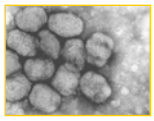
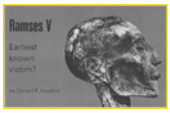
Slide 1	Smallpox *Variola*	The word *variola* (smallpox) comes from the Latin word *varius*, meaning "stained," or from *varus*, meaning "mark on the skin". Any confirmed case should be considered an international emergency and should be reported to public health authorities immediately.
Slide 2	**Overview** • Organism • History • Epidemiology • Transmission • Disease in Humans • Disease in Animals • Prevention and Control Center for Food Security and Public Health Iowa State University - 2004	In today's presentation we will cover information regarding the organism that causes smallpox and its epidemiology. We will also talk about the history of the disease, how it is transmitted and how it affects humans, and the clinical signs observed. Finally, we will address prevention and control measures for smallpox virus.
Slide 3	The Organism	
Slide 4	**The Organism** • Double stranded DNA • Orthopoxvirus – Variola, cowpox, vaccinia, monkeypox, • Variola major or minor • Stable out side host – Retains infectivity • Last case, 1977 • Eradicated, 1980  Center for Food Security and Public Health Iowa State University - 2004	Smallpox is a double stranded DNA virus in the genus Orthopoxvirus. Smallpox disease can be caused by variola major or variola minor. Variola major is the more common and severe form, causing an extensive rash and a higher fever. Variola minor is much less common and causes a less severe disease. There are four forms of variola minor (ordinary, modified, flat, and hemorrhagic). Other orthopoxviruses include cowpox, vaccinia, monkeypox and others. Variola is stable outside the host and retains its infectivity. The last case of smallpox occurred in 1977 and was declared eradicated from the world in 1980. http://www.bt.cdc.gov/agent/smallpox/overview/disease-facts.asp Image: Smallpox virus
Slide 5	History	

Slide 6

History of Smallpox

- First appeared in Northeastern Africa around 10,000 BC
- Skin lesions on mummies
  - 1570-1085 BC
  - Ramses V



Center for Food Security and Public Health
Iowa State University - 2004

Smallpox is believed to have appeared around 10,000 BC during the first agricultural settlements in northeastern Africa. The earliest evidence of skin lesions resembling those of smallpox is found on the faces of mummies (1570 to 1085 BC) and in the well-preserved mummy of Ramses V, who died as a young man in 1157 BC. While poxvirus was never isolated or identified in tissue samples from Ramses V, skin lesions were consistent with smallpox. Source: World Health, May 1980. Published by World Health Organization.

Slide 7

History of Smallpox

- 1763, Sir Jeffrey Amherst
  - Smallpox in blankets for Indians
- 18th century Europe
  - 400,000 deaths
- Case fatality, 20-60%
  - Scars, blindness
- Infants, 80-98% CF

Center for Food Security and Public Health
Iowa State University - 2004

The devastating effects of smallpox gave rise to one of the first examples of biological warfare. In a letter written in 1763, Sir Jeffrey Amherst, commander-in-chief of British forces in North America, suggested grinding the scabs of smallpox pustules into blankets that were to be distributed among disaffected tribes of Indians. In the late 18th century in Europe, 400,000 people died of smallpox each year and one third of the survivors went blind. The case-fatality rate associated with smallpox varied between 20% and 60% and left most survivors with disfiguring scars. Many persons went blind as a result of corneal infection. The case-fatality rate in the infant population was even higher; among children younger than 5 years of age in the 18th century, 80% of those in London and 98% of those in Berlin who developed the disease died. Statue depicting the distribution of smallpox lesions in a historical Chinese painting.

Slide 8

Variolation

- Ground scabs, pus, vesicles used to vaccinate
  - China, powdered scabs blown into nostrils
    - Pills from fleas of cows
  - India, application of scab or pus to scarified skin
- Children exposed to mild smallpox

Center for Food Security and Public Health
Iowa State University - 2004

Physicians realized that smallpox survivors became immune to the disease. Thus the method of variolation was started. This involved taking samples (vesicles, pus, ground scabs) from benignly diseased patients and introduce the material into susceptible patients via the nose or skin. In China, powdered scabs of smallpox pustules were blown into the nostrils of healthy persons through a tube. Also in China, 100 years before Edward Jenner, healthy persons took pills made from the fleas of cows to prevent smallpox; this is the first recorded example of oral vaccination. In India, variolation took several forms, the most common of which was the application of scabs or pus from a person with smallpox to the intact or scarified skin of a healthy person. Children were exposed to organisms from persons with mild cases of smallpox, and various forms of material from persons with smallpox were administered to healthy adults in different ways.

