (see Bambery et al. 2016: 98).

By pre-empting the need for field-based efficacy trials, the Global Bioheroes approach would also reduce the level of research risk to which many other people might otherwise be exposed in the challenging context of a natural disease outbreak. And, in comparison to the experience of doing early-stage Ebola vaccine research during an outbreak in West Africa, the effectiveness-testing of advanced Global Bioheroes vaccines is less likely to be seen as an unwelcome distraction from non-pharmaceutical disease-control efforts. Unlike CEPI, Global Bioheroes would also involve no transfer of research risk from the developed to the developing world. Rather, the entry of volunteers from around the world into pre-outbreak efficacy trials would be based on a solidarist commitment: that there should be global sharing of exposure to research risks when developing new vaccines against potentially global-scale disease risks. The standard of medical care for individual global bioheroes would be the world’s best (not merely the best available locally in a resource-poor outbreak zone), and superior research conditions would also be more conducive to the provision of rigorous ethical oversight. People with diminished capacity to give their informed consent could be more easily excluded from participation. And, in the manner of Operation Whitecoat, great care could be taken (using interviews, written tests, and cooling-off periods) to ensure that research participants are fully informed about, and free to decline, the risks of being a global biohero. A payment scheme would need to be carefully designed to minimise undue financial temptation, but at a minimum it could include compensation for income lost while participating in research and the free provision of any necessary follow-up medical care.

**Conclusion**

The increasing emphasis on pharmaceutical approaches to global health security requires ongoing normative evaluation, and this should encompass the clinical research that produces new vaccines. The West African Ebola outbreak showed how an emerging infectious disease can cause death and dread on a large scale, and it highlighted the value of deploying vaccines early to end an outbreak quickly. In response, CEPI was established to provide the world with ‘health security’ by accelerating the vaccine research process, but its approach to this is arguably lacking in ambition. If the diseases listed on the WHO Blueprint really do threaten global health security, a security-oriented pharmaceutical response could justifiably include a greater degree of research acceleration and research risk. The logic underpinning CEPI’s plan for pre-outbreak safety-testing of candidate vaccines is that time saved means lives saved. However, a safe vaccine might yet prove to be a non-efficacious one, and conducting efficacy-testing during a naturally-occurring outbreak is likely to have some serious ethical downsides. Under the alternative Global Bioheroes model, a candidate vaccine would be propelled further along the development pathway to the point where it is more likely to yield a timely public-health benefit in the event of a disease outbreak. Pre-outbreak testing of a vaccine’s efficacy would be dangerous to research volunteers from around the world, but today there are already people who are willing to risk their health for the sake of others in human challenge studies. Under world-class medical supervision, and with great care taken to ensure their free and informed consent, global bioheroes motivated by solidarity would enable a fairer distribution of the risks of securing global health pharmaceutically.

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1. In this article, the noun ‘hero’ is gender-neutral. It replaces ‘heroine’ in the same way that the gender-neutral nouns ‘author’, ‘actor’ and ‘waiter’ now commonly replace ‘authoress’, ‘actress’ and ‘waitress’ respectively. [↑](#endnote-ref-1)