As efforts to successfully contain the largest outbreak of Ebola virus disease in history prove elusive, the mounting number of cases and deaths has brought research to develop much-needed treatments and protective vaccines into the spotlight. Although the approval process for drugs and vaccines is typically slow and deliberate, the latest outbreak, declared by the World Health Organization (WHO) on August 8 as an international health emergency, has galvanized regulatory officials to consider proposals for providing as-yet unproven treatments under special emergency New Drug Applications.

“No one wants to see potentially unsafe drugs causing more harm than good. But on the other hand, given a virus that can cause up to 90% case-fatality rates, we all want to see something done to help,” said Thomas Geisbert, PhD, of the University of Texas Medical Branch at Galveston. This latest outbreak appears to have a 55% to 60% fatality rate.

Investigational Therapies
Current treatment for Ebola virus disease consists of supportive care. As the virus reproduces and spreads in the body, it interferes with blood clotting and disrupts electrolyte balance. As a result, severely ill patients are frequently dehydrated and need intravenous fluids or oral rehydration with solutions that contain electrolytes. Such interventions can help sustain some patients and allow them to recover, but in many cases, patients progress toward multiorgan failure, shock, and death.

Ebola virus disease is rare: fewer than 2400 cases (more than 1500 of which were fatal) have been recorded from all earlier outbreaks of the disease since it was first identified in 1976. “Because there is a small global market for Ebola countermeasures, I think the financial support for these products will need to come from governments or perhaps from philanthropists,” said Geisbert. Indeed, the US government, among others, has provided substantial funding for research aimed at preventing and treating Ebola infection, in part because of concern over the potential use of Ebola virus as a bioweapon. Several drugs and vaccines are under development; according to Geisbert, researchers have made considerable progress over the last 5 to 10 years in preclinical studies of preventive vaccines and postexposure therapies, including studies in nonhuman primates. But none of them are available for clinical use.

In studies in nonhuman primates, researchers have tested several therapies that helped animals exposed to Ebola virus survive when given at various times after exposure. These include vaccines, small interfering RNAs that block the expression of...
essential viral proteins, and recombinant anti-Ebola monoclonal antibodies.

“I think any of these 3 postexposure strategies can work under the right conditions,” said Geisbert. The National Institutes of Health (NIH) recently awarded Geisbert’s laboratory a 5-year, $26-million grant to research these 3 types of treatments. Other strategies also have clinical potential. For example, a drug called BCX4430, which is a nucleoside analog that blocks viral RNA synthesis, is generating promising results in rodents and monkeys (Warren TK et al. Nature. 2014; 508[7496]:402-405).

Experimental Medicines During an Outbreak
An experimental monoclonal antibody-based therapy against Ebola virus made headlines recently after 2 Americans who became infected while treating patients in Liberia received ZMapp, a combination of 3 different monoclonal antibodies that has been tested only in animals. The Americans may have received the treatment out of a compassionate use exemption allowed by the US Food and Drug Administration (FDA) under such situations (http://1.usa.gov/1ifaR50). Both patients were transported to the United States for treatment, and it is unclear whether the drug played a role in their recovery. A priest in Spain who contracted Ebola in Liberia also reportedly received ZMapp but subsequently died.

The company developing ZMapp, Mapp Biopharmaceutical, said very limited amounts of the drug were available because ZMapp was first identified as a drug candidate in January 2014 and it has not yet been evaluated for safety in humans. On August 12, the company said in an online statement that it had complied with every request for the drug that had the necessary legal and regulatory authorization, providing the drug at no cost, and that it had exhausted its supply.

Regarding other treatments, a developer of RNA interference therapeutics recently announced that the FDA modified a clinical hold it had placed on a trial that was testing a small interfering RNA called TKM-Ebola in healthy volunteers. The company said the FDA had halted the trial of TKM-Ebola, which blocks an enzyme that catalyzes the replication of RNA, and had “requested additional data related to the mechanism of cytokine release, observed at higher doses.” The modified hold may allow the company to make the drug available to infected individuals (http://bit.ly/1zYE3C0).

Assessments of preventive vaccines are also under way. The US government plans to fast-track development of an adeno-virus-based vaccine that can protect macaque monkeys, with the NIH supporting a phase I clinical trial that is expected to begin in September. Even if the treatment proves effective, it likely would not be available until next year. In addition, the NIH and Thomas Jefferson University are collaborating to develop a candidate Ebola vaccine based on the established rabies vaccine (http://1.usa.gov/1oDqoMY). The agency is also supporting development of Ebola vaccines by Crucell (a subsidiary of Johnson & Johnson) and Profectus Biosciences.

