As local and international public health officials work to end the Ebola epidemic in West Africa, efforts to develop therapies and vaccines against the virus are ramping up.

In late January, officials from the World Health Organization (WHO) announced that the Ebola epidemic had slowed. The WHO noted that for the first time since June 29, 2014, there were fewer than 100 new confirmed cases in the 3 hardest hit countries, Guinea, Liberia, and Sierra Leone (http://bit.ly/1LimWSP).

"Things are currently trending in a good direction, suggesting growing control," said Inger Damon, MD, PhD, the US Centers for Disease Control and Prevention’s (CDC’s) Ebola Response Team Incident Commander. "But there is still considerable work to be done."

International response efforts are shifting from reducing the number of new infections to trying to completely eliminate new infections. To do this, they are focusing on thorough contact tracing and surveillance of potentially exposed individuals for the 21-day period during which symptoms may emerge.

"When we do that efficiently, it allows us to rapidly identify new cases and break the chain of transmission," Damon said.

Damon and other experts are quick to caution that ongoing vigilance is necessary to prevent resurgence. About 200 CDC staffers remain in Guinea, Liberia, and Sierra Leone, providing technical advice on infection control, health communications, exit screening for travelers, and coordination of surveillance and contact tracing.

"A single new case is enough to reignite an outbreak," said Brice de la Vingne, Médecins Sans Frontières’ (MSF’s) director of operations in a statement on the organization’s website (http://bit.ly/1SKGdfrr). "Until everyone who has come into contact with Ebola has been identified, we cannot rest easy."

As Ebola Epidemic Begins to Slow, Trials of Drugs and Vaccines Speed Up

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Fast-Tracking Interventions

The ongoing epidemic has sparked an unprecedented level of multinational cooperation to speed clinical trials of potential therapeutics and vaccines. Currently, the most effective treatment for Ebola virus disease is fluid and electrolyte replacement and other supportive care, said Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), during a press briefing hosted by the US Department of Health and Human Services (HHS) in late January (http://www.hhs.gov/news/press/2015pres/01/20150127a.html). There are no drugs proven to be safe and effective against Ebola virus disease, Fauci said.

But some experimental therapies have been used to treat patients with Ebola virus disease under compassionate care exemptions. For example, several infected patients in the United States and other countries received ZMAPP, a combination of 3 different neutralizing antibodies against the Ebola virus, based on promising results from animal studies. Now ZMAPP and other therapies and vaccines are being fast-tracked into phase 1 and 2 clinical trials.

Several interventions for Ebola currently entering early-phase clinical trials were developed years ago, said Thomas Geisbert, PhD, of the University of Texas Medical Branch at Galveston. But until the current large-scale, multicountry outbreak that began in 2013, there wasn’t a sense of urgency or much funding for clinical trials. "I’ve never seen anything like this," said Geisbert. "It really was the outbreak that pushed things to the forefront."

In coming weeks, NIAID is planning to start phase 1 and phase 2 clinical trials of ZMAPP in the United States and Liberia in cooperation with the government of Liberia, Fauci said. The trial will undergo multiple reviews in the United States and Liberia before it begins and will be overseen by independent safety monitors, Fauci said. The trial

Cases of Ebola Virus Disease in Guinea, Liberia, and Sierra Leone, March 25, 2014 – February 1, 2015

Source: Centers for Disease Control and Prevention.
organizers are also working closely with Liberian community leaders, who played a critical role in containing the epidemic, Fauci said.

“It is important to balance the urgency to deploy investigational medical countermeasures in an emergency with the need to evaluate these countermeasures through rigorously designed clinical trials,” Fauci said.

To supply sufficient quantities of ZMAPP for the trial, the US Biomedical Advanced Research and Development Authority (BARDA) has worked with pharmaceutical companies that use tobacco plant–based biologic production systems to help scale up antibody production, said BARDA director Robin Robinson, PhD, during the HHS briefing.

Robinson explained that tobacco-based products were chosen based on evidence from a nonhuman primate study demonstrating that antibodies produced in tobacco plants more effectively bind and neutralize the virus (Olinger GG et al. Proc Natl Acad Sci. 2012;109[44]:18030-18035). Robinson and his colleagues at BARDA also reached out to other manufacturers to try to develop ZMAPP-like products.

Another therapeutic in development, known as TKM-Ebola, blocks the enzyme that catalyzes the replication of the Ebola virus and was found to protect against the disease in nonhuman primates (Geisbert TW et al. Lancet. 2010;375[9729]:1896-1905). In August 2014, the US Food and Drug Administration modified a hold it had placed on a phase 1 trial of the agent (http://bit.ly/1zYE3CI), allowing it to be used on a compassionate basis in some patients infected with Ebola.

Clinical trials of 2 antivirals, favipiravir and brincidofovir, were also launched in late 2014 at MSF treatment centers in West Africa led by the French National Institute of Health and Medical Research and the University of Oxford, respectively (http://bit.ly/1IzGqR).

Blood and plasma from patients who survived an Ebola virus infection have also been used on a compassionate basis. This strategy capitalizes on Ebola antibodies in survivor’s blood, an approach that has been used successfully to treat other infections. Multiple clinical trials of convalescent whole blood and plasma are currently under way in the affected countries (Butler D. Nature. doi:10.1038/nature.2014.16564 [published online December 15, 2014]). A recent analysis projected that transfusion therapy could save 151 to 3586 lives depending on the hospitalization rate and is an inexpensive and scalable intervention (Gutfraen J and Meyers LA. J Infect Dis. doi:10.1093/infdis/jiv042 [published online January 29, 2015]).