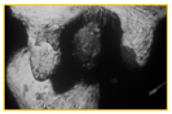
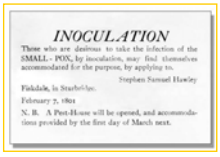
Slide 9

Variolation

- Variolation came to Europe early 18th century
- 1715, Lady Mary Wortley Montague
  - 1718, Inoculated her 5 yr. old son
  - 1721, inoculated her daughter
- 1745, London Smallpox Inoculation Hospital founded

Center for Food Security and Public Health
Iowa State University - 2004

The English aristocrat Lady Mary Wortley Montague was responsible for the introduction of variolation into England. She had an episode of smallpox in 1715 that disfigured her beautiful face. She was so determined to prevent the ravages of smallpox and so impressed by the Turkish method that she demanded they inoculate her 5-year-old son in Turkey in March 1718 and her 4-year-old daughter in London in April 1721. This was the first professional variolation performed in England. In 1745, the London Smallpox and Inoculation Hospital was founded. This center was dedicated exclusively to the treatment and prevention of smallpox.

Slide 10	**Variolation** • 1721, variolation reaches U.S. • 1765, connection between milkmaid, cowpox, and smallpox made • 1777, George Washington had all soldiers variolated  Center for Food Security and Public Health Iowa State University - 2004	Variolation soon reached the New World, and in 1721, Dr. Zabdiel Boylston used the technique to stop the smallpox epidemic in Boston.. In 1765, Dr. Fewster of Thornbury, Gloucestershire, wrote to the Medical Society of London to report that variolation induced no reaction in persons who had had cowpox. By 1777, George Washington had all his soldiers variolated before beginning new military operations. It was well known that milkmaids became immune to smallpox after developing cowpox
Slide 11	**Edward Jenner** • 1796, England, May – Inoculated James Phipps with fluid from milkmaid's pustule ▪ Subsequent variolation of boy produced no reaction • Development of vaccine using cowpox – Protective for smallpox  Center for Food Security and Public Health Iowa State University - 2004	In Gloucestershire, England, on May 14th, 1796, Jenner extracted fluid from a pustule on a milkmaid and used it to inoculate a healthy 8-year-old boy (James Phipps). Six weeks later, Jenner variolated the child but produced no reaction. Jenner, in combination with George Pearson and others, developed a vaccine using cowpox. This prevented the vaccinee from developing smallpox if variolated or exposed to smallpox.
Slide 12	**Smallpox Vaccine** • Vaccine comes from *vaca*, Latin for cow • Cows used in early 19th century for vaccine production  Center for Food Security and Public Health Iowa State University - 2004	The word vaccine comes from the Latin word, *vaca*, which means cow. Vaccination done by using pustule fluid spread rapidly. By 1800, it had reached most European countries and about 100 000 persons had been vaccinated worldwide. By the end of the 19th century, arm-to-arm smallpox vaccination was illegal in many countries and the vaccine was obtained from animal skin. Cows were first used in the early 19th century for vaccine production. Image: scraping the scabs from the belly of a cow to create vaccines.
Slide 13	**Smallpox Vaccination** • 1800, new vaccine used in U.S. • 1805, Napoleon begins vaccination of troops  INOCULATION Center for Food Security and Public Health Iowa State University - 2004	By 1801 over 100,000 persons in England had been vaccinated. Benjamin Waterhouse, professor at Harvard Medical School, vaccinated his 5-year-old son and six servants with vaccine from England, the first vaccinations done in the United States. In 1805, Napoleon himself insisted that all his troops who had not had smallpox should be vaccinated with the "Jennerian vaccine." He ordered the vaccination of French civilians 1 year later. Image: Smallpox Inoculation sign from 1801.
Slide 14	**WHO Smallpox Eradication Campaign Begins**  1967 Center for Food Security and Public Health Iowa State University - 2004	This map depicts the endemic areas of smallpox worldwide in 1967, the year the WHO declared the beginning of the eradication campaign. It is important to note that the areas that had eliminated smallpox did not re-establish infection in this time frame. The United States had not had a case of smallpox since 1949. Series of maps from: *Smallpox and its eradication.* F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, I.D. Ladnyi

Slide 15

WHO Smallpox Eradication Campaign Continues

Center for Food Security and Public Health
Iowa State University - 2004

By 1975, smallpox had dwindled to sporadic cases in Bangladesh, Nepal, India, and Somalia.

Slide 16

The End of Smallpox

- Oct. 26, 1977, last case of smallpox
- May 8, 1980, official declaration by WHO - Smallpox Eradicated!

