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Vol. 12, No. 1 Spring 2002

SMALLPOX - VARIOLA

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- Is smallpox a threat to the US and the world? Yes.
- Do we have an effective vaccine in the US for smallpox? Yes.
- If there is a smallpox bioterrorism attack on the US, will people die? Yes.
- How many will die? That depends on how quickly the initial cases are recognized and the response instituted by the public health service. If there is early recognition, the first day that the first patient has a rash, the response will significantly limit the number of deaths. If recognition does not occur until several of the initially infected patients present with the characteristic rash, several to many deaths will probably occur. If recognition of them does not occur, then these initially infected patients will spread the disease to their families and other close contacts (face-to-face contact); and the number of deaths could easily exceed 100. In the worst case scenario, several thousands deaths would be expected. The numbers listed here are significantly less than those that have been reported in the media; however, they are based on a careful reading of the scientific literature by the authors.
- Should we vaccinate everyone in the US now? No. That is a bad idea, because of vaccine side effects, which are discussed below.
- Does the Centers for Disease Control and Prevention (CDC) have a response plan in the event of a smallpox bioterrorism attack? Yes.
- Is there a new smallpox vaccine under development? Yes.

Smallpox is an ancient disease that probably appeared sometime after 10,000 BC. Evidence of the disease has been found in Egyptian mummies from as early as 1580 BC. In the past, it had a worldwide scope and virtually everyone contracted the disease at some point during his or her lifetime. Attempts were made over the centuries by various cultures around the world to deliberately inoculate healthy persons with smallpox (variolation) to induce a milder infection (hopefully), which would lead to permanent immunity. Infections were induced by blowing dried, pulverized smallpox crusts into the nose of a healthy individual (China) or putting crusts into veins by needle techniques (Africa, Asia) or pounding the skin with a broom smeared with smallpox pus after taking a sauna (Russia) or scratching smallpox material into the skin (Africa, Greece, Turkey). These induced infections, however, were often more deadly than naturally occurring smallpox. In 1796, Edward Jenner, an English country doctor who had been practicing for 24 years, changed the course of history. He had been aware of the folklore that milkmaids and dairymen, who recovered from cowpox (mild compared to smallpox), did not contract smallpox. On May 14, 1796, he applied cowpox pus taken from a pustule on a milkmaid earlier that day, into a needle scratch of an eight-year-old boy. Six weeks later, Jenner inoculated the boy with smallpox and he did not contract the disease. Two weeks later, Jenner re-inoculated the boy and again, no smallpox developed. Jenner termed his procedure *vaccination* after the Latin word *vacca* for cow.

The use of cowpox virus to produce an infection that subsequently protected the patient from smallpox illustrates a major fact relevant to the biology of smallpox. There are several viruses in the genus *Orthopoxviurs*, e.g., camelpox, cowpox, ectromelia, vaccinia, and variola (smallpox) that are similar enough that infection by one will confer immunity against the others. Humans can only be infected with camelpox, cowpox, smallpox, and vaccinia. The virus currently used for the smallpox vaccine is vaccinia, not smallpox. The origin of vaccinia is unclear at this time, but when used for the smallpox vaccine, it is highly effective.

Smallpox occurs only in humans. The last documented case of it occurred in Somalia in 1977. The World Health Assembly certified the world free of smallpox in May 1980. Although it has been eliminated as a disease, it does exist in special laboratories in the US and Russia. There is legitimate concern, though, that several other countries have smallpox virus in their laboratories.

Smallpox virus is spread (transmission) by droplets from the mouth, nose, and throat. That means that for transmission to occur, a person must be in close contact with the patient at a distance close enough to touch them (face-to-face contact). When the distance exceeds six feet, the risk of transmission becomes negligible. Transmission can occur from scabs; however it is negligible because the virus is tightly bound to the fibrin protein in the scab. Historically, there have been a few reports noting transmission to ▶ *2*

"ECONOMY CLASS SYNDROME"

By: Peter W. Nord, M.D.
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Richard Nixon, while President, nearly died as a result of it. And this was on Air Force One.

After a long flight, then President Nixon felt a twinge of pain in his calf, which soon became severe. Immediately upon landing, he was taken to a hospital where it was determined that a blood clot had developed in his leg, and now had fragmented, traveling to his lungs. Life-saving blood thinners were immediately started in order to stop the progression of the clots, diagnosed as Deep Vein Thrombosis or DVT.

