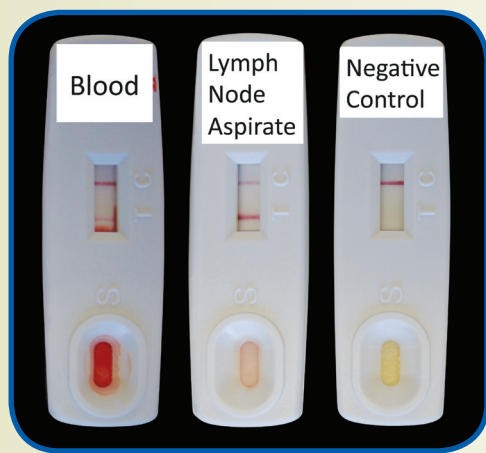


Innovative Technologies

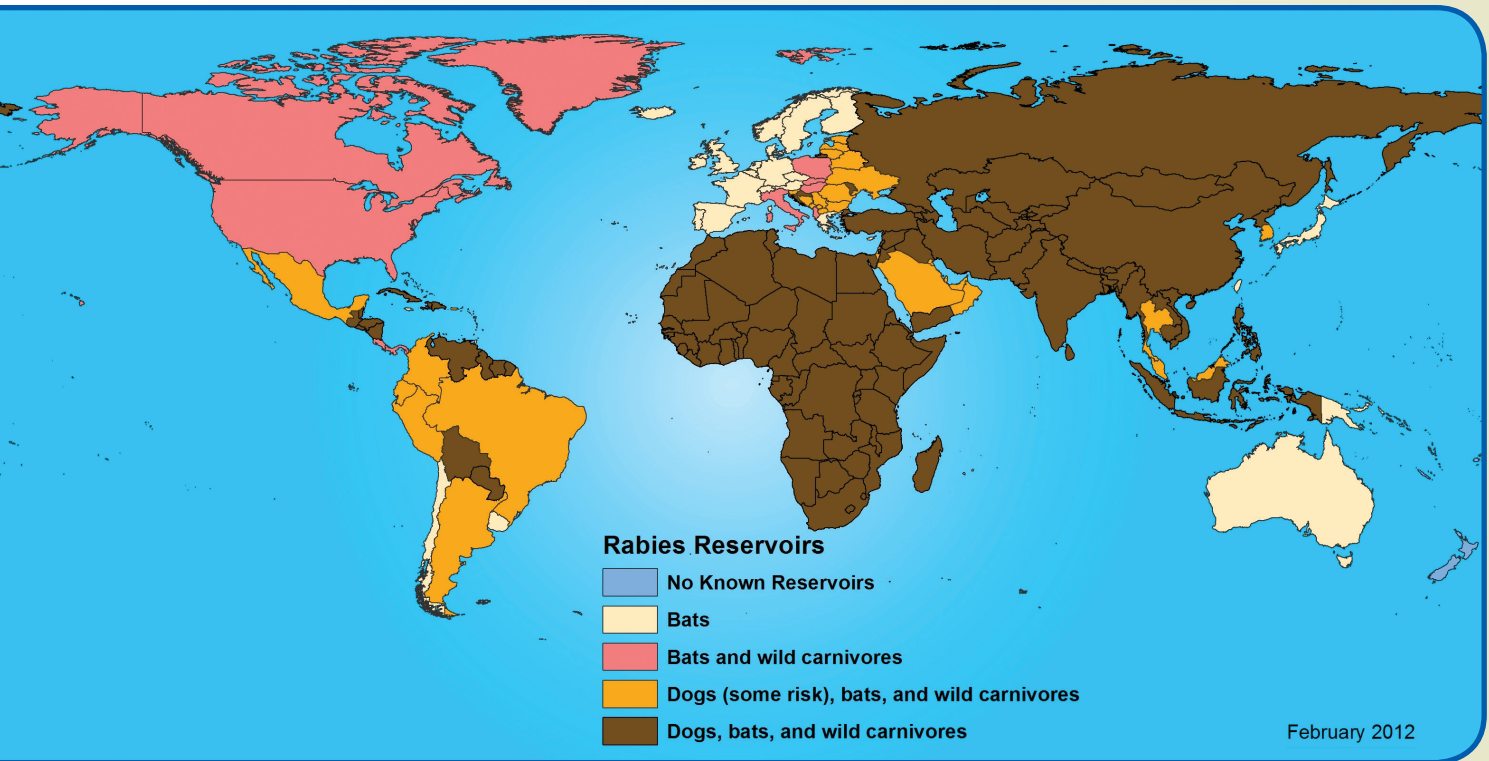
The National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) has developed the following new tests and vaccines to better protect people from wide-ranging, ever-changing infectious disease threats.

