BIODEFENSE: INFORMATION ON ANTHRAX, SMALLPOX AND THE PLAGUE

2.0 Contact Hours

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BIODEFENSE: INFORMATION ON ANTHRAX, SMALLPOX AND THE PLAGUE

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The contents of this course are taken from the Centers for Disease Control and Prevention and the U.S. Deaprtment of Labor. Learning objectives and post test have been prepared by Dr. Ratnakar P. Kini

Objectives:

Upon the completion of this course, the learner will be able to:

1. Define bioterrorism agents
2. Discuss anthrax and its causative agent
3. Explain the signs and symptoms, diagnosis, treatment and prevention of anthrax infection
4. Discuss the plague and its causative agent
5. Explain the different types, signs and symptoms, diagnosis, treatment and prevention of plague
6. Discuss smallpox and its causative agent
7. Explain the signs and symptoms, diagnosis, treatment and prevention of smallpox infection

Anthrax

ABOUT ANTHRAX AND BIOTERROR

Anthrax, notorious for its role in the fall 2001 bioterror attacks, is a disease caused by a microbe known as *Bacillus anthracis*. In the fall of 2001, lethal anthrax bacteria were spread deliberately through the U.S. mail. Twenty-two people became ill, and five died. The perpetrator has not been caught.

Even before this bioterror attack, public health officials were concerned about the potential for such an event. In 1999, the Centers for Disease Control and Prevention (CDC) created A, B, and C lists of biological agents that terrorists could use to harm civilians. An expert panel of doctors and scientists classified *Bacillus anthracis* as a Category A bioterror agent. The CDC bioterror lists represent the biological agents that pose the greatest threats to national security due to their ease of transmission, high rate of death or serious illness, potential for causing public panic, and special public health measures an epidemic would require.

Since the creation of the CDC lists, public health officials and researchers have worked to plan and prepare for a possible bioterror attack. Following the 2001 anthrax attacks, federal funding for these efforts increased dramatically.

ABOUT THE DISEASE

Anthrax infects livestock far more often than people, but it can cause three forms of human disease: cutaneous (affecting the skin), inhalational (in the lungs), and gastrointestinal (in the digestive tract).

Cutaneous anthrax

Cutaneous anthrax is the most common form of the disease. People with cuts or open sores can get cutaneous anthrax if they come in direct contact with the bacteria or its spores, usually through contaminated animal products. The skin will redden and swell, much like an insect bite, and then develop a painless blackened lesion or ulcer that may form a brown scab. Cutaneous anthrax responds well to antibiotics but may spread throughout the body if untreated. People who work with certain animals or animal carcasses are at risk of getting this form of the disease. Cutaneous anthrax is rare in the United States. According CDC, there are only one to two U.S. cases per year.

Inhalational anthrax

When spores of *B. anthracis* are inhaled, they germinate and the bacterial cells infect the lungs and then spread to the lymph nodes in the chest. As the bacteria grow, they produce two kinds of deadly toxins. Symptoms usually appear 1 to 7 days after exposure, but they may first appear more than a month later. Fever, nausea, vomiting, aches, and fatigue are among the early symptoms of inhalational anthrax; it progresses to labored breathing,

shock, and often death. Historically, the mortality rate for naturally occurring inhalational anthrax has been high-about 75 percent. But inhalational anthrax is also rare. Prior to 2001, the last known U.S. case was in 1976 when a California craftsman died after getting the infection from imported yarn contaminated with anthrax spores.

Gastrointestinal anthrax

People can acquire gastrointestinal anthrax from eating meat contaminated with anthrax bacteria or their spores. Symptoms are stomach pain, loss of appetite, diarrhea, and fever. Antibiotic treatment can cure this form of anthrax, but untreated, it may kill half of those who get it. It occurs naturally in warm and tropical regions of Asia, Africa, and the Middle East. There have been no confirmed cases of gastrointestinal anthrax in the United States, although a Minnesota farm family may have experienced symptoms of the disease in 2000 after eating meat from a steer that had anthrax.

ABOUT THE MICROBE

Bacillus anthracis is a bacterium that lives in soil and has developed a survival tactic that allows it to endure for decades under the harshest conditions. An anthrax bacterial cell can transform itself into a spore, a very hardy resting phase, to withstand extreme heat, cold, and drought, without nutrients or air. When environmental conditions are favorable, the spores will germinate into thriving colonies of bacteria. For example, a grazing animal may ingest spores that begin to grow, spread, and eventually kill the animal. The bacteria will form spores in the carcass and then return to the soil to infect other animals in the future.

While its spore form allows the bacteria to survive in any environment, the ability to produce toxins is what makes the bacteria such a potent killer. Together, the hardiness and toxicity of *B. anthracis* make it a formidable bioterror agent. Its toxin is made of three proteins: protective antigen, edema factor, and lethal factor.

Protective antigen binds to select cells of an infected person or animal and forms a channel that permits edema factor and lethal factor to enter those cells.

Once inside the cell, *edema factor* causes fluid to accumulate at the site of infection. Edema factor can contribute to a fatal build-up of fluid in the cavity surrounding the lungs. It also can inhibit some of the body's immune functions.

Lethal factor also works inside the cell, disrupting a key molecular switch that regulates the cell's functions. Lethal factor can kill infected cells or prevent them from working properly.

TREATMENT AND PREVENTION

Antibiotics

If diagnosed early, anthrax is easily treated with antibiotics. Unfortunately, infected people often confuse early symptoms with more common infections and do not seek medical help until severe symptoms appear. By that time, the destructive anthrax toxins have already risen to high levels, making treatment difficult. Antibiotics can kill the bacteria, but antibiotics have no effect on anthrax toxins.