Richard Nixon survived this episode; however, recently this condition has become recognized as the cause of death in greater and greater numbers of air travelers. The reasons for this are twofold: increased physician awareness, and increased blood clotting risk factors. Physicians have become more aware of this association, and so when presented with a patient with a blood clot are now beginning to ask about recent air travel. The risk factors for developing blood clots include immobility, dehydration, hormone use, smoking, increased age, and obesity. The link between air travel and DVT was not confirmed until recently because the symptoms often appear days after a trip's conclusion.

The incidence of DVT is increasing due to the following factors:

The average age of air travelers is increasing. This is due to the "baby boomers" traveling for business and pleasure in unprecedented numbers. Moreover, they are traveling for longer periods, as the world becomes smaller and smaller, and as the strong economy continues. Studies have shown that the risk for DVT increases markedly with air travel greater than three hours, especially in older travelers.

Hormone use among men and women is on the rise. The benefit to menopausal women of using Hormone Replacement Therapy (HRT), predominately estrogens, is well documented, and is now routinely recommended. In some individuals, these hormones lead to a slightly increased risk of blood clots. Sitting immobile for hours, ▶3

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laundry workers handling patient's sheets, and by airborne outbreak within a hospital. Because the virus cannot survive long periods of time at room temperature, inanimate objects do not play a significant role in the spread of this disease.

In a bioterrorism attack, the virus could be put into a special solution to be sprayed. The virus in this aerosol might survive up to 1 - 2 days, before becoming noninfectious. If an attack occurs, close contacts of the smallpox patients would need to be vaccinated. A contact, in this instance, is defined as a member of the patient's household, someone who has been in the same household as the patient, or someone who has otherwise had face-to-face contact with the patient, after the patient has developed a fever.

The incubation period after infection with smallpox virus is usually 12 days with a range of 7 - 17 days. Then a prodrome of fever, chills, backache, and malaise develops and quickly evolves into prostration and toxemia, all of which lasts 2 - 5 days before the rash breaks out. The rash begins as a maculopapular (flat or raised lesions ≤ 1 cm diameter) rash of mucous membranes (mouth, throat, nose, and conjunctivae), face, and forearms. It spreads quickly to the trunk (chest, abdomen, back) and legs. One to two days after beginning, the rash becomes vesicular (small blister-like lesions in the maculopapular lesions) and then pustular. These pustules are deep enough (dermal level) to cause scarring, when they heal. They rupture leaving a crust at 8 - 9 days after the rash begins. It will separate and fall off at three weeks, leaving a pitted scar.

Looking at smallpox from a different perspective, the virus enters the body via the mucosa, usually the nose, and is carried to the lymph nodes in the area and begins to multiply in the white blood cells. Only one or two virus particles (virions) are necessary to cause an infection. Three to four days later, the virus spreads via the blood (viremia #1) with no symptoms occurring to the spleen, bone marrow, and other lymph nodes all over the body. Other organs are seldom being involved. There the virus multiplies again and four days (or more) later spreads via the blood (viremia #2) with prodromal symptoms occurring. The virus is then localized in the white blood cells in the skin and mucous membranes. The rash develops 2 - 5 days later. The rash is worse on the face, forearms, and lower legs. It typically develops in the mouth and nose before erupting on the skin and the virus levels are highest in the saliva during this period (the first week of symptoms). As a result, the patient is most infectious at a time when the diagnosis is not clear and the characteristic skin rash has not manifested.

Death can occur as a result of the toxemia that accompanies the second viremia, secondary bacterial infections, encephalitis, pulmonary edema [flat-type or hemorrhagic type (see below)], and/or hemorrhage (hemorrhagic type). Smallpox (variola) manifests in different intensities. Variola minor causes a mild-to-moderate toxemia with a 1% death rate in the unvaccinated person. Variola major (VM) manifests in three forms. Classic smallpox (~75% VM cases) with a 30% death rate in the unvaccinated person and 3% in the vaccinated person. In the past, malnutrition or other diseases often debilitated the populations infected with smallpox, making them more vulnerable to smallpox. In a healthy population, such as the US, the expected death rate with classic smallpox, for example, might be closer to 10%. The second form of VM is flat-type smallpox (2 - 5% VM) and has a flat rash that develops more slowly than the other forms. The death rate is 95% in the unvaccinated and 66% in the vaccinated. The third form of VM is hemorrhagic smallpox (< 3% VM), which causes severe toxemia and mucosal hemorrhage with death occurring in a few days and, typically, before the onset of the rash. Death related to all four types of variola, would probably be decreased with aggressive intensive care that we currently have available in the US; however, this has never been tested for obvious reasons.