NCEZID A rapid, inexpensive, point-of-care bedside diagnostic 'dipstick' test for plague

- Plague is a potentially highly fatal illness that is harbored in rodents and spread by fleas to people. It can be transmitted from person to person, resulting in local outbreaks and posing the risk for spreading globally. In the event of exposure and infection, a point-of-care test is critical for early diagnosis and treatment. Currently, no test that has been validated or cleared by the US Food and Drug Administration (FDA) for use with human clinical specimens is available in the United States. CDC developed a diagnostic assay to fill this need. The assay is currently undergoing evaluation for FDA clearance.



- The Plague Rapid Test (PRT) yields results in 15 minutes, does not require electricity or refrigeration, and costs less than \$1.00 to produce.
- A supply of PRTs was delivered to Uganda in anticipation of the 2012–2013 plague season. During a recent outbreak involving four patients and three deaths, the PRT successfully diagnosed pneumonic plague in a patient, allowing for rapid prophylaxis of 130 contacts. As a result, no other cases occurred.

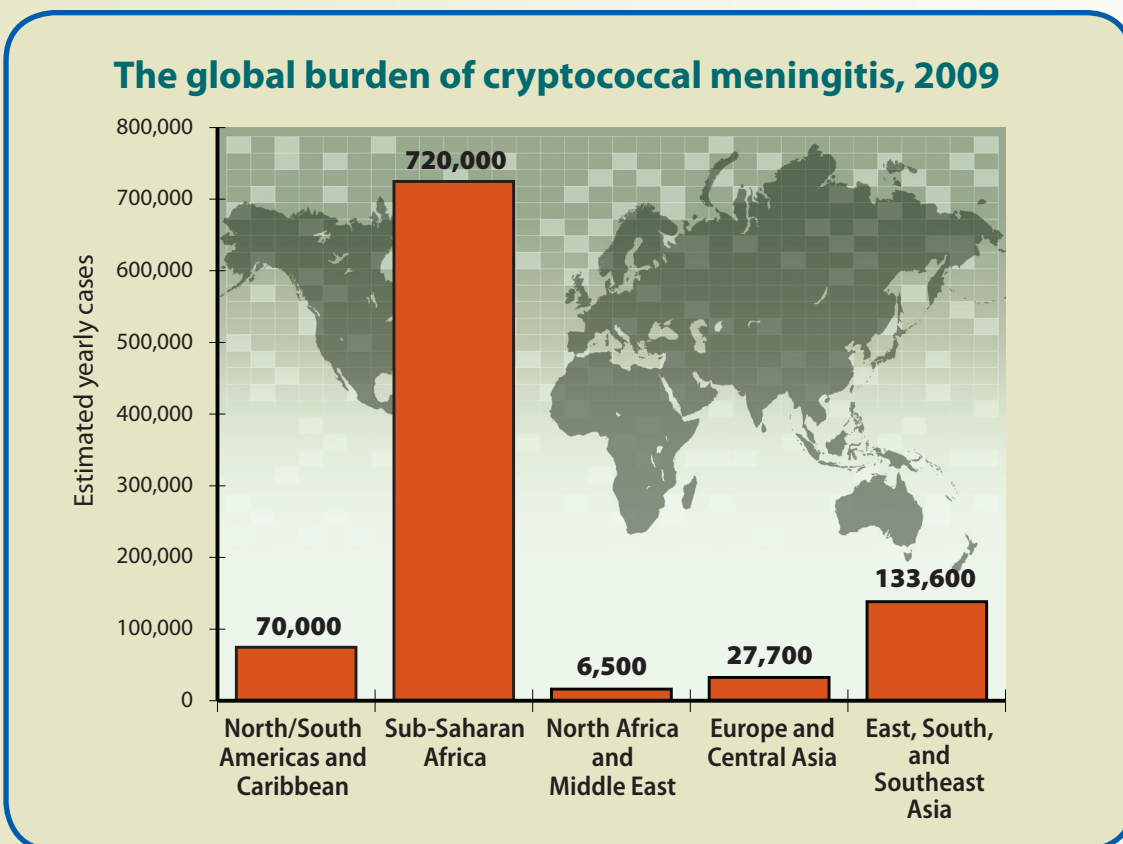


A new diagnostic test for rabies that requires no specialized equipment or refrigeration, and allows a diagnosis to be made in less than 1 hour