Vaccines

An existing anthrax vaccine is licensed for limited use. The vaccine is currently used to protect members of the military and individuals most at risk for occupational exposure to the bacteria, such as slaughterhouse workers, veterinarians, laboratory workers, and livestock handlers. The vaccine does not contain the whole bacterium; rather, it is made mostly of the anthrax protective antigen protein.

Health experts currently do not recommend the vaccine for general use by the public because anthrax illness is rare and the vaccine has potential adverse side effects. Researchers have not determined the safety and efficacy of the vaccine in children, the elderly, and people with weakened immune systems. Although the results of recently conducted CDC vaccine trials indicate that three to four doses of anthrax vaccine can generate significant protective immunity, the recommended vaccination schedule is six doses given over an 18-month period. To quickly protect the public during a bioterror attack, scientists are seeking to develop a new vaccine.

NIAID RESEARCH

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, conducts and funds research to improve our ability to prevent, diagnose, and treat anthrax. Anthrax research was under way prior to the 2001 bioterror attack, but it has expanded significantly since then. New research findings are improving our understanding of how *B. anthracis* causes disease and how to better prevent and treat it.

Basic research

Several biologic factors contribute to *B. anthracis'* ability to cause disease. NIAID researchers and grantees are uncovering the molecular pathways that enable the bacterium to form spores, survive in people, and cause illness. Scientists envision this basic research to be the underpinnings of new vaccines, drugs, and diagnostic tools.

Toxin biology

Scientists are studying anthrax toxins to learn how to block their production and action. Recently, scientists discovered the three-dimensional molecular structure of the anthrax protective antigen protein bound to one of the receptors (CMG2) it uses to enter cells. The separate structures of protective antigen and CMG2 previously had been determined, but the structure of both bound together is more valuable, much as a roadmap connecting two cities is more useful than separate maps of the cities. Using a specific fragment of the CMG2 receptor protein, researchers have been able to block the attachment of protective antigen in test-tube experiments, thereby inhibiting all anthrax toxin activity.

Previously, NIAID grantees had determined the three-dimensional structure of the lethal factor protein as it attaches to its target inside cells. Their research showed that lethal factor uses a long groove on its side to latch onto the target.

In another recent advance, NIAID and other scientists have synthesized a small cyclic molecule that blocks anthrax toxin in cell culture and in rodents. The molecule blocks the pore formed by anthrax protective antigen. Blocking the pore effectively prevents lethal factor and edema factor toxins from entering cells. The scientists anticipate that this discovery will lead to new and effective treatments for anthrax.

Anthrax bacterium genome

The instructions that dictate how a microbe works are encoded within its genes. Bacteria keep most of their genes in a chromosome, a very long stretch of DNA. Smaller circular pieces of DNA called plasmids also carry genes that bacteria may exchange with each other. Because plasmids often contain genes for toxins and antibiotic resistance, knowing the DNA sequence of such plasmids is important. Scientists have sequenced plasmids carrying the toxin genes of *B. anthracis*. In addition, researchers have sequenced the complete chromosomal DNA sequence of several *B. anthracis* strains, including one that killed a Florida man in the 2001 anthrax bioterror attack.

By comparing the DNA blueprints of different *B. anthracis* strains, researchers are learning why some strains are more virulent than others. Small variations among the DNA sequences of different strains may also help investigators pinpoint the origin of an anthrax outbreak. Knowing the genetic fingerprint of *B. anthracis* might lead to gene-based detection mechanisms that can alert scientists to the bacteria in the environment or allow rapid diagnosis of anthrax in infected people. Variations between strains might also point to differences in antibiotic susceptibility, permitting doctors to immediately determine the appropriate treatment.

Scientists are now analyzing the *B. anthracis* genome sequence to determine the function of each of its genes and to learn how its genes interact with each other or with host-cell components to cause disease. Genes are the instructions for making proteins, which in turn build components of the cell or carry out its biochemical processes. Knowing the

sequence of *B. anthracis* genes will help scientists discover key bacterial proteins that can then be targeted by new drugs or vaccines.

Spore biology

B. anthracis spores are essentially dormant and must "wake up," or germinate, to become reproductive, disease-causing bacteria. Researchers are studying the germination process to learn more about the signals that cause spores to become active once inside an animal or person. Efforts are under way to develop models of spore germination in laboratory animals. Scientists hope those models will enable discoveries leading to drugs that block the germination process.

Host immunity

People who contract anthrax produce antibodies to protective antigen protein. Similar antibodies appear to block infection in animals. Recent studies also suggest that some animals can produce antibodies to components of *B. anthracis* spores. Those antibodies, when studied in a test tube, prevent spores from germinating and increase their uptake by the immune system's microbe-eating cells. These discoveries suggest that scientists might be able to develop a vaccine to fight both *B. anthracis* cells and spores.

Researchers also are studying how the immune system responds to *B. anthracis* infection. Part of the immune system response, known as adaptive immunity, consists of B and T cells that specifically recognize components of the anthrax bacterium. The other type of immune response-innate immunity-aims more generally to combat a wide range of microbial invaders and likely plays a key role in the body's front-line defenses. Scientists are conducting studies of how those two arms of the immune system act to counter infection, including how *B. anthracis* spore germination affects individual immune responses.

Natural history of anthrax

In 2002, NIAID physician researchers initiated a clinical protocol to study the natural history of anthrax. The goal is to look at the infectious disease process over time, from initial infection through the clinical course and beyond recovery. A small number of anthrax survivors from the 2001 attacks have enrolled. Because the medical literature on anthrax does not include any findings regarding long-term complications in survivors, information gained in this study will be valuable to patients and doctors.

