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Vaccine Combined with Short-Term Postexposure Antibiotics Protects Monkeys from Inhalational Anthrax

Anthrax vaccine administered in combination with a short course of antibiotics completely protected nonhuman primates from inhalational anthrax, the most lethal form of the disease, according to scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

In a collaborative study involving USAMRIID and the National Institute of Allergy and Infectious Diseases (NIAID), investigators demonstrated that postexposure vaccination can shorten the duration of antibiotic treatment required to protect against inhalational anthrax. The findings, which appear in this week's online edition of *Proceedings of the National Academy of Sciences*, could have important implications for public health management of anthrax bioterrorism events.

Anthrax is caused by the spore-forming bacterium *Bacillus anthracis*, and causes three types of disease—cutaneous, gastrointestinal, and inhalational—depending upon the route of exposure. Inhalational anthrax—the type likely to occur following a bioterrorist attack—is difficult to diagnose early, and despite antibiotic therapy, has a high fatality rate. In addition, because anthrax spores can remain in the body for extended periods, antibiotic treatment is typically recommended for 60 days or more following exposure.

As noted by the authors, following the 2001 anthrax attacks in the United States, approximately 10,000 people were offered 60 days of antibiotic therapy to prevent inhalational anthrax. Adverse events associated with this regimen—including diarrhea, nausea, vomiting, and dizziness—were commonly reported. More importantly, only about 44 percent of people completed the whole 60-day course. Thus, minimizing the duration of postexposure antibiotic treatment could be crucial to a successful defense against a large-scale anthrax attack.

In the study, two groups of rhesus macaques were exposed to very high amounts of anthrax spores by aerosol. Both groups were then given ciprofloxacin twice daily for 14 days, beginning one to two hours after exposure. One group also received three doses of the licensed human anthrax vaccine (anthrax vaccine adsorbed) postexposure.

In the group that received ciprofloxacin but no vaccine, only four of nine monkeys, or 44 percent, survived the challenge. The animals remained healthy while on antibiotics but succumbed when the antibiotics were discontinued after 14 days. In contrast, all 10 monkeys that received 14 days of antibiotics plus vaccination survived when the antibiotics were discontinued. Thus, postexposure vaccination enhanced the protection afforded by 14 days of

antibiotic prophylaxis alone, and completely protected all the animals against inhalational anthrax.

"This provides direct evidence that the combination of anthrax vaccine with a short course of antibiotics given postexposure can completely protect nonhuman primates from inhalational anthrax," said senior author Arthur M. Friedlander, M.D., of USAMRIID. "Our results also suggest that the appearance of an antibody response—after treatment with antibiotics alone or in conjunction with vaccination—might be useful in determining when antibiotics can be safely discontinued."

According to Friedlander, inhalational anthrax begins when anthrax spores are ingested into the deep recesses of the lung. When the spores germinate, they are transformed into vegetative cells that produce three components contributing to virulence—lethal toxin, edema toxin, and capsule. The capsule surrounds the vegetative cell and prevents it from being ingested by host white blood cells that would otherwise destroy it, thus allowing anthrax infection to progress. The toxins are thought to act mainly by damaging defensive cells called phagocytes, causing the immune system to malfunction. The organism then spreads unimpeded to all major organs of the body, causing tissue damage and death.

While most spores probably germinate within a few days, some spores can remain dormant for much longer periods, which poses special challenges with regard to postexposure treatment. According to Friedlander, antibiotics are active only after spores have germinated; therefore, dormant spores that germinate after therapy has been discontinued can cause disease and death. This delayed germination necessitates prolonged use of antibiotics after an inhalational exposure.

Animal experiments have confirmed the prolonged persistence of spores and incubation period after aerosol exposure. In one study, rhesus macaques were protected during a 30-day course of antibiotics after aerosol exposure. However, some animals developed fatal infection after the antibiotic therapy was discontinued.

"In spite of the low compliance rates we saw in 2001—where more than half of the people did not take the full 60-day course—there were no additional anthrax cases," Friedlander commented. "This suggests that the doses of inhaled spores were probably very low. In contrast, computer modeling suggests that protection against higher doses of anthrax spores could require that antibiotics be continued for as long as four months. Adding vaccine to a postexposure regimen of antibiotics may shorten the duration and thus avoid the problems of noncompliance associated with a prolonged course."

Colonel George W. Korch, Jr., USAMRIID commander, added, "The tremendous value of interagency collaboration cannot be understated in this very important finding, which stands to potentially improve the course of therapeutic intervention, as well as enhance overall protection against this significant biological threat."

USAMRIID, located at Fort Detrick, Maryland, is the lead medical research laboratory for the U.S. Department of Defense Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute's mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

NIAID is a component of the National Institutes of Health. NIAID conducts and supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from

potential agents of bioterrorism. NIAID also conducts and supports research on basic immunology, transplantation and immune-related disorders, including autoimmune diseases, asthma and allergies.

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