In addition to aggressive intensive care management of active cases of smallpox, there are a couple measures that might lessen the severity (morbidity) or death rate (mortality) of the disease. First, vaccination of exposed persons within 4 days of the exposure has been shown to decrease the number of people developing smallpox and the number of deaths from the disease. Second, there is active research to bring to market an oral antiviral drug that could be used to treat smallpox. That drug is HDP-cidofovir, an oral form of the intravenous drug cidofovir (Vistide®) used in the treatment of cytomegalovirus retinitis in HIV patients to prevent blindness. Experimentally, this drug has been shown to stop the replication of smallpox virus in cells in test tubes and to prevent death in animals infected with cowpox, a virus closely related to smallpox, after a single dose of the drug. More work has to be done. The Federal Drug Administration has approved the drug's use for experimental purposes. Research is ongoing to discover other antiviral drugs that might be used in the treatment of smallpox.

The current proven method for containing and eradicating a smallpox outbreak is called ring vaccination and is the same method that was used to eliminate smallpox as a disease in humans in the 1970's. The method is basically a fourfold process:

- Identify and isolate patients with confirmed and suspected smallpox;
- Trace and vaccinate all contacts of these patients;
- Trace and vaccinate all contacts of these contacts;
- Monitor closely all suspected patients and contacts for the development of smallpox.

By this method, a "ring" of monitored and vaccinated people is placed around each and every case of smallpox to prevent the disease from spreading further and, consequently, to allow it to end with the cases that have developed. It is important to note that there is no human carrier state for smallpox. That means that healthy people without symptoms cannot "carry" and spread the disease. There is no animal reservoir, where the virus can "hide out" only to return another day to cause infection. The CDC, through state and local health departments, is coordinating the plan outlined here. It is also continually updating that plan.

The vaccine currently available is derived from vaccinia virus and is a live-virus vaccine. It is effective and after primary vaccination (first time ever) will produce protective antibodies at 10 - 14 days, which is several days sooner than naturally occurring infection from smallpox. It is established that primary vaccination within 4 days of exposure to smallpox often aborts the development of smallpox or significantly reduces the mortality from it. It is hard to predict how long the incubation period will be in any given individual (known range 7 - 17 days). It would seem judicious, then, to vaccinate an exposed person up until the time he or she develops symptoms with the expectation that they might have a less adverse outcome. The vaccine is inoculated using a special needle to slightly puncture the skin several times in a small area with a trace of blood evident on the skin at the completion of the process. With primary vaccination, erythema develops (3 - 5 days) at the site, then a pustule develops and enlarges (maximum size at 8 - 12 days), it scabs over (14 - 21 days) and leaves a typical scar after the scab falls off. In some people, this vaccination response may vary. When someone is revaccinated (booster), the sequence of events is more rapid and, as well, the antibodies are detected ≤ 7 days. The duration of protection (immunity) by vaccination is in question, because the scientific data is not clear. However, there is data to support the contention that significant immunity after primary vaccination lasts at least 10 years in most individuals and up to 20 years or more in others. Further research is needed to better define the duration of immunity.

Mass vaccination of the whole population of the US is not a good idea at this time, because the overall number of serious vaccine side effects (62.9 per million persons vaccinated) would be too high, including death in one per million (age ≤ 19 years). The worst side effect is encephalitis (3 per million, age ≤ 9 years) leading to death in 10-35% and neurological deficit in most who recover. Another major side effect is progressive vaccinia (0.8 per million), which is a generalized infection that occurs in people with compromised immune systems and has a death rate of 30%. Eczema vaccinatum (10.3 per million) presents as severe inflammation of an area of skin, where there is or has been eczema. It occurs mostly in children (age ≤ 9 years) and may be severe, with rare deaths reported in the past. Vaccinated persons can pass vaccinia virus to immunocompromised patients and to eczema patients, leading to the respective complications outlined. The other two major side effects, generalized vaccinia (23.4 per million) and accidental infection [e.g. transferring vaccinia virus from vaccination site to eye, vulva, or another person by hands] (25.3 per million) occur mostly, but not exclusively in those under age 19 years. Recovery in these two entities is typically uneventful.