Vaccines

Researchers have developed new, more effective anthrax vaccines intended for broad use. If approved by the Food and Drug Administration (FDA), it could be given to children, the elderly, and those with weakened immune systems more easily than the existing military anthrax vaccine. NIAID is currently funding two companies to develop, produce, and perform clinical trials of a next-generation vaccine based on a genetically modified

recombinant protective antigen (rPA) protein. Antibodies produced by the immune system in response to rPA are thought to be the primary mode of protection against anthrax spores. NIAID is also funding research on the application of new vaccination technologies and novel compounds that can boost the immune response to a vaccine.

Diagnostics

Research is under way to develop improved techniques for spotting *B. anthracis* in the environment and diagnosing it in infected individuals. A key part of that research is the functional genomic analysis of the bacterium, which should lead to new genetic markers for sensitive and rapid identification. Genomic analysis will also reveal differences in individual B. anthracis strains that may affect how those bacteria cause disease or respond to treatment.

Therapies

Following the discoveries of how the protective antigen and lethal factor proteins interact with cells, researchers are screening thousands of small molecules in hopes of finding an anti-anthrax drug. In addition, NIAID is working with FDA, CDC, and the Department of Defense to accelerate testing of collections of compounds for their effectiveness against inhalational anthrax. Many of those compounds already have been approved by the FDA for other conditions and therefore could quickly be approved for use in treating anthrax, should they prove effective.

NIAID is also seeking new drugs that attack *B. anthracis* at many levels. These include agents that prevent the bacterium from attaching to cells, compounds that inhibit spore germination, and inhibitors that block the activity of key enzymes such as anthrax lethal factor. NIAID also will develop the capacity to synthesize promising anti-anthrax compounds in sufficient purity and quantity for preclinical testing.

For more information on anthrax, visit the Web sites of the organizations listed below.

Plague

Overview

Plague is an infectious disease caused by bacteria called *Yersinia pestis*. These bacteria are found mainly in rodents, particularly rats, and in the fleas that feed on them. Other animals and humans usually contract the bacteria from rodent or flea bites.

Historically, plague destroyed entire civilizations. In the 1300s, the "Black Death," as it was called, killed approximately one-third (20 to 30 million) of Europe's population. In the mid-1800s, it killed 12 million people in China. Today, thanks to better living

conditions, antibiotics, and improved sanitation, current World Health Organization statistics show there were 2,118 cases in 2003 worldwide.

Transmission

Yersinia pestis is found in animals throughout the world, most commonly in rats but occasionally in other wild animals, such as prairie dogs. Most cases of human plague are caused by bites of infected animals or the infected fleas that feed on them. In almost all cases, only the pneumonic form of plague (see below) can be passed from person to person.

Forms of Plague

Y. pestis can affect people in three different ways: bubonic, septicemic, or pneumonic plague.

Bubonic plague

In bubonic plague, the most common form, bacteria infect the lymph system and become inflamed. (The lymph or lymphatic system is a major component of your body's immune system. The organs within the lymphatic system are the tonsils, adenoids, spleen, and thymus.)

How is it contracted? Usually, bubonic plague is contracted by being bitten by an infected flea or rodent. In rare cases, *Y. pestis* bacteria, from a piece of contaminated clothing or other material used by a person with plague, enter through an opening in your skin.

What are the symptoms? Bubonic plague affects the lymph nodes (another part of the lymph system). Within three to seven days of exposure to the bacteria, flu-like symptoms will develop such as fever, headache, chills, weakness, and swollen, tender lymph glands (called buboes-hence the name bubonic).

Is it contagious? Bubonic plague is rarely spread from person to person.

Septicemic plague

This form of plague occurs when the bacteria multiply in the blood.

How is it contracted? Septicemic plague is contracted the same way as bubonic plague-usually through a flea or rodent bite. Septicemic plague also can appear as a complication of untreated bubonic or pneumonic plague.

What are the symptoms? Symptoms include fever, chills, weakness, abdominal pain, shock, and bleeding underneath the skin or other organs. Buboes, however, do not develop.

Is it contagious? Septicemic plague is rarely spread from person to person.

Pneumonic plague

This is the most serious form of plague and occurs when *Y. pestis* bacteria infect the lungs and cause pneumonia.

How is it contracted? Pneumonic plague can be contracted in one of two ways.

- Primary pneumonic plague is contracted when plague is inhaled. This type of plague can be spread to someone else.
- Secondary pneumonic plague develops when bubonic or septicemic plague goes untreated after the disease has spread to the lungs. At this point, the disease can be transmitted to someone else.

What are the symptoms? Within 1 to 3 days of exposure to airborne droplets of pneumonic plague, fever, headache, weakness, rapid onset of pneumonia with shortness of breath, chest pain, cough, and sometimes bloody or watery sputum develop.

Is it contagious? Pneumonic plague is contagious. If someone has pneumonic plague and coughs, *Y. pestis* bacteria suspended in respiratory droplets is released into the air. An uninfected person can then develop pneumonic plague by breathing in those droplets.

Diagnosis

A health care provider can diagnosis plague by doing laboratory tests on blood or sputum or on fluid from a lymph node.

Treatment

When the disease is suspected and diagnosed early, a health care provider can prescribe specific antibiotics, generally streptomycin or gentamycin as treatment options. Certain other antibiotics are also effective. Left untreated, bubonic plague bacteria can quickly multiply in the bloodstream, causing septicemic plague, or even progress to the lungs, causing pneumonic plague.

