

the risks of air transport, given the hemodynamic instability associated with EVD.

Recently, substantial attention has been paid to unlicensed therapies and vaccines. Among the therapies in development is a “cocktail” of humanized-mouse antibodies (“ZMapp”), which has shown promise in nonhuman primates. ZMapp was administered to two U.S. citizens who were recently evacuated from Liberia to Atlanta, and both patients have had clinical improvement. However, it is not clear whether ZMapp led to the recovery, and with only two cases, conclusions regarding its efficacy should be

 **An audio interview with Dr. Fauci is available at NEJM.org**

withheld. Moreover, the supply of ZMapp remains limited to a handful of doses, and production scale-up, though under way, will take time. Other candidate therapeutics include RNA-polymerase inhibitors and small interfering RNA nanoparticles that inhibit protein production.⁵

Preclinical evaluation of several vaccine candidates is also under way, and it is anticipated that a

candidate developed at the National Institutes of Health will enter a phase 1 trial this fall, pending a decision from the Food and Drug Administration. This vaccine, a chimpanzee adenovirus-vector vaccine, includes two inserted Ebola genes encoding glycoproteins. Two other vaccine candidates involve vesicular stomatitis virus pseudotypes. Human clinical testing of one of these vaccines is expected to begin in early 2015.

While these interventions remain on accelerated development paths, public health measures are available today that have a proven record of controlling EVD outbreaks. Moreover, premature deployment of unproven interventions could cause inadvertent harm, compromising an already strained relationship between health care professionals and patients in West Africa. Rapid but proper evaluation of candidate therapies and vaccines is needed. Should exemptions be offered for compassionate or emergency use, distribution of scarce interventions must be conducted with careful

ethical guidance and regulatory review. It is unlikely that any miracle cure will end the current epidemic. Rather, sound public health practices, engagement with affected communities, and considerable international assistance and global solidarity will be needed to defeat Ebola in West Africa.

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Studying “Secret Serums” — Toward Safe, Effective Ebola Treatments

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Ebola virus (EV), the cause of an ongoing deadly epidemic in West Africa, has been one of the world’s most feared pathogens, causing catastrophic clinical disease and high mortality. Although the highest priority must be given to public health and infection-control measures

that have contained past outbreaks, the current outbreak — the largest ever recorded — also highlights the need for effective treatment.

The report that two seriously ill American volunteers, Kent Brantly and Nancy Writebol, received an experimental cocktail

of three monoclonal antibodies, never before administered to humans, has raised questions around the globe. Dubbed “secret serum” by the media, the treatment has generated hope, suspicion, accusations of inequity, and requests for additional product, of which, since the manufacturers provided

three remaining doses to Liberia, there is now none.

The product received by Brantly and Writebol is ZMapp, containing antibodies against three EV glycoprotein epitopes, manufactured by expression in tobacco plants.¹ The product conferred a survival benefit in infected nonhuman primates when administered 24 to 48 hours after infection¹ and also appears to be beneficial even if started 4 to 5 days after infection, using fever and positive polymerase chain reaction as the treatment trigger² — but these findings may not predict response in humans. No human safety studies were performed before the drug was administered to these two patients, whose condition reportedly improved soon after they received it. Although this report engenders hope, one cannot reach a sound conclusion on the basis of two patients' survival. Moreover, a third patient has now died despite reportedly having received ZMapp.

In addition, the likelihood that the first two recipients would have died without therapy may have been significantly less than the approximately 50% so far noted in the current epidemic. Surviving beyond the first several days of EV illness may be predictive of overall survival, as it was in the 1995 Congo outbreak. Brantly reportedly became ill 9 days before receiving the product, and Writebol may have been sick at least as long. Brantly received a transfusion from a recovered patient, for which there is conflicting evidence of effectiveness, and high-quality supportive medical care may well improve survival, an issue that merits further emphasis. Finally, mortality often de-

creases over the course of Ebola outbreaks, perhaps because of enhanced diagnosis and care. More detailed clinical information from these and any other patients treated may help clarify the likelihood that any improvement is attributable to the treatment.

Similar or greater uncertainty pertains to other experimental therapies in clinical development for EV. These include the following: TkM-Ebola, small interfering RNAs targeting EV RNA polymerase L, which reduced mortality in a nonhuman primate model³ (the Food and Drug Administration placed a hold on a human safety study of TkM-Ebola owing to "cytokine release" but partially relaxed it to allow use in EV-infected patients); AVI-7537, which targets EV protein VP24 through an RNA interference technology, confers a survival benefit in nonhuman primates,⁴ and was tested as part of an earlier product in an unpublished safety trial (listed in ClinicalTrials.gov); and BCX-4430, an adenosine analogue that is active against EV in rodents and protected nonhuman primates from Marburg virus⁵ — but for which there are no recorded human safety trials. Several other therapeutics are in earlier phases of development, and some drugs approved for other indications, which have known safety profiles at clinically used doses, including chloroquine and imatinib, have shown activity against EV *in vitro*⁶ and, in some cases, in rodent models.