Smallpox vaccine made from vaccinia virus is highly effective, but it is not a benign vaccine and must be used judiciously. The current stockpile of 15 million doses in the US has been shown that it can be diluted to 150 million doses. It should be sufficient in the short run to provide the necessary number of doses to manage a bioterrorism attack. By the end of 2002, an additional 200 million doses of the new smallpox vaccine (made from vaccinia virus) is projected to be developed and produced, so that the entire US population will be covered should it become necessary to vaccinate everyone.

Further Reading

Websites

http://www.cdc.gov/nip/smallpox/
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=vacc.chapter.d1e2084
http://www.bt.cdc.gov/DocumentsApp/FAQSmallpox.asp?link=2&page=bio
http://jama.ama-assn.org/issues/v281n22/ffull/jst90000.html

Books

Chase A. Magic Shots: A Human and Scientific Account of the Long and Continuing Struggle to Eradicate Infectious Diseases by Vaccination. New York, William Morrow and Company, 1982.

Garrett L. Betrayal of Trust: The Collapse of Global Public Health. New York, Hyperion, 2000.

Economy Class Syndrome *continued from page 1*

and having the lower leg circulation slow as a result, allows the hormones to activate the body's clotting mechanism, leading to a DVT. Men, as well, are now using hormones for various reasons, including hair loss, decreased libido, impotence, and prostate conditions.

Smoking has a strong relationship with clotting due to its effect on the body's clotting factors, as well as its direct effect on the small arteries of the body. Smoking any kind of tobacco product leads to a constriction of small arteries, and eventually to permanent narrowing of these arteries. Blood flows more slowly through the smaller arteries to the veins, thereby, increasing the chance of blood clots.

Obesity is another independent risk factor for developing DVT, which tends to increase with age as well.

Dehydration, either from not drinking enough fluids, or from drinking beverages containing caffeine or alcohol, will also make a blood clot more likely.

Immobility, in this case due to the confines of an "economy class" seat, may be the final straw that adds to existing factors to create a DVT. Not only the lack of mobility, but compression of the legs (from crossing the legs, or where the seat applies pressure to the legs) can lead to the development of a blood clot.

Other risk factors include recent surgery and some forms of cancers.

What can be done to prevent "Economy Class Syndrome"?

- Wear compression gradient hosiery such as TravelSox™.
- Take one coated aspirin the day before, and the day of travel.
- Decrease or stop using tobacco products.
- Lose weight if you are greater than 30% over your ideal body weight.
- Drink plenty of fluids while traveling; and avoid caffeine and alcohol.
- Move your legs! Get up and walk up the aisle. Stretch your legs and perform muscle-tightening exercises at your seat.

With these precautions, "Economy Class Syndrome" and the risk of DVT can be greatly reduced, and lives saved. Richard Nixon was out of the hospital within days, with only a slight limp, giving away the fact that even on Air Force One it is possible to be struck down by "Economy Class Syndrome".

TravelSox™ are high quality, gradient compression, knee-high socks that have been selected for their ability to prevent "Economy Class Syndrome" and death due to blood clot formation associated with air travel. TravelSox™ are comfortable to wear for prolonged periods, keeping the feet warm, and permitting the traveler to kick off his or her shoes, knowing that they can be replaced easily at the end of the flight. They are durable, come in all sizes, and are available in several colors. The FDA and The Air Travelers Association have approved TravelSox™ to aid in the prevention of DVT. TravelSox™ are available at Passport Health in multiple colors and sizes for $16.00 per pair.