- Although rare in the United States, rabies causes more than 55,000 deaths worldwide each year. Today, in much of the developing world, rabies surveillance and diagnosis in domestic animals and wildlife is challenging. High temperatures make it difficult to collect and preserve fresh specimens. The gold standard test currently used to diagnose rabies requires a fluorescent microscope, which is very expensive to buy and maintain. These difficulties have led to widespread underreporting of disease.
- Scientists have found that this new test, referred to as dRIT (direct rapid immunohistochemical test), is as reliable as the gold standard test. It requires only a light microscope, which is widely available and 10 times less expensive than a fluorescent microscope. dRIT's reduced cost suggests its high potential for making rabies diagnosis much more widely available in Africa.
- The new test could also be used to improve the management of rabies and response to outbreaks. dRIT supports the critical need for vaccination to prevent rabies after exposure to rabid animals and helps reduce unnecessary use of post-exposure rabies shots.

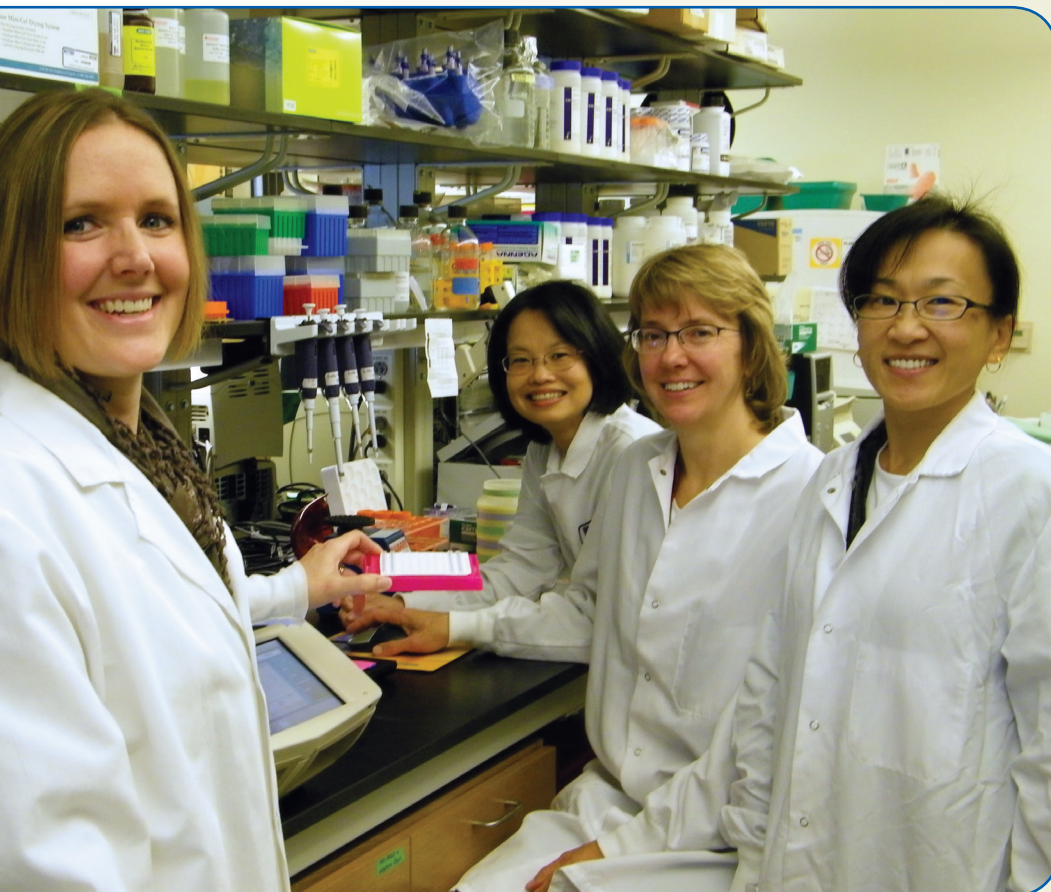
A new screening test for *Cryptococcus*

- Each year, the fungus *Cryptococcus neoformans* causes life-threatening meningitis in almost 1 million people with weakened immune systems (like people who have advanced HIV/AIDS infection). In sub-Saharan Africa, cryptococcal meningitis (when the infection has spread from the lungs to the brain) is one of the leading causes of death among HIV/AIDS patients and it may kill as many people each year as tuberculosis. Although it is not possible to prevent the initial infection, a blood test can catch the infection before meningitis develops.
- CDC has worked with other public health partners to perform targeted screening in HIV clinics, using a point-of-care dipstick screening test that is simple, quick, and effective. The test, which was developed by Oklahoma-based Immunologics, Inc., is inexpensive (\$2), FDA-approved, and can be performed in the clinic so it can be used by people who live in remote rural areas where there are no laboratories nearby.
- If screening detects the presence of cryptococcal antigen, beginning treatment before meningitis develops is affordable—the medication is sometimes free or only \$1 to \$2 dollars per month. It is estimated that if one-half of HIV clinics in those parts of Africa and Asia with a high prevalence of HIV/AIDS could perform *Cryptococcus* screening and treatment, then 50,000 to 100,000 lives could be saved every year.



NCEZID A dengue candidate vaccine that targets all four dengue viruses

- Dengue is a painful and sometimes deadly viral disease spread by mosquitoes that infects up to 390 million annually and that threatens more than 3.5 billion people worldwide. Dengue is a major public health problem in the tropics and subtropics, including the US territories and Mexico.
- No licensed dengue vaccine is available. Dengue is caused by infection with any of four closely related dengue viruses, and a successful dengue vaccine must offer immunity against all four.