Center for Food Security and Public Health
Iowa State University - 2004

Left image is a photo of 23 year old Al Maow Maalin of the Somali village Merka. He had the last case of variola minor smallpox in the world on October 26, 1977. Laboratory accidents did happen late in the eradication plan. There were 4 cases of smallpox that occurred in 1973 in London, resulting in 2 deaths, and another 2 cases in 1978 from the Medical School of University of Birmingham resulting in 1 death. The image on the right is a child that had the last case of variola major in October 1975 in Bangladesh. Smallpox was declared by the WHO as being eradicated from the globe on May 8, 1980.

Slide 17

Smallpox Eradication

- 1967-1980, $300 million
  - $24 billion to put a man on the moon
- 1967
  - 10 million cases
  - 2 million deaths
- 1972
  - Last U.S. vaccination

Center for Food Security and Public Health
Iowa State University - 2004

Between 1967 when WHO began the smallpox eradication campaign, and 1980, when smallpox was officially eradicated, the total cost was $300 million. It cost $24 billion for the U.S. to put a man on the moon. In 1967 is was estimated that there were 10 million cases and 2 million deaths. The United States discontinued smallpox vaccinations in 1972. Source: World Health, May 1980. Published by World Health Organization.

Slide 18

Eradication Success

- Vaccine available
- No animal reservoir
- Vaccinees easily identifiable
- Vaccinees could "vaccinate" close contacts
- Diseased easily identifiable

Center for Food Security and Public Health
Iowa State University - 2004

Eradication of smallpox was made possible for several reasons: there was a good, protective vaccine available, there was no animal reservoir, vaccinees were easily identifiable and could "vaccinate" friends and family through contact, and those who acquired smallpox were easily identifiable.

Slide 19

Smallpox Stores

- CDC in Atlanta, Georgia, U.S.
- Vector Laboratories in Koltsovo, Russia
- Unknown others?

Center for Food Security and Public Health
Iowa State University - 2004

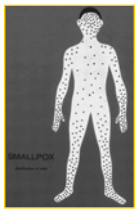
Since 1983, there have existed two WHO-approved and –inspected repositories of variola virus: the CDC in the United States and Vector Laboratories in Russia. Some speculate that other countries may have it, possibly even terrorist groups.

Slide 20	Transmission	
Slide 21	**Smallpox Transmission** • Person-to-person – Inhalation of droplets • Direct contact – With infected body fluids • Scabs • Contaminated objects – Bedding, clothing, bandages • Aerosol – Rarely Center for Food Security and Public Health Iowa State University - 2004	To sustain itself, the virus must pass from person to person in a continuing chain of infection and is spread by inhalation of respiratory droplets, typically within 2 meters or less. CDC: "Generally, direct and fairly prolonged face-to-face contact is required to spread smallpox from one person to another. Smallpox also can be spread through direct contact with infected bodily fluids or contaminated objects such as bedding or clothing. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains."
Slide 22	**Smallpox Transmission** • Spread more easily in cool, dry winter months – Can be transmitted in any climate • No transmission by insects or animals Center for Food Security and Public Health Iowa State University - 2004	Smallpox spreads most readily during the cool, dry winter months but can be transmitted in any climate and in any part of the world. Smallpox is not transmitted by insects or animals.
Slide 23	**Smallpox Transmission** • Transmission from a smallpox case – Prodrome phase, less common ▪ Fever, no rash yet – Most contagious with rash onset ▪ First 7-10 days • Contagious until last scab falls off Center for Food Security and Public Health Iowa State University - 2004	A person with smallpox is sometimes contagious with onset of fever (prodrome phase), but the person becomes most contagious with the onset of rash (during the first 7-10 days). At this stage the infected person is usually very sick and not able to move around in the community. The infected person is contagious until the last smallpox scab falls off.
Slide 24	Disease in Humans	

Slide 25

Smallpox Clinical Disease

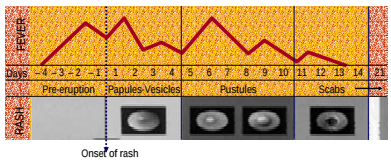
- Incubation period 7-17 days
  - Range 12-14 d
- Initial signs
  - Small red spots in mouth and on tongue
- Rash on face
  - Spreads to arms, legs, hands, feet (centrifugal)
  - Entire body within 24 hours



Center for Food Security and Public Health
Iowa State University - 2004

The incubation period for smallpox is 7-17 days, but generally averages 12-14 days. Small red spots in the mouth and on the tongue are the initial signs of smallpox. Around the time the sores in the mouth break down, a rash appears on the skin, starting on the face. It then spreads to the arms and legs and then to the hands and feet. Usually the rash spreads to all parts of the body within 24 hours. As the rash appears, the fever usually falls and the person may start to feel better. Image from CDC depicting the centrifugal rash, being more on the extremities and less on the trunk.