The current situation, though crystalizing relatively common issues of balancing access to investigational agents with the need for answers about what works, is nonetheless highly unusual: an

acute outbreak of a frightening, often lethal disease, a high risk to health workers and their families, no known effective treatments, and a tantalizing suggestion of benefit from a drug not previously given to humans but in extremely limited supply. Furthermore, at this time, meaningful clinical evaluation of such new treatments is likely to be possible only in the countries where the outbreak is occurring, where the challenge is complicated not only by pressing demands of the crisis on health care and lack of clinical trial infrastructure but also by history and mistrust. In the heat of this moment, we need to think both carefully and humanistically.

A group of ethicists urgently convened by the World Health Organization to consider issues of access to experimental treatments stated both that it is "ethical to offer unproven interventions with an as yet unknown efficacy and adverse effects" and that "there is a moral duty to evaluate these interventions in the best possible clinical trials" (www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en). The group has not yet discussed criteria and approaches for determining when and how to study such products or how to determine which ones are suitable for use. These questions are important because the consequences of unforeseen harm, both to patients and public trust, from premature or ill-advised widespread use of an experimental therapy that proves unsafe could be substantial and jeopardize both the outbreak response and efforts to develop treatments.

Clinical drug development is

usually only begun once preclinical laboratory and animal testing have minimized concerns about toxicity and provided evidence supporting potential benefit. Some such core preclinical data should, even in an emergency, be required before new EV drugs are tested in humans, since without reasonable assurance regarding toxicity and potential benefit, there will almost always be too little information to presume equipoise. Next, before a drug is tested in sick people, unless it is expected to be potentially toxic as part of its action (e.g., some cancer drugs), it is almost always tested in small safety and pharmacokinetic studies in healthy volunteers, permitting determination of appropriate dosing and detection of common serious adverse effects. If an experimental product is used first in acutely ill, unstable patients, it may be impossible to recognize even severe adverse effects such as organ failure and death if such events are commonly part of the disease itself.

One approach to studying safety while making particularly promising drugs available early for patients with this devastating illness would be to allow limited emergency use in parallel with safety studies in healthy volunteers, provided that available data suggest potential benefit and low risk, that full informed consent can be obtained, and that patients can be carefully monitored and supported. Similarly, the experience in the first two people treated with ZMapp at least ruled out a universally severe adverse response. Thus, the regulatory flexibility shown in the United States, Spain, and Liberia in al-

lowing its emergency use is not unreasonable.

Can and should controlled clinical trials be performed for EV therapeutics? It is worth remembering that the majority of new drugs entering into clinical trials fail, most often because they lack efficacy or, less often, because of safety problems. Furthermore, using unproven therapies during emergencies, without adequately evaluating their effectiveness, may result in misleading, even harmful, conclusions. Before the 2001 anthrax attacks, for example, inhalational anthrax was considered to be 80 to 90% fatal even with antibiotic treatment. Yet with early diagnosis and state-of-the-art supportive care, mortality in 2001 was only 45%. If we had administered a harmless but ineffective investigational product to patients and compared the results with historical ones, we could have concluded that it saved many lives. And even if it had been highly toxic, killing 20% of recipients, we would have observed 65% survival and might have erroneously concluded that it had reduced mortality by 20%.

Thus, the current state of clinical evidence for EV investigational products makes meaningful clinical trials both ethical and essential. Furthermore, given the insufficiency of supply, a randomized trial could provide an equitable way of allotting drugs while finding out whether they work. Any studies should be designed to include interim analyses and stopping rules for clear benefit or toxicity. Practical questions must also be considered: study designs and data requirements should be streamlined to focus

on the most critical information and outcomes, and performed in the most capable facilities. When sufficient doses of an unproven but promising therapy become available, it may be reasonable to consider administering it both within clinical trials and for “compassionate use,” particularly in places where trials cannot be conducted, provided that all patients can be adequately monitored. Full transparency, including culturally appropriate communication of what is known and not known about a drug’s risks and benefits, and voluntary consent, under the appropriate country’s leadership and authority, are critical for any investigational use.

As we move forward, quickly but cautiously, in using and testing new therapies, we have already learned some lessons from this outbreak — regarding the need to build trust, the need to enhance public understanding of experimental treatments and their safe evaluation, and the critical nature of the capacity both for public health intervention and to ethically field clinical studies under challenging conditions. When it comes to infectious diseases, we are increasingly one world and dependent on each other for knowledge, safety, and security.

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