- NCEZID scientists in Fort Collins, Colorado have developed a dengue vaccine candidate that is being evaluated in Puerto Rico, Singapore, Thailand, and Colombia for safety and immunogenicity (ability to stimulate an adequate immune response). The first human Phase-I trial showed that the vaccine was safe, could be well tolerated, and produced antibody levels that should protect against all four dengue viruses. Because of these encouraging results, a Phase-II clinical trial to assess immunogenicity began in late 2011.
- Four additional Phase 1 trials are being conducted to further investigate the optimal vaccine dose, formulation, schedule, and/or injection route. Phase-III trials to determine the efficacy of the vaccine to prevent dengue are expected to begin in late 2014.



- NCEZID's dengue vaccine team has partnered with vaccine developer Inviragen, recently acquired by Takeda. Takeda has produced the vaccine, named DENVax, and is testing the vaccine for human use. The goal is to provide a safe, effective, and affordable vaccine to protect people living in or traveling to dengue-endemic countries.

A new diagnostic test to detect the presence of dengue virus in people with symptoms of dengue fever or severe dengue

- Half a million patients are hospitalized with severe dengue every year, many of whom may die without timely intervention. Most infections are cases of uncomplicated dengue fever (DF). However, 1% to 5% progress to more debilitating or life-threatening forms of the disease—severe dengue, formerly known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Currently available diagnostic methods for dengue cannot provide confirmation of dengue infection when symptoms first appear. Dengue patients may not be correctly identified and monitored during the first week of infection when the risk of developing severe dengue is highest and prompt intervention can reduce mortality.
- This is the first FDA-approved molecular test for dengue that detects evidence of the virus itself.
- The new test will help diagnose dengue within the first 7 days after symptoms appear, which is when most people are likely to see a healthcare professional, and the dengue virus is likely to be present in their blood. The test can identify all four dengue virus types.
- One of the new test's most important features is that it can be performed using equipment and supplies that many public health laboratories already use to diagnose influenza. New dengue test kits were made available for distribution in July 2012.



New assay that rapidly detects fungal DNA in patients

- In fall 2012, one of the largest outbreaks of healthcare-associated infections in US history exposed more than 14,000 patients in 20 states. Fungal infections linked to steroid injections caused more than 750 illnesses and 64 deaths. NCEZID laboratories responded quickly, developing a new diagnostic assay for testing specimens in 2 days. This was far quicker than culture, the existing gold standard testing method, which took up to 2 weeks to produce results.
- The new rapid assay, in addition to other fast action by CDC and local, state, and other federal public health agencies, illustrates the power of public health in action to protect the country from infectious disease threats.