Slide 26



Center for Food Security and Public Health
Iowa State University - 2004

This diagram depicts the clinical onset of smallpox signs following exposure. The initial signs include a fever that subsides a bit upon the onset of the rash, which occurs after an incubation period of 7-17 days. The rash progresses through macules, papules, vesicles, pustules, and finally scabs. Fever, malaise, headache, prostration, backache, possibly abdominal pain and/or vomiting occur. (Numbers on chart represent days.) The scabs fall off at the end of the 3rd or 4th week and the patient is no longer considered contagious. Source: WHO slide set. For more information, see the link at the end of this presentation.

Slide 27

Clinical Forms of Smallpox

- Variola major
  - Most common and severe form
  - Extensive rash, higher fever
  - Ordinary (discrete, confluent, semi-confluent)
  - Modified
  - Flat
  - Hemorrhagic (early and late)
- Variola minor
  - Less common, less severe disease

Center for Food Security and Public Health
Iowa State University - 2004

There are two major forms of smallpox, variola major and variola minor. Variola major is the more common and severe form, causing an extensive rash and a higher fever. There are four forms of variola major (ordinary, modified, flat, and hemorrhagic). Variola minor is much less common and causes a less severe disease. The next few slides will better describe the various forms of variola major.

Slide 28

Variola Major

- Discrete
  - Pustules separate and not merging with one another
  - Most common form of smallpox

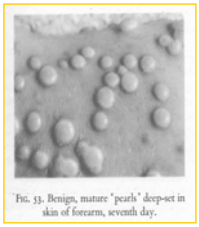


Fig. 53. Benign, mature 'pearls' deep-set in skin of forearm, seventh day.

Center for Food Security and Public Health
Iowa State University - 2004

In the discrete form of variola major smallpox disease, the pustules remain separate and distinct from one another. This is the most frequent form of smallpox.

Slide 29

Variola Major

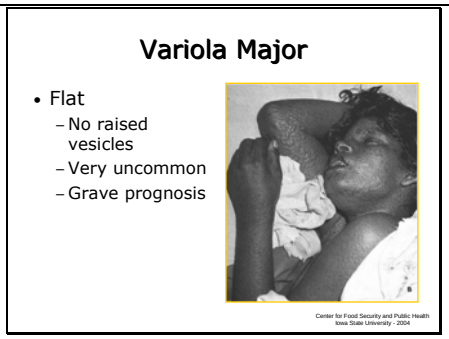
- Semi-Confluent
  - Pustules begin to merge

- Confluent
  - Pustules joining and becoming confluent

Center for Food Security and Public Health
Iowa State University - 2004

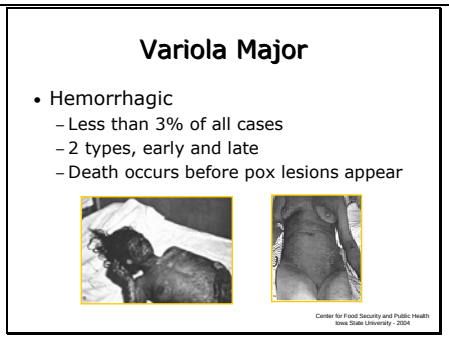
The image on the left depicts pustules that are semi-confluent on the child's face, and the rest remain discrete. The photo on the left depicts the confluent form of variola major. The pustules on this child's hand are joining together. Photos: WHO

Slide 30



Flat-type smallpox remain more or less flush with skin, not forming the raised vesicles as in ordinary-type smallpox. This was an uncommon manifestation in unvaccinated individuals, and even more uncommon in those vaccinated. Prognosis is grave. Photo from WHO.

Slide 31

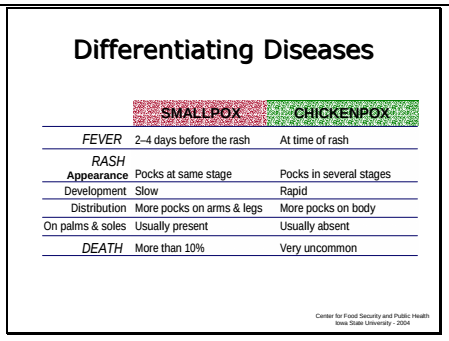


Hemorrhagic smallpox occurs in less than 3% of patients. There are 2 types of hemorrhagic smallpox, early and late, as based upon the time during the disease at which the hemorrhage appears. It causes the appearance of extensive petechiae, mucosal hemorrhage, and intense toxemia; death usually intervened before the development of typical pox lesions could occur. From: Textbook of Military Medicine: Medical aspects of chemical and biological warfare, 1997.