Prevention

Antibiotics

Health experts recommend antibiotics if you have been exposed to wild rodent fleas during a plague outbreak in animals, or to a possible plague-infected animal. Because there are so few cases of plague in the United States, experts do not recommend taking antibiotics unless its certain there has been exposure to plague-infected fleas or animals.

Vaccine

Currently, there is no commercially available vaccine against plague.

How Common Is Plague?

Approximately 10 to 20 people in the United States develop plague each year from flea or rodent bites-primarily from infected prairie dogs-in rural areas of the southwestern United States. About one in seven of those infected die from the disease. There has not been a case of person-to-person infection in the United States since 1924.

Worldwide, there have been small plague outbreaks in Asia, Africa, and South America.

Plague and Bioterror

Bioterrorism is a real threat to the United States and around the world. Although the United States does not currently expect a plague attack, it is possible that pneumonic plague could occur via an aerosol distribution. The *Y. pestis* bacterium is widely available in microbiology banks around the world, and thousands of scientists have worked with plague, making a biological attack a serious concern.

NIAID Research

The National Institute of Allergy and Infectious Diseases (NIAID) supports research on the diagnosis, prevention, and treatment of infections caused by microbes, including those that have the potential for use as biological weapons. The research program to address biodefense includes both short- and long-term studies targeted at designing, developing, evaluating, and approving specific tools (diagnostics, therapies, and vaccines) needed to defend against possible bioterrorist-caused disease outbreaks.

Current research projects include

- Identifying genes in the *Y. pestis* bacterium that infect the digestive tract of fleas and researching how the bacterium is transferred to humans
- Studying the disease-causing proteins and genes of *Y. pestis* that allow the bacterium to grow in humans and how they function in human lungs

NIAID is also working with the U.S. Department of Defense, the Centers for Disease Control and Prevention, and the Department of Energy to

- Develop a vaccine that protects against inhalationally acquired pneumonic plague
- Develop promising antibiotics and intervention strategies to prevent and treat plague infection

Smallpox

OVERVIEW

Smallpox is a disfiguring and potentially deadly infectious disease caused by the *Variola major* virus. Before smallpox was eradicated, there were two forms of the disease worldwide: *Variola major*, the deadly disease, and *Variola minor*, a much milder form. According to some health experts, over the centuries smallpox was responsible for more deaths than all other infectious diseases combined. The disease spreads in any climate and during all seasons. Although a worldwide immunization program eradicated smallpox disease decades ago, small quantities of smallpox virus officially still exist in two research laboratories in Atlanta, Georgia, and in Russia.

The last naturally occurring case of smallpox was reported in 1977. In 1980, the World Health Organization declared that smallpox had been eradicated. Currently, there is no evidence of naturally occurring smallpox transmission anywhere in the world.

THE MICROBE

Scientists have not studied variola virus well because of the hazards associated with potential exposure. In addition, by international agreement, smallpox may only be studied at the Centers for Disease Control and Prevention (CDC) high containment facility or one in the former USSR (Union of Soviet Socialist Republics), and experiments must be approved in advance by an international committee. Vaccinia virus, however, used to make a smallpox vaccine and closely related to variola, has been studied thoroughly. There is one major difference between the two viruses: vaccinia can infect several types of living beings, while variola infects only humans naturally and cynomolgus monkeys under highly artificial laboratory conditions.

Researchers are now investigating vaccinia as a possible way to deliver genes from other viruses to make new vaccines.

TRANSMISSION

Smallpox is highly contagious. In most cases, people get smallpox by inhaling droplets of saliva, which are full of virus, during face-to-face contact with an infected person. When someone becomes infected, they do not immediately feel sick or shed virus to their household contacts. In addition, they have no symptoms for 10 to 12 days. After the virus has multiplied and spread throughout the body, a rash and fever develop. This is the "illness" portion of the disease, and it's when someone is most infectious. In short, someone who becomes infected is not going to be ill until 10 to 12 days later.

Some risk of transmission lasts, however, until all scabs have fallen off. Contaminated clothing or bed linens also can spread the virus. Those caring for people with smallpox need to use special safety measures to ensure that all bedding and clothing from the infected person are cleaned appropriately with bleach and hot water. Caretakers can use disinfectants such as bleach and ammonia to clean contaminated surfaces.

SYMPTOMS

Symptoms of smallpox infection usually appear within 7 to 17 days after exposure to the virus, and on average appear after 12 days. The first symptoms of smallpox may be difficult to distinguish from other flu-like illnesses and include

- High fever
- Tiredness, malaise
- Headache, backache

Rash

A characteristic rash, most prominent on the face, arms, and legs, follows 2 to 3 days after the first symptoms. The rash starts with flat red lesions (sores) that develop at the same rate. After a few days, the lesions become filled with pus, and they begin to crust early in the second week. Scabs develop and then separate and fall off after about 3 weeks.

TREATMENT

There is no proven treatment for smallpox. People with the disease can benefit from intravenous fluids and medicine to control fever or pain as well as antibiotics for any secondary bacterial infections that may occur. If an infected person gets the smallpox vaccine within 4 days after exposure to the virus, it may lessen the severity of illness or even prevent it. The majority of people with smallpox recover, but death may occur in up to 30 percent of cases. Those who do recover are often left with disfiguring scars.

Research to evaluate new antiviral agents is ongoing. Early results from laboratory studies suggest that the drug cidofovir may fight against the smallpox virus. (In 1996, the Food and Drug Administration [FDA] approved the use of cidofovir to treat cytomegalovirus infections.) Scientists are doing studies with animals to better understand the drug's ability to treat smallpox. In addition, the National Institute of Allergy and Infectious Diseases (NIAID) has applied to FDA to use the antiviral drug cidofovir as an experimental treatment for smallpox in the event of a bioterrorist-initiated re-emergence.