On The Horizon- What's New

Vaccines have been one of the most significant advances in human health, but no one likes the prick of a needle. You may no longer have to look away and grimace when you get your vaccine. Researchers at IOMAI Corporation have developed an entirely new way to deliver vaccines, through a small skin patch. Much like a nicotine patch, the vaccine patches can be worn on the arm to deliver the vaccine. This discovery is now in clinical testing and approval of a vaccine delivered by a patch may come in the next few years. Travelers may be especially pleased to find that they can be protected against travelers' diarrhea by a vaccine delivered in this manner. In the April 2002 issue of *Infection and Immunity*, researchers report on the successful delivery of a candidate vaccine against travelers' diarrhea. The vaccine will continue to be developed in further trials this summer in addition to a tetanus booster, often needed by travelers who need to update their more traditional vaccines before traveling. IOMAI Corporation is focused on developing the technology that uses patches both for the convenience of patch use and the strength of the immune responses elicited by targeting the skin. This powerful combination has been recognized by Berna Biotech, who has brought their long standing interest and expertise in travelers medicine into a commercial agreement with IOMAI to further develop a portfolio of travelers vaccines delivered by a patch. When the patches become available, the future of safe travel to distant lands may no longer require shots.

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Q. I am planning a trip to Brazil and my travel agent says I don't need Yellow Fever vaccine but I have heard from some that I do. I am confused about whether to take the vaccine, can you help?

A. Travel agents are usually well versed on where to go and what to see; however, they have no medical training and do not keep up on outbreaks. Brazil has recently had an upsurge in Yellow Fever cases, and although Brazil only recommends the vaccine it is advisable to be vaccinated. Not too long ago there were 38 confirmed cases in the south eastern state of Minas Gerais. Travelers often visit this rich mining area and shop for emeralds and other precious and semi precious stones. Yellow Fever is a viral disease transmitted by mosquitoes. In the most severe outbreaks, over a half of those affected can die. The World Health Organization estimated that 200,000 people in 34 countries across Africa and South America are infected with Yellow Fever every year, leading to around 30,000 deaths. The disease can be prevented by vaccination, which protects for at least 10 years.

Q. I have recently heard about shark attacks in Florida and was wondering if there are other areas where sharks pose a danger. I am planning to spend some time at the beach in South Africa.

A. Yes, the white shark is likely responsible for more attacks on humans than any other species, especially in the waters of southern Australia and the east coast of South Africa. Shark behavior can be unpredictable. There is no such thing as a friendly shark. Shark-infested water should be avoided, particularly at dusk and at night. Swimmers should remain in groups. Isolation creates a primary target and eliminates companion surveillance. If a shark appears in shallow water, swimmers should leave the water with slow, purposeful movements, facing the shark if possible and avoiding erratic behavior that could be interpreted as distress. If a shark approaches in deep water, the diver should remain submerged, rather than wildly surface to escape. Blood and other body fluids attract sharks. No one should be in waters with an open wound or keep captured fish in nearby waters.

Q. I am traveling to India and Nepal and understand there is quite a bit of Cholera. Isn't there a Cholera vaccine available?

A. Not at this time in the United States. Cholera is an acute diarrhea-causing bacterial disease that is generally limited to areas with very poor sanitation in Africa, Asia and Latin America. The previously available product was discontinued in 2000. The whole-cell killed product had many shortcomings: a protection rate of only about 50%; frequent and unpleasant side effects; reliable immunity that lasted for only 6 months, with most of that protection in the first few months, and protection could be overwhelmed by a large number of cholera bacteria. Two oral, single-dose cholera vaccines are presently available in other countries. Healthy travelers who follow food and beverage precautions rarely become clinically ill. We do recommend rehydrating fluids and, if necessary antibiotics. Our diarrhea kit includes a treatment regimen.

Q. I have been traveling to underdeveloped countries for quite some time and have received Immune Globulin on several occasions. Do I need to repeat this shot for my upcoming trip to China?

A. The advent of hepatitis A vaccine has curtailed the use of immune globulin (IG) in travel medicine. The hepatitis A vaccine is virtually 100% protective, while IG is about 85% protective and immunity lasts only several months. The specific anti-hepatitis A antibodies found in IG will likely decline as the incidence of the disease decreases in the population of developed countries, which is another reason for using the vaccine rather than IG.

Q. I am going to Malaysia and heard travelers' diarrhea is rampant. What do you suggest I take along to quell the problem?

A. We suggest our travelers' diarrhea kit that contains several remedies including Imodium to stop symptoms, Ceralyte, an oral rehydration solution and an antibiotic. You may want to take several antibiotics, as the campylobacter bug, which is very prevalent in the area, has become resistant to a class of antibiotics called quinolones. The antibiotic Azithromycin fights the bug and is hard to find in Malaysia.