Slide 32

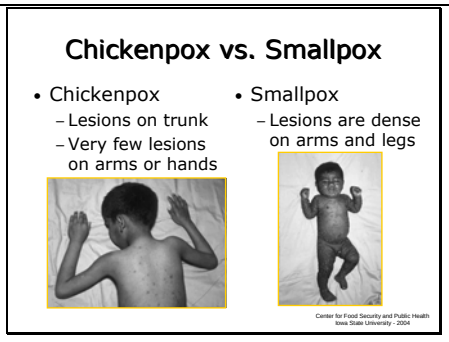
Variola minor in a 30 year old unvaccinated Somali woman 12 days after rash onset. In photo A, Lesions on face were sparse and developed more quickly than those on arms (photo B) or legs (photo C). This woman was not very ill and was ambulatory throughout the disease.

Slide 33

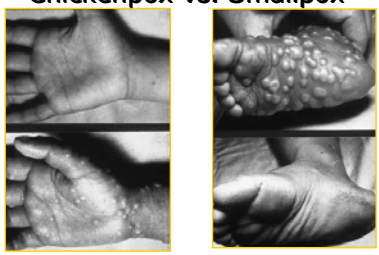


Since chickenpox has been a common childhood disease for many years, it is important to be able to differentiate the two diseases. There are particular points that help to differentiate smallpox from chickenpox:
– In smallpox, the fever precedes the rash by 2 to 4 days,
– The pocks on any part of the body are at the same stage of development, and they develop slowly,
– The pocks are more numerous on the arms and legs than on the body,
– The pocks are usually present on the palms and soles,
– Death following smallpox is not uncommon, while in chickenpox death is very rare.
When death occurs in a patient in whom chickenpox has been diagnosed, smallpox should always be suspected.

Slide 34



In the left photo, a patient with chickenpox has many pocks on his back but very few on his arms or hands. In the patient on the right with smallpox however, the pocks are more dense on the arms and legs than on the trunk.

Slide 35	**Chickenpox vs. Smallpox**  Center for Food Security and Public Health Iowa State University - 2004	In smallpox (shown in the lower left and upper right photographs), pocks are usually present on the palms of the hands and the soles of the feet. In chickenpox there may be few or no lesions on the palms of the hands or the soles of the feet.
Slide 36	• Smallpox or chickenpox?  Center for Food Security and Public Health Iowa State University - 2004	Smallpox is most commonly confused with chickenpox and during the first 2-3 days of rash it may very difficult to differentiate the two diseases. This patient first developed a rash 10 days before this picture was taken. What is the diagnosis? Smallpox or chickenpox? After discussion, it is smallpox. Note: (1) the pocks are at a similar stage of development in each area; (2) the distribution of the rash is characteristic for smallpox, with more pocks on the face and extremities than on the body; (3) although it is day 10 of rash, only a few scabs have formed.
Slide 37	• Smallpox or chickenpox?  Center for Food Security and Public Health Iowa State University - 2004	This patient developed a rash three days before this picture was taken. What is the diagnosis? Smallpox or chickenpox? After discussion, it is chickenpox. Note: (1) there are more pocks on the trunk than on the extremities, a distribution of rash that is characteristic for chickenpox (2) different stages of the rash are seen–papules, vesicles, pustules and scabs (3) pustules and scabs are present although it is only day 3 of rash (4) most of the lesions are very small in size.
Slide 38	**Treatment** • If exposed but not showing signs, vaccinate – Within 3 days, lessens severity – Within 4-7 days, some protection – Quarantine • If showing clinical signs – Isolate patient – Supportive therapy – Cidofovir? Center for Food Security and Public Health Iowa State University - 2004	If a patient has been exposed to smallpox but is not showing any signs of disease, vaccination within 3 days of exposure will prevent or significantly lessen the severity of symptoms in the vast majority of people and affords almost complete protection against death. Vaccination 4 to 7 days after exposure likely offers some protection from disease or may modify the severity of disease. This person should also be quarantined and monitored for signs of disease. If the person is showing signs of smallpox, then isolation and supportive care are essential. There is some experimental evidence that the drug Cidofovir may be of clinical use.
Slide 39	**Prognosis** • Variola major – Ordinary cases, 20-40% case fatality rate – Flat and hemorrhagic cases, usually fatal – Blindness, limb deformities • Variola minor – Less than 1% case-fatality rate • Recovered cases, lifelong immunity Center for Food Security and Public Health Iowa State University - 2004	Case fatality for smallpox caused by variola major ranged between 20-40%. The flat and hemorrhagic forms are usually fatal. Fatality rates in vaccinated persons were around 3%. Blindness and limb deformities could also be sequelae from smallpox. Variola minor is a much less severe disease and had a case-fatality rate of 1%. Persons who recovered from smallpox possessed long-lasting immunity, although a second attack could occur in 1 in 1,000 persons after an intervening period of 15 to 20 years.