PREVENTION

To prevent the spread of smallpox, health care providers must

- Isolate infected people
- Vaccinate close contacts of infected people

Vaccine

The currently licensed smallpox vaccine, which consists of a laboratory strain of vaccinia virus, is highly effective in preventing infection. Medical experts believe that the vaccine may lessen the severity of, or even prevent, illness in unvaccinated people if given within 4 days of exposure to the virus.

The smallpox vaccine helps the body develop immunity to smallpox. The vaccine is made from a “pox”-type virus related to smallpox. The smallpox vaccine contains live vaccinia virus—unlike many other vaccines that use killed virus. The vaccine does not contain the smallpox virus and cannot transmit smallpox (http://www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp).

Few data exist showing just how long vaccinia vaccines protect people against smallpox infection. Therefore, those vaccinated against the smallpox virus before 1972 may be susceptible to the disease. U.S. health officials are inoculating health care workers and those who will be on the front lines of medical care should there be a smallpox outbreak. Military and other high-risk groups (for example, scientists who work with vaccinia and other orthopoxviruses related to *Variola major*) have been getting the vaccine since the United States stopped routine smallpox vaccinations in 1972.

Getting the vaccine

Health care providers do not use a hypodermic needle, usually used for vaccinations, to give the smallpox vaccine. Instead, they use a tiny, two-pronged needle that is dipped into the vaccine solution. When removed, the needle keeps a droplet of the vaccine. The needle is used to prick the skin, usually in the upper arm, a number of times within a few seconds. The pricking is not deep, but it will cause a sore spot and one or two droplets of blood to form.

If the vaccination is successful, a red and itchy bump develops at the vaccine site in 3 or 4 days.

- In the first week, the bump becomes a large blister, fills with pus, and begins to drain
- During the second week, the blister begins to dry up and a scab forms
- In the third week, the scab falls off, leaving a small scar

People who get the vaccine for the first time have a stronger reaction than those who are revaccinated.

Reactions and complications

The vaccine often causes fever as well as large skin reactions at the vaccination site. These reactions usually go away, leaving only the telltale smallpox vaccine scar.

The vaccine, however, can cause several complications, some life-threatening, particularly in people with immune deficiencies and skin disorders. Based on reactions to smallpox vaccines in the past, CDC estimates that between 14 and 52 people out of every 1 million people vaccinated for the first time will have potentially life-threatening complications that require medical attention including

- Eczema vaccinatum (EV)—spread of vaccinia skin lesions to areas of the body once or presently afflicted by eczema
- Progressive vaccinia—uncontrolled spread of the vaccinia virus to adjacent and underlying tissues resulting in tissue death
- Postvaccinal encephalitis—spread of the vaccinia virus to the central nervous system that is probably made worse by an over-response by the immune system

CDC estimates that 1 or 2 people in 1 million who receive the vaccine may die as a result of vaccination. Because of serious and potentially deadly reactions, health care providers must carefully screen potential vaccine recipients to ensure that those at increased risk do not receive the vaccine (http://www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp).

Health care providers treat certain serious complications with anti-vaccinia immune globulin—pooled antibodies taken from people recently immunized with the smallpox vaccine. Because the United States discontinued routine smallpox vaccination programs in 1972, vaccinia immune globulin (VIG) is in extremely short supply. A government-funded program to produce sufficient VIG to treat all predicted cases of complications is underway. In addition, NIAID-funded researchers are trying to develop replacements for VIG based on antibodies made in the laboratory. Cidofovir also may be used in some situations. Neither drug is currently licensed for this purpose, and they may have side effects of their own.

NIAID RESEARCH

NIAID supports research on the diagnosis, prevention, and treatment of infections caused by microbes, including those that have the potential for use as biological weapons. The research program to address biodefense includes both short- and long-term studies to design, develop, evaluate, and approve specific tools (diagnostics, treatments, and vaccines) needed to defend against possible bioterrorist-caused disease outbreaks.

Recently, NIAID launched the Atopic Dermatitis and Vaccinia Network (ADVN), a nationwide research group that seeks to reduce the risk of EV, a severe and potentially deadly complication of smallpox immunization. EV occurs almost exclusively in people with a history of atopic dermatitis (AD), a chronic, itchy skin condition commonly referred to as eczema. While uncommon, EV can develop when AD patients are given the smallpox vaccine or come into close personal contact with people who recently received the vaccine. If untreated, EV can kill between 1 and 6 percent of those affected. In children younger than 2 years of age, health experts estimate that EV can kill up to 30 percent.

Vaccine Supply and Strength

Expanding the U.S. smallpox vaccine supply is a high priority of the bioterrorism preparedness plan. Results from an NIAID study show that the existing U.S. supply of smallpox vaccine—15.4 million doses—could successfully be diluted up to five times and retain its potency, effectively expanding the number of individuals it could protect from the contagious disease. The vaccine, called Dryvax, had been stored since production stopped in 1983.

The trial compared the full-strength vaccine with fivefold, as well as tenfold, dilutions in 680 young adults with no history of smallpox vaccination. More than 97 percent of all participants in the trial responded with a vaccine "take," a blister-like sore at the injection site that serves as an indirect measure of the vaccine's effectiveness. A new study has been conducted to determine how effective the diluted Dryvax is in people who have been previously vaccinated against smallpox.

In addition to Dryvax, NIAID is sponsoring clinical trials of another vaccine against smallpox called APSV. Eighty million doses of APSV, a different formulation of a vaccinia smallpox vaccine produced by Aventis Pasteur, had been in storage for 40 years. In on-going studies, researchers are testing various concentrations of APSV in adults who have never received vaccinia.