A recombinant vaccine against Rift Valley fever virus for use in livestock

- Rift Valley fever virus infection is caused by a serious and potentially lethal virus that has caused illness in animals and humans throughout Africa. Outbreaks are characterized by sweeping “abortion storms” and high-level neonatal and adult livestock deaths often involving millions of animals. Epidemics in people can be extensive, with cases numbering into the tens or hundreds of thousands. A key risk factor for infection and lethal disease in people is direct contact with infected animal blood, aborted fetal materials, and other tissues from virus-infected livestock, especially sheep and cattle.
- Using a newly-developed biotechnology system, NCEZID scientists developed the first “rationally designed” Rift Valley fever virus vaccine, in which the 2 main proteins that cause disease and death were specifically targeted and removed. “Rational design” means making vaccine functioning and safety more predictable. This “recombinant” vaccine was shown to be safe and 100% effective in preventing Rift Valley fever virus infection in livestock animals. “Recombinant” means that it involved new combination of genetic material.
- CDC has partnered with two commercial companies to license and produce this vaccine for use by herdsmen in endemic areas in Africa, and as part of vaccine stockpiles for North America and Europe for use against this potential bioterrorism threat. The vaccine is expected to be commercially available by the end of 2013 or early 2014.

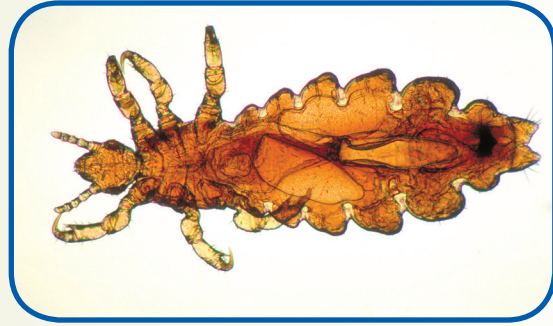
Several diagnostic tests to identify cases of disease from Heartland virus

- Heartland virus is a recently discovered human pathogen. In 2009, two Missouri residents presented to healthcare facilities with a flu-like illness. Based on their symptoms, low blood counts, and exposure to ticks, they initially were thought to have ehrlichiosis, a tick-borne disease.
- Samples sent to NCEZID were negative for *Ehrlichia* spp. but cytopathic effects were seen. Subsequent tests found a virus consistent with members of the *Bunyaviridae* family.
- NCEZID used next-generation sequencing and analysis to identify the virus as a novel member of the phlebovirus genus, later named Heartland virus.
- Following the identification and description of Heartland virus, CDC developed four different tests that have been used to identify subsequent cases of Heartland virus disease. NCEZID is working with state health departments in Missouri and several neighboring states to better define the epidemiology and clinical characteristics of the disease.



NCEZID A new diagnostic test to detect *Rickettsia prowazekii*, the cause of epidemic typhus, in people

- Epidemic typhus occurs in refugee populations where body lice are prevalent. The disease is spread by the human body louse and can cause explosive outbreaks in humans living in unsanitary conditions. Typhus fever reportedly has been studied by several countries as a potential bioweapon.
- Epidemic typhus occurs worldwide and has a case-fatality rate of 10% to 40% if untreated.
- The new NCEZID-developed molecular test is more sensitive than previous tests, which means that if the test result is negative you can be nearly certain that they don't have disease.
- In 2012, this test was used to diagnose an outbreak of epidemic typhus in Rwanda. Serum and blood samples and blood clots taken from symptomatic patients tested positive for *Rickettsia prowazekii*. The patients were treated, and control measures were put in place to prevent additional cases. The test will be extremely useful for the detection and control of future outbreaks worldwide.



NCEZID A point-of-care assay to diagnose monkeypox and orthopoxviruses in Africa

- NCEZID's poxvirus team has developed an assay for monkeypoxvirus and orthopoxviruses (the group of viruses that includes smallpox) by working with outside companies (BioGX and Cepheid). The assay performs clinical sample nucleic acid extraction and quantitative analysis within an hour.
- The quantitative PCR assay is run in a multiplex format for the diagnosis of monkeypox virus specifically and orthopoxviruses generically. An internal control monitors the DNA extraction process and possible inhibition of the test.
- The packed cartridge is stable in tropical conditions for at least 2 months. Only limited technical skill is required to run the assay.
- The assay is now in evaluation under a human subjects protocol in the Democratic Republic of Congo.