Slide 40

Smallpox and Animals

- Animals do not show signs of disease
- No animal reservoir for smallpox
- Not zoonotic
- Some animals naturally susceptible to pox viruses
  - Cats and cowpox

Center for Food Security and Public Health
Iowa State University - 2004

Animals have never been found infected with or showing signs of smallpox and it is not a zoonotic disease. There are, however, reports that vaccinia virus can infect animals. Some animals are naturally susceptible to pox viruses. Cats, for example, are susceptible to cowpox.

Slide 41

Smallpox and Animals

- Vaccinia transmission from milkers to cows
  - No cow-to-cow spread
- Experimental vaccinia infection
  - Dogs
    - No signs
  - Cows and horses
    - Lesions

Center for Food Security and Public Health
Iowa State University - 2004

The risk of a person transmitting smallpox vaccine (vaccina virus) to animals is very unlikely. The only reported instance includes the transmission of vaccinia virus to cows by their recently vaccinated milkers. The virus did not spread cow-to-cow. Cows had a drop in milk production. Experimental infection of dogs produced no clinical signs, whereas in cattle and horses, skin lesions were produced in both species.

Slide 42

Smallpox and Animals

- Cantagalo virus, Brazil
  - Mutant of virus used in smallpox eradication
  - Outbreaks of lesions in dairy cattle and human contacts
  - Established in nature
  - Animal reservoir unknown

Center for Food Security and Public Health
Iowa State University - 2004

Cantagalo virus, an virus that is an apparent mutation of the vaccinia virus used decades ago in Brazil during smallpox eradication efforts, appears to have established itself in nature and is, to this day, responsible for outbreaks of pox lesions in dairy cattle and their human contacts. The exact animal reservoir for this virus is unknown.

Slide 43

Smallpox and Vaccinia

- Concerns of vaccination
  - Could pets serve as a vector?
    - Dog chews bandage, then licks child's face
    - Close contact of pet to vaccinee and an immunocompromised person
    - No evidence to date
    - More research needed
  - Wildlife eats garbage with bandage in it
    - Establish enzootic cycle like Brazil?

Center for Food Security and Public Health
Iowa State University - 2004

There are still concerns as to whether or not pets might serve as vectors for vaccinia. Wildlife that acquire vaccinia laden bandages might establish an enzootic cycle, such as that which occurs in Brazil. A recent publication reports direct transmission of cowpox from a wild rat to a human in the Netherlands (Tom F.W. Wolfs, et. al. Rat-to-human transmission of cowpox infection. EID 2002;8:1495-6.)

Slide 44

Prevention and Control

Slide 45

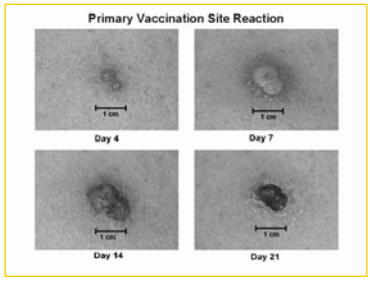
The Smallpox Vaccine

- Vaccinia virus
  - Protects against variola virus
  - Origins unknown
- Live vaccine
  - Used in US until 1972
- Immunity high for 3-5 years
  - Potentially protective much longer

Center for Food Security and Public Health
Iowa State University - 2004

The only prevention for smallpox is vaccination. As described earlier, the practice of vaccination with vaccinia virus began in the early 20th century. The origins of vaccinia virus remain unknown, but this virus is distinct from both variola and cowpox. Some speculate the vaccinia virus is a hybrid between cowpox and variola. Vaccinia (smallpox) vaccine is derived from calf lymph, and was used in the United States up until 1972. It is a lyophilized, live-virus preparation of infectious vaccinia virus. It does not contain smallpox (variola) virus. The needle is dipped in to the vaccine and then the vaccinee to be is jabbed 2-3 times on the upper arm (deltoid muscle) for the initial vaccine (15 times for a booster). Smallpox vaccination provides high level immunity for 3 to 5 years and decreasing immunity thereafter. If a person is vaccinated again later, immunity lasts even longer. Historically, the vaccine has been effective in preventing smallpox infection in 95% of those vaccinated. There is some evidence to indicate that some degree of immunity lasts much longer than 3-5 years.