NIAID also conducts and supports research studies to develop and test a safer, weakened form of smallpox vaccine based on modified vaccinia Ankara (MVA) vaccine. MVA is being developed for use in people who are at risk for complications from Dryvax vaccination, for example, those who are HIV positive or have eczema. Unlike Dryvax, MVA is unable to grow in human cells and therefore cannot form a lesion at the site of vaccination. A recent NIAID study showed that MVA is nearly as effective as the standard smallpox vaccine in protecting monkeys against monkeypox (an orthopoxvirus). (Monkeypox is used to test the effectiveness of a smallpox vaccine because of its similarity to the variola viruses.)

Microbe biology

Variola and vaccinia belong to the *Orthopoxvirus* genus of poxviruses. Scientists who have sequenced the genes of several strains of variola and vaccinia have

- Found that genes for structural, membrane, and inner proteins appear to vary little among orthopoxviruses
- Identified some of the genes responsible for virus growth in human cells

NIAID will actively pursue further research in these areas.

Treatment

In collaboration with the U.S. Department of Defense (DoD), NIAID has screened more than 500 compounds against smallpox and related viruses. In addition, NIAID supports studies that evaluate experimental antiviral compounds in a number of mouse models of vaccinia and cowpox (another member of the orthopoxvirus family).

NIAID also supports mousepox virus and rabbitpox virus models. Compounds that are effective in these small-animal models are given priority for evaluation by DoD researchers in the monkeypox primate model.

In addition to collaborating with DoD scientists, NIAID is working with scientists at other federal agencies, such as CDC and the Department of Energy, to develop and test at

least three antiviral drugs against smallpox and determine whether existing antiviral compounds and those being developed are effective against variola virus. In addition to those treatment studies, NIAID is collaborating on studies to

- Extend the usefulness of the currently available older smallpox vaccine, Dryvax
- Help develop a safer, sterile smallpox vaccine using modern technology
- Explore developing a vaccine that can be used safely in all segments of the population
- Increase scientific knowledge about the genome of variola and related viruses

RESPONDING TO A BIOTERRORISM INCIDENT

Infection Control

Isolation Precautions:
Agents of bioterrorism are generally not transmitted from person to person; re-aerosolization of these agents is unlikely4. **All** patients in healthcare facilities, including symptomatic patients with suspected or confirmed bioterrorism-related illnesses, should be managed utilizing **Standard Precautions**. Standard Precautions are designed to reduce transmission from both recognized and unrecognized sources of infection in healthcare facilities, and are recommended for all patients receiving care, regardless of their diagnosis or presumed infection status5. **For certain diseases or syndromes (e.g., smallpox and pneumonic plague), additional precautions may be needed to reduce the likelihood for transmission.**

Standard Precautions prevent direct contact with all body fluids (including blood), secretions, excretions, nonintact skin (including rashes), and mucous membranes. Standard Precautions routinely practiced by healthcare providers include:

- **Handwashing**
Hands are washed after touching blood, body fluids, excretions, secretions, or items contaminated with such body fluids, whether or not gloves are worn. Hands are washed immediately after gloves are removed, between patient contacts, and as appropriate to avoid transfer of microorganisms to other patients and the environment. Either plain or antimicrobial-containing soaps may be used according to facility policy.

- **Gloves**
Clean, non-sterile gloves are worn when touching blood, body fluids, excretions, secretions, or items contaminated with such body fluids. Clean gloves are put on just before touching mucous membranes and nonintact skin. Gloves are changed between tasks and between procedures on the same patient if contact occurs with contaminated

material. Hands are washed promptly after removing gloves and before leaving a patient care area.

- Masks/Eye Protection or Face Shields
A mask and eye protection (or face shield) are worn to protect mucous membranes of the eyes, nose, and mouth while performing procedures and patient care activities that may cause splashes of blood, body fluids, excretions, or secretions.

- **Gowns**
A gown is worn to protect skin and prevent soiling of clothing during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, excretions, or secretions. Selection of gowns and gown materials should be suitable for the activity and amount of body fluid likely to be encountered. Soiled gowns are removed promptly and hands are washed to avoid transfer of microorganisms to other patients and environments.

Cleaning, disinfection, and sterilization of equipment and environment:
Principles of Standard Precautions should be generally applied for the management of patient-care equipment and environmental control.

- Each facility should have in place adequate procedures for the routine care, cleaning, and disinfection of environmental surfaces, beds, bedrails, bedside equipment, and other frequently touched surfaces and equipment, and should ensure that these procedures are being followed.

- Facility-approved germicidal cleaning agents should be available in patient care areas to use for cleaning spills of contaminated material and disinfecting non-critical equipment. Used patient-care equipment soiled or potentially contaminated with blood, body fluids, secretions, or excretions should be handled in a manner that prevents exposures to skin and mucous membranes, avoids contamination of clothing, and minimizes the likelihood of transfer of microbes to other patients and environments.

- Policies should be in place to ensure that reusable equipment is not used for the care of another patient until it has been appropriately cleaned and reprocessed, and to ensure that single-use patient items are appropriately discarded.

- Sterilization is required for all instruments or equipment that enter normally sterile tissues or through which blood flows.

- Rooms and bedside equipment of patients with bioterrorism-related infections should be cleaned using the same procedures that are used for all patients as a component of Standard Precautions, unless the infecting microorganism and the amount of environmental contamination indicates special cleaning. In addition to adequate cleaning, thorough disinfection of bedside equipment and environmental surfaces may be indicated for certain organisms that can survive in the inanimate environment for extended periods

of time. The methods and frequency of cleaning and the products used are determined by facility policy.

