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Tularemia vaccine for lab researchers to be in clinical trials by June 2003

A live vaccine strain (LVS) tularemia vaccine for laboratory investigators researching Francisella tularensis is expected to go into animal toxicology and early clinical trials by June 2003. There is no licensed vaccine currently available in the U.S. against tularemia.

DynPort Vaccine Company (DVC), contracted by the Defense Department's Joint Vaccine Acquisition Program, hopes to license its LVS tularemia vaccine for DoD by 2009, DVC representative Robert House told the International Conference on the Current Status of Tularemia and Plague Vaccines, held by the National Institute of Allergy & Infectious Diseases/Office of Rare Diseases November 21 at NIH's Bethesda, MD, campus.

Tularemia is listed as a Category "A" disease under NIAID's bioterrorism research agenda. Other diseases in that category are anthrax, smallpox, plague, viral hemorrhagic fevers and botulism. (see Washington Fax 3/19/02a)

Researchers currently working with F. tularensis, the bacterium that causes tularemia, use protective gear, including full-body suits, in biocontainment facilities.

Although vaccinating researchers working with F. tularensis could be advantageous, Ned Hayes, a CDC public health specialist, noted mass vaccination for tularemia would not be practical as the bacteria could be bioengineered to be vaccine resistant. "It seems to me that you're better off funding research dollars for some types of strategies [such as those for] preventing infections or ameliorating infection once exposure has occurred," Hayes said.

NIAID Director of Biodefense Research Affairs Ernest Takafuji warned, "Tularemia represents probably the biggest challenge that we have right now, because, from my perspective, here in the United States, we're pretty far behind." In the past, little priority was placed on tularemia research and now more research on the disease is necessary to "lead us to an actual product that we consider...an effective countermeasure," he continued.

Takafuji lauded the Bush Administration for its focus on product development, saying, "It's not just doing research for research purposes, but to really aim that research in a targeted way to develop countermeasures that are effective against these threats."

F. tularensis is "one of the most infectious bacterial pathogens known," requiring 10 or fewer organisms to cause disease, however, tularemia is "not known to be contagious," Dennis explained. As a Category "A" biological agent, F. tularensis poses "a national security risk because

it could be easily disseminated, cause high mortality, and require special action for public health preparedness," he stated.

Aerosolized tularemia exposure potentially can result in pneumonitis and sepsis, as well as infections of the throat, eyes, glands and skin. Naturally occurring inhalational tularemia cases have been documented in the U.S., including on Martha's Vineyard, MA, in 2000 and 2001.

The antibiotics gentomycin, doxycycline and ciprofloxacin currently are recommended for tularemia prevention and treatment. "We need to have clinical trials started and completed as quickly as possible, particularly looking at gentomycin and ciprofloxacin as agents used [to treat] tularemia," David Dennis, from CDC's Fort Collins, CO, facility, said.

A World Health Organization model for a "sizeable" tularemia release over a metropolitan area with 5 million inhabitants predicted 250,000 people incapacitated and 19,000 deaths, Dennis cited. With antibiotic treatment, tularemia mortality rate is under 10%; the rate rises to over 30% without treatment.

Tularemia and anthrax were aerosolized for use as weapons by the U.S.S.R. and the U.S. during the post World War II/Cold War era. In 1956, the U.S. acquired a live vaccine for tularemia from the Soviet Union, which had used it to vaccinate a large number of individuals in the 1940s and 1950s, DVC's House explained.

Thereafter, the U.S.' Salk Institute National Drug Company developed the live vaccine into LVS, which DoD studied under specific investigational new drug application and vaccinated over 3,000 individuals -- a majority of whom were healthy males 20-49. The vaccine "apparently provided good protection," House said.

FDA, however, rejected Salk's license application and LVS is still on hold. Among FDA's concerns were problems with manufacturing and trial data documentation, as well as characterizations of the bacterial strain and the vaccine product, such as potency and safety.

DVC has produced cell banks and established a process for current Good Manufacturing Practice (cGMP)-compliant vaccine product, House said. Part of the process involves eliminating "components of regulatory concern," such as the removal of agar and providing extensive characterization of the product.

"A critical part of our program is to develop appropriate animal models to assess protection in humans, and to determine if there are predictive measures of immunity," House said.

"Studies to date suggest that a live vaccine product provides the best protection against infections including tularemia," he remarked. Use of adjuvants is not usually required, a single vaccine administration provides sufficient protection and long-lasting immunity and the vaccine induces

cell-mediated immunity, which is required for protection against tularemia, House explained.

Other vaccine options against tularemia could include killed vaccines, such as phenol-killed vaccine, LVS protein complexes and subcellular elements. However, killed vaccines provide "suboptimal" protection, as they only induce antibody response and not cell-mediated response; LVS protein complexes and subcellular elements may require multicomponent vaccines -- as the necessary protection has not yet been determined -- and the use of adjuvant, he noted.

LVS vaccines would be "equally advantageous" for the military and for the general public, House said. However, LVS vaccines also are able to produce "varying degrees" of infection, rendering them a potential threat to immunocompromised populations.

The stability of DVC's LVS "remains to be determined," House cautioned, with both real-time and accelerated stability tests planned to examine the product. The original product was stable for four decades in storage, and "we have no reason to expect that this will be different," he assured.

Among other tests, the company will be investigating reversion to virulence or attenuation as "the mechanism of attenuation at present...has not been identified," House said. Genome sequencing of LVS is under way at other laboratories and is "nearing completion." Also, other types of genetic analyses are ongoing.

Another confounding factor is "We don't know the exact parental strain of LVS, we don't have it to compare LVS against. Determination of actual mechanism of virulence or attenuation of this particular bug is going to be quite difficult," House said. DVC intends to identify and monitor levels of LVS virulence.

The vaccine was released November 22 for animal immunogenicity studies beginning in December. A meeting is slated for December to discuss reproductive toxicity and other animal studies that probably will need to be conducted. Animal efficacy studies will be "pivotal" to DVC's clinical design, House emphasized.

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