Slide 46



Center for Food Security and Public Health
Iowa State University - 2004

If the vaccination is successful, a red, itchy bump develops at the vaccine site in three or four 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. The scab falls off in the third week, leaving a small scar. People who are being vaccinated for the first time have a stronger reaction than those who are being revaccinated.

Slide 47

Duration of Immunity

- 2000, over 140 million Americans vaccinated
- 2003, Hammerlund et al study
  - Virus specific T cells
    - Half-life of 8-15 years
    - Detected up to 75 yrs. after vaccination
  - Serum antibody levels stable for 1-75 yrs
- Booster vaccination increase Ab response, not T cell memory

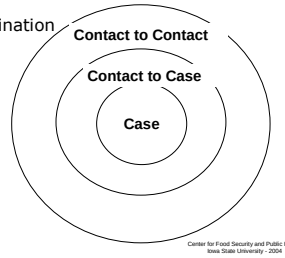
Center for Food Security and Public Health
Iowa State University - 2004

The question is often posed, how long does immunization against smallpox really last? As of 2000, over 140 million people were vaccinated at least once in their lifetime for smallpox (this constitutes over 90% of Americans older than 35 years). Should these people need a booster dose to protect them today from this devastating disease? In a study by Hammarlund and colleagues (Nature 2003), they investigated the duration of immunity. It was discovered that virus-specific T cells were had a half-life ranging from 8-15 years, and were detectable up to 75 years. Serum antibody levels, however, were very stable between 1 and 75 years after vaccination. This indicates T cell numbers and antibody titers function independently but both play a key role in life-long immunity against smallpox. Booster vaccinations may increase a suboptimal antibody response but it will not enhance T-cell memory.

Slide 48

US Outbreak Control Strategy

- Ring vaccination



Center for Food Security and Public Health
Iowa State University - 2004

The ring vaccination strategy is the strategy that will be used if a case of smallpox were to break out in the U.S. Contacts of the case will be found and vaccinated, as will contacts of those contacts. This appears to be the most effective way to contain an outbreak. There is currently enough vaccine available to vaccinate all Americans should the need arise.

Slide 49

US Smallpox Vaccination

- Terrorist threats upon US real
- Bush recommends vaccinating healthcare and military personnel
  - December 2002
- Jan 2003, CDC ships vaccine and needles to the states
- Nov 2003, 38,908 civilians in 50 states and 526,677 military vaccinated

Center for Food Security and Public Health
Iowa State University - 2004

Due to the events of September 11, 2001, the threat of a terrorist act upon the United States was amplified. Government officials felt the threat of a smallpox attack on the US was a real possibility. To protect its citizens, President Bush recommended on December 13, 2002 that a smallpox vaccination of healthcare personnel and the military begin. In January, 2003, the CDC began distributing smallpox vaccine and bifurcated needles to the states for voluntary vaccination of first responders in the health care system. As of November 2003, 38,908 civilians in 50 states and 526,677 military personnel have been vaccinated. The number of adverse reactions is minimal and will be discussed later.

Slide 50

Who Should Not Get the Vaccine?

- Eczema or atopic dermatitis
- Skin conditions
  - Chickenpox, herpes, psoriasis, shingles
- Weakened immune system
  - Transplant, chemotherapy, HIV, others
- Pregnant women
- Less than 18yr.
- Breastfeeding mothers
- If exposed, get vaccine no matter what

Center for Food Security and Public Health
Iowa State University - 2004

Some people are at greater risk for serious side effects from the smallpox vaccine. Individuals who have any of the following conditions, or live with someone who does, should NOT get the smallpox vaccine unless they have been exposed to the smallpox virus: Eczema or atopic dermatitis (this is true even if the condition is not currently active, mild or experienced as a child); Skin conditions such as burns, chickenpox, shingles, impetigo, herpes, severe acne, or psoriasis (people with any of these conditions should not get the vaccine until they have completely healed); Weakened immune system (cancer treatment, an organ transplant, HIV, or medications to treat autoimmune disorders and other illnesses can weaken the immune system); Pregnancy or plans to become pregnant within one month of vaccination; Individuals who are allergic to the vaccine or any of its ingredients; anyone younger than 12 months of age, (however, the Advisory Committee on Immunization Practices (ACIP) advises against non-emergency use of smallpox vaccine in children younger than 18 years of age); persons with a moderate or severe short-term illness should wait until they are completely recovered to get the vaccine; and women who are currently breastfeeding. People who have been directly exposed to the smallpox virus should get the vaccine, regardless of their health status because the risk of the disease greatly outweighs their risk factors. This information was provided by the CDC.