- Patient linen should be handled in accordance with Standard Precautions. Although linen may be contaminated, the risk of disease transmission is negligible if it is handled, transported, and laundered in a manner that avoids transfer of microorganisms to other patients, personnel and environments. Facility policy and local/state regulations should determine the methods for handling, transporting, and laundering soiled linen.

- Contaminated waste should be sorted and discarded in accordance with federal, state and local regulations.

- Policies for the prevention of occupational injury and exposure to bloodborne pathogens in accordance with Standard Precautions and Universal Precautions should be in place within each healthcare facility.

Discharge management

Ideally, patients with bioterrorism-related infections will not be discharged from the facility until they are deemed noninfectious. However, consideration should be given to developing home-care instructions in the event that large numbers of persons exposed may preclude admission of all infected patients. Depending on the exposure and illness, home care instructions may include recommendations for the use of appropriate barrier precautions, handwashing, waste management, and cleaning and disinfection of the environment and patientcare items.

Post-mortem care

Pathology departments and clinical laboratories should be informed of a potentially infectious outbreak prior to submitting any specimens for examination or disposal. All autopsies should be performed carefully using all personal protective equipment and standards of practice in accordance with Standard Precautions, including the use of masks and eye protection whenever the generation of aerosols or splatter of body fluids is anticipated. Instructions for funeral directors should be developed and incorporated into the Bioterrorism Readiness Plan for communication.5

Post Exposure Management

Decontamination of Patients and Environment

The need for decontamination depends on the suspected exposure and in most cases will not be necessary. The goal of decontamination after a potential exposure to a bioterrorism agent is to reduce the extent of external contamination of the patient and contain the contamination to prevent further spread. Decontamination should only be considered in instances of gross contamination. Decisions regarding the need for decontamination

should be made in consultation with state and local health departments. Decontamination of exposed individuals prior to receiving them in the healthcare facility may be necessary to ensure the safety of patients and staff while providing care. When developing Bioterrorism Readiness Plans, facilities should consider available locations and procedures for patient decontamination prior to facility entry.

Depending on the agent, the likelihood for re-aerosolization, or a risk associated with cutaneous exposure, clothing of exposed persons may need to be removed. After removal of contaminated clothing, patients should be instructed (or assisted if necessary) to immediately shower with soap and water. **Potentially harmful practices, such as bathing patients with bleach solutions, are unnecessary and should be avoided**. Clean water, saline solution, or commercial ophthalmic solutions are recommended for rinsing eyes. If indicated, after removal at the decontamination site, patient clothing should be handled only by personnel wearing appropriate personal protective equipment, and placed in an impervious bag to prevent further environmental contamination.

Development of Bioterrorism Readiness Plans should include coordination with the FBI field office. The FBI may require collection of exposed clothing and other potential evidence for submission to FBI or Department of Defense laboratories to assist in exposure investigations.

Prophylaxis and post-exposure immunization

Recommendations for prophylaxis are subject to change. However, up-to-date recommendations should be obtained in consultation with local and state health departments and CDC. Facilities should ensure that policies are in place to identify and manage health care workers exposed to infectious patients. In general, maintenance of accurate occupational health records will facilitate identification, contact, assessment, and delivery of post-exposure care to potentially exposed healthcare workers.

Triage and management of large scale exposures and suspected exposures

Each healthcare facility, with the involvement of the IC committee, administration, building engineering staff, emergency department, laboratory directors and nursing directors, should clarify in advance how they will best be able to deliver care in the event of a large scale exposure. Facilities should incorporate into their Bioterrorism Readiness Plan processes for triage and safe housing and care for potentially large numbers of affected individuals. Facility needs will vary with the size of the regional population served and the proximity to other healthcare facilities and external assistance. Triage and management planning for large-scale events may include:

- Establishing networks of communication and lines of authority required to coordinate onsite care.

- Planning for cancellation of non-emergency services and procedures.

- Identifying sources able to supply available vaccines, immune globulin, antibiotics, and botulinum anti-toxin (with assistance from local and state health departments).

- Planning for the efficient evaluation and discharge of patients.

- Developing discharge instructions for patients determined to be non-contagious or in need of additional on-site care, including details regarding if and when they should return for care or if they should seek medical follow-up.

- Determining availability and sources for additional medical equipment and supplies (e.g., ventilators) that may be needed for urgent large-scale care.

- Planning for the allocation or re-allocation of scarce equipment in the event of a largescale event (e.g., duration of ventilator support of terminally afflicted individuals).

- With assistance from the Pathology service, identifying the institution's ability to manage a sudden increase in the number of cadavers on site.

FACILITIES AND EQUIPMENT

Evaluating Existing Resources: In evaluating existing resources, hospitals are challenged to identify spaces that will support decontamination activities (including equipment storage) and ensure operations can continue in the event one area of the hospital becomes contaminated. Hospitals planning additions or remodeling projects have a unique opportunity to design spaces appropriately. Other hospitals should use creative planning to identify existing architectural features that they can use to their advantage.

Isolation and Lockdown: Hospitals use a variety of methods to limit unauthorized access to the ED during emergencies until the victims have been decontaminated. The methods range from a guard with a key at the door to sophisticated keycard systems controlled at a central command center. The more complex systems tend to be associated with urban or recently modernized hospitals and are intended for use in any type of disturbance. Hospitals intend to use these methods if situations suggest that an unruly crowd will force its way into the hospital.