Convalescent blood does carry the risk of potentially transmitting blood-borne disease, but experts note that the vaccine and antiviral therapies under investigation are expensive and may be hard to scale in resource-constrained countries (Tully CM et al. Lancet Infect Dis. doi:10.1016/S1473-3099(14)71071-0 [published online January 13, 2015]).

Accelerating Vaccine Trials
Clinical trials are also advancing on experimental vaccines against Ebola virus in the hopes of protecting frontline health workers, burial crews, and others at high risk in future epidemics. To achieve this goal, the National Institutes of Health (NIH) has collaborated with manufacturers of 2 different vaccines derived from the Zaire strain of Ebola virus. One vaccine, developed by NIAID and GlaxoSmithKline, uses chimpanzee adenovirus type 3 (ChAd3) as a vector to deliver noninfectious Ebola genes into the body to stimulate an immune response to the virus. The US Department of Defense has worked with NIH and co-manufacturers NewLink and Merck to conduct phase 1 trials of another vaccine that uses vesicular stomatitis virus (VSV) as a vector.

“A safe and effective Ebola vaccine will undoubtedly be a critically important tool to help prevent Ebola virus infections in future outbreaks,” said Fauci.

The US and Liberian governments are jointly launching a phase 2-3 randomized double-blind trial that will compare both the VSV and ChAd3 Ebola virus vaccines and a placebo in 27 000 health workers and others at risk in Liberia (http://1.usa.gov/16LmCMe). Preliminary results from a phase 1 trial of the ChAd3 vaccine in 60 health volunteers in United Kingdom reported no safety concerns and found that the vaccine stimulated an immune response (Rampling T et al. N Engl J Med. doi:10.1056/NEJMoa1411627 [published online January 28, 2015]). The immune response was not as robust as that seen in studies of the vaccine in macaques, but the authors suggest this might be remedied by adjusting the vaccine dose.

The CDC is also preparing for a 6000-person vaccine trial in Sierra Leone, said Anne Schuchat, MD, director of the CDC’s National Center for Immunization and Respiratory Diseases, during the HHS briefing. Participants in the phased-induction trial will be vaccinated on a rolling basis, and rates of infection in those vaccinated early will be compared with those vaccinated later. The agency hasn’t finalized whether they will use the VSV or ChAd3 Ebola virus vaccine for the trial, she said. Other Ebola vaccines are also in development, including one produced by Johnson & Johnson and another by Novavax (http://www.who.int/medicines/emp_ebola_q_as/en/).

Geisbert said the head-to-head trial of the 2 leading vaccine candidates, ChAd3 and VSV, is helpful because it can be hard to predict how results from nonhuman primate studies will translate into humans.

“It’s good to have options,” he said.

Challenges Ahead
Major challenges remain for the affected countries and international groups working to eliminate the transmission of Ebola. The already fragile health systems of Liberia, Guinea, and Sierra Leone have suffered serious damage. More than 800 health workers have had confirmed Ebola infections and at least 488 have died of the disease, according to the WHO. Liberia is just beginning to reopen hospitals shuttered during the epidemic, and MSF is running mobile clinics to help meet primary care needs.

“An added struggle is the paralysis of the public health system [in Sierra Leone],” said Karline Kleijer, MSF’s emergency coordinator, in a statement. “One in ten of the country’s health workers have died of Ebola, the medical facilities are in disarray, and people with non-Ebola illnesses struggle to get the treatment they need,” she said.

Some populations have been difficult to reach, such as those communities in forested areas of Guinea, or are resistant to public health measures aimed at reducing the spread of Ebola virus disease. In certain regions, it is customary to wash the body in preparation for burial, explained Damon. If proper precautions are not taken during this process, the high levels of virus still present on the body may infect others.

Damon said that the CDC and others are working to develop alternative, safe burial practices, “that are respectful of religious beliefs and allow the family and clergy to be appropriately attired and protected.”

Although sustained reductions in infection rates would be welcome news, the
dwindling number of new infections could pose challenges for clinical trials that rely on large cohorts of patients to produce robust results. Already, Chimerix, the manufacturer of brincidofovir, ended its participation in the University of Oxford-led clinical trial of the drug for Ebola treatment, citing declining case numbers in Liberia (http://bit.ly/18HJqh0).

Nonetheless, even trials with inadequate statistical power to demonstrate efficacy can still provide useful safety and subgroup efficacy data that can be used to gain approvals for an intervention, Fauci explained. Schuchat noted that the CDC Sierra Leone trial testing the efficacy of the yet-to-be-chosen vaccine has been designed to account for reduced cases.

Some emerging evidence suggests that the Ebola virus might be evolving (Kugelman JR et al. MBio. doi:10.1128/mBio.02227-14 [published online January 20, 2015]). Geisbert and his colleagues are currently investigating genetic changes in the Ebola virus and acknowledge that this presents a valid concern, particularly because such changes could influence the effectiveness of experimental interventions in development. "Our work is focused on the leading candidate vaccines and therapies and making sure they still protect [against mutated forms of the virus]," he said. ■