Beyond Efficacy and Safety
Vaccines and drugs typically must go through phase I clinical trials to test their safety before being used in an outbreak setting. “Using experimental Ebola vaccines, monoclonals, or antivirals should be done under the same rigorous protocols and study conditions as anywhere,” said David Heymann, MD, a professor of infectious disease epidemiology at the London School of Hygiene and Tropical Medicine who was on site at the first human Ebola outbreak in 1976. “Safety must be examined and monitored, quality of production monitored and assured, and better understanding of efficacy must be a major goal,” he explained. Heymann and others believe that authorities would likely speed access to investigational medications if a similar disease was rampant in Western countries.

Proving that Ebola treatments work in humans can only be done by testing them in people infected by or exposed to the virus, but the sporadic nature of the disease creates a significant challenge. Even if an effective preventive treatment were developed, it is unclear who should receive it in the years between outbreaks.

The World Health Organization recently convened a panel discussion of medical ethicists, scientific experts, and lay people from affected countries to assess the role of experimental therapies in the Ebola outbreak response. In a unanimous decision, the panel concluded that it is ethical to offer experimental therapies to combat the Ebola virus, even in the absence of data about their effectiveness or adverse effects in humans. The Obama administration also recently announced that it was forming a special Ebola working group, consisting of scientists and officials from institutions including the Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases, that will consider setting policy for the potential use of experimental drugs to help those who are infected.

Working to overcome an infectious disease in Africa can bring additional challenges beyond those in many other parts of the world. Fragile health systems with inadequate resources pose problems for health care professionals, who often provide care without personal protective equipment or adequate infection controls. According to media reports, mistrust of health workers in some regions of the continent or perceptions of hospitals treating patients with Ebola as unsafe places has caused some affected patients to evade treatment. Bringing an insufficiently tested vaccine or postexposure drug to West Africa would have the potential to add fuel to such mistrust.

In wealthier countries, resources are available to closely monitor patients given an experimental medication for adverse effects and to treat them if necessary, but doing so would be difficult for the numerous people in Africa who are infected. In addition, obtaining adequate informed consent would be a challenging in resource-limited settings.

Timing of treatment is also critical. Geisbert worries that if a therapy is given when patients are near death, people might consider it useless if it does not save lives. “This does not mean that you should not try to treat people in advanced stages of disease, just that things need to be taken into the appropriate context,” he said. “The other concern is the flip side of the coin where you treat someone who would have survived anyway and attribute survival to the use of a particular treatment without appropriate data,” he added.

While the global community waits for much-needed prophylactic and therapeutic treatments for Ebola, experts say it is critical to take certain actions proven to effectively stop an outbreak. The more than 40 known outbreaks of varying size and geographic location in sub-Saharan Africa have shown that it can be controlled even in the
Routine Cancer Screening in Older Adults May Offer Few Benefits

Joan Stephenson, PhD

Many older adults may receive cancer screening that is unlikely to offer much benefit, suggest 2 new studies appearing in JAMA Internal Medicine.

In one study, researchers used data for 27,404 participants aged 65 years or older in the National Health Interview Survey from 2000 through 2010 to probe patterns of routine screening of prostate, breast, cervical, and colorectal cancer in the United States (Royce T et al. JAMA Intern Med. doi:10.1001/jamainternmed.2014.3895 [published online August 18, 2014]). Participants were grouped into those with low, intermediate, high, and very high risks of 9-year mortality, based on a validated mortality index.

Although screening rates generally declined as life expectancy decreased, a substantial number of individuals classified at very high risk (75% risk or greater) of dying within 9 years were screened. Of those with a very high 9-year mortality risk, about 31% of women received a Papanicolaou test for cervical cancer within 3 years, 38% of women had a mammogram within 2 years, 41% of men and women had colorectal screening within 5 years, and 55% of men had received a prostate-specific antigen test for prostate cancer within 5 years.

The researchers found similar trends when they analyzed the data by patient age (some clinical guidelines use age rather than life expectancy), with a substantial proportion of individuals undergoing screening not recommended by guidelines.

“These results raise concerns about overscreening in these individuals [with limited life expectancy], which not only increases health care expenditure but can lead to patient net harm,” the authors wrote.

In the second study, researchers used a modeling approach to simulate screening colonoscopy according to guidelines (at 10-year intervals, at age 65 or 75 years) vs more intensive screening (every 3 to 5 years) in average-risk 65-year-old Medicare beneficiaries previously screened at age 55 years with negative results (Van Hees F et al. JAMA Intern Med. doi:10.1001/jamainternmed.2014.3889 [published online August 18, 2014]). They found that more intensive screening was associated with only small increases in preventing colorectal cancer deaths and quality-adjusted life-years gained.

Compared with screening at 10-year intervals, decreasing the screening interval to 5 years was not cost-effective. Screening every 3 years or beyond age 75 years resulted in net harm.