Personal Protective Equipment: Hospitals should select PPE (e.g., respirators, suits, gloves, face and eye protection) based on a hazard assessment that identifies the hazards to which employees might be exposed. Under OSHA's Personal Protective Equipment Standard (29 CFR 1910.132) or the parallel State Plan standards, all employers, including hospitals, must certify in writing that the hazard assessment has been performed.

OSHA's Personal Protective Equipment Standard also requires that employees be provided with equipment that fits appropriately. Some hospitals assign a set of protective equipment (except the PAPR respirator) to a specific individual. The equipment is stored

in a container marked with the individual's name. Other hospitals maintain general supplies of PPE, storing sets of equipment by size (one set includes a large suit, large gloves, and large boots). In this case, the packages are clearly marked only with the size. Each first receiver tries on equipment to determine what size group fits best, then, during an emergency, the employee can quickly locate an appropriate PPE set. One hospital reported that boot size serves as the basis for its PPE sets. It is sometimes necessary to include two sizes of each type of glove in the set to ensure proper fit for everyone who wears the PPE set. Suits do not need to fit as closely and excess fabric can be taped or rolled to fit. To prevent protective suits from tearing at the crotch, hospitals should order over-sized suits (larger than the individuals normal size) (SBCCOM, 2003). Loose-fitting PAPR respirator hoods offer a universal fit, thus are not included in individual or size-based PPE sets; however, tight fitting facepieces do require fit testing.

Triage: Hospital A notes that pre-decontamination triage serves three purposes:

- Distinguish contaminated individuals from other patients arriving at the hospital (e.g., by identifying symptoms and victim's proximity to a known chemical release).
- Identify victims who require immediate stabilization before they enter the decontamination system (e.g., shock and respiratory arrest).
- Identify injuries or critical pre-hospital treatment materials that will require special handling inside the decontamination system (e.g., a tourniquet that must be replaced with an uncontaminated compression device).

A plan for pre-decontamination triage should be included in the EMP.

Post-decontamination triage for medical treatment should occur in the Hospital Post-decontamination Zone, after victims are inspected and found to be free of contamination. Some hospitals combine decontamination and initial medical treatment (such as antidotes), which means either the healthcare worker attempts medical triage while wearing PPE (preferred) or the worker is at risk of exposure from victims that have not been adequately decontaminated.

Decontamination Procedures: Decontamination procedures can have a large impact on first receiver exposure to hazardous substances. All the hospitals interviewed agree that the basic steps include:

1. Activate the EMP.
2. Learn as much as possible (as soon as possible) about the number of victims, the contaminant, and associated symptoms. Previous arrangements with first responder organizations can improve the timeliness and quantity of information received.
3. Activate the decontamination system and assemble the decontamination team and site security staff.
4. Perform any medical monitoring (e.g., vital signs), if specified by the EMP.

5. Put on PPE.
6. Triage victims to determine which individuals require decontamination and provide critical medical treatment to stabilize them before decontamination (e.g., atropine).
7. Assist victims (ambulatory and non-ambulatory) in removing contaminated clothing and securing personal property as soon as possible (within minutes of arrival).
8. Place clothing and other contaminated items in an approved hazardous waste container that is isolated outdoors so the items are not a continuing source of exposure.
9. Wash victims using soap, with good surfactant properties, and water (preferably tepid water to improve victim compliance). This step should include copious rinsing. [See discussion below.]
10. Inspect victims to evaluate the effectiveness of decontamination and guide decontaminated victims to the medical treatment area (Hospital Post-decontamination Zone). Return inadequately decontaminated victims to the shower area and repeat cleansing.
11. Decontaminate equipment and the decontamination system (if not disposable).
12. Staff remove PPE and decontaminate themselves.

All of the steps above can influence the extent of healthcare workers' exposure to the contaminant. However, certain steps should be highlighted for their direct impact on the concentrations of contaminant first receivers will encounter. For example, disrobing might remove as much as 75 to 90 percent of the contaminant arriving on a victim (Macintyre et al., 2000; Vogt, 2002; USACHPPM, 2003a).[69] By isolating (in an approved hazardous waste container) the contaminated clothing, staff prevent these materials from off-gassing into the work area. To minimize first receiver exposure levels, these steps should be implemented immediately as victims arrive.

REPORTING

As the likely first responders to a bioterrorism incident, for hospital workers the first step to take upon being notified or becoming aware that a bioterrorism incident has occurred in your community is to notify the appropriate departments of the hospital. At a minimum this would include the laboratory and infection control departments. All relevant management should be notified as well. Next, steps should be taken by the organization to notify the state and federal authorities. When an appropriate emergency response plan has been implemented in the state and local governments, the notification process can most effectively begin by contacting the local health department. For example, for Texas state residents, the appropriate department to contact is the Texas Department of State Health Services, Center for Public Health Preparedness and Response (800) 705-8868 (daytime) and (512) 458-7111 (evenings and weekends). Local health departments will then contact local infection control personnel and

communicate with the local and state health departments, FBI field office, local police, CDC, and medical emergency services.

Each health care facility should include a list containing the following telephone notification numbers in its readiness plan:

INTERNAL CONTACTS:
INFECTION CONTROL ___-____
EPIDEMIOLOGIST ___-____
ADMINISTRATION/PUBLIC AFFAIRS ___-____

EXTERNAL CONTACTS:
LOCAL HEALTH DEPARTMENT ___-____
STATE HEALTH DEPARTMENT 1-___/___-____ *****
FBI FIELD OFFICE 1-___/___-____ *****
BIOTERRORISM EMERGENCY NUMBER, CDC Emergency Response Office 770/488-7100
CDC HOSPITAL INFECTIONS PROGRAM 404/639-6413