Slide 51

Adverse Vaccine Reactions

- Prior to 2003 vaccination campaign
- For every 1 million people vaccinated
  - 1,000 serious reactions
  - 14-52 life-threatening reactions
  - 1-2 deaths
- Vaccinia immune globulin (VIG)
  - Effective treatment for serious or life-threatening reactions to the vaccine
  - IV form, Investigational new drug

Center for Food Security and Public Health
Iowa State University - 2004

Most people vaccinated with vaccinia experienced normal, usually mild reactions that include a sore arm, fever, and body aches. However, other people experience reactions ranging from serious to life-threatening. Prior to the 2003 US vaccination campaign, about 1,000 people for every 1 million people vaccinated for the first time experienced reactions that, while not life-threatening, were serious. These types of reactions may require medical attention. In the past, between 14 and 52 people out of every 1 million people vaccinated for the first time experienced potentially life-threatening reactions to the vaccine. Based on past experience, it is estimated that 1 or 2 people in 1 million who receive the vaccine may die as a result. Careful screening of potential vaccine recipients has helped ensure that those at increased risk do not receive the vaccine. Vaccinia immune globulin is made from the plasma of vaccinated donors and can be given intramuscularly to those with extensive inadvertent inoculation, eczema vaccinatum, severe generalized vaccinia, and progressive vaccinia. An intravenous VIG is being produced but it is considered an investigational new drug and only available through the CDC. Manufacturers feel this IV-VIG product will continue to be available to support any large scale emergency should the need arise

Slide 52

Serious Vaccine Reactions

- Inadvertent inoculation
  - A vaccinia rash or sores in one area
- Generalized vaccinia
  - Widespread vaccinia rash or sores
- Erythema multiforme
  - Toxic or allergic reaction

Center for Food Security and Public Health
Iowa State University - 2004

Some serious vaccine reactions occurred in the past. Inadvertent inoculation occurs when the vaccinia virus is accidentally spread by touching the vaccination site and then touching another part of the body or another person. A vaccinia rash or outbreak of sores limited to one area usually occurs on the genitals or face, including the eyes, where it can damage sight or lead to blindness. Washing hands with soap and water after touching the vaccine site will help prevent this. Generalized vaccinia occurs when the virus spreads from the vaccination site through the blood causing a widespread rash. Sores break out on parts of the body away from the vaccination site. Erythema multiforme is due to a toxic or allergic rash in response to the vaccine that can take various forms. These reactions may require medical attention. Image depicts an accidental auto-inoculation of cheek with vaccinia virus, approximately 5 days old. Primary take on arm, 10-12 days old. Photo courtesy of John M. Leedom, MD

Slide 53

Life Threatening Vaccine Reactions

- Progressive vaccinia (*vaccinia necrosum*)
  - Ongoing skin infection
  - Common in immunocompromised
  - Virus continues to grow
  - Vaccinia immune globulin necessary
    - Without it = death

Center for Food Security and Public Health
Iowa State University - 2004

Smallpox vaccination is also associated with some risk for life threatening reactions; the two most serious are progressive vaccinia and postvaccinal encephalitis. Progressive vaccinia (or vaccinia necrosum) is an ongoing infection of skin with tissue destruction frequently leading to death. It occurs among those who are immunosuppressed because of a congenital defect, malignancy, radiation therapy, or AIDS. The vaccinia virus simply continues to grow, and unless these patients are treated with vaccinia immune globulin, they may not recover. The photo depicts skin destruction, or vaccinia necrosum at the site of a smallpox vaccination. This is a 64 year old patient after having received a smallpox vaccination. (From CDC)

Slide 54

Life Threatening Vaccine Reactions

- Postvaccinal encephalitis
  - 3 per million vaccinees
    - 40% fatal
    - Permanent neurological damage
- Eczema vaccinatum
  - Skin rashes
  - Widespread infection

Center for Food Security and Public Health
Iowa State University - 2004

Postvaccinal encephalitis occurs in people with certain medical conditions. People with weakened immune systems or certain skin conditions are more likely to have these reactions and should not get the smallpox vaccine unless they have been exposed to smallpox. Postvaccinal encephalitis occurs at a rate of 3 per million primary vaccinees; 40% of the cases are fatal, and some patients are left with permanent neurologic damage. People with skin conditions such as eczema or atopic dermatitis can develop eczema vaccinatum. It manifests as serious skin rashes and a widespread skin infection. Photo depicts eczema vaccinatum in a child. (Courtesy of John M. Leedom, M.D., CDC)

Slide 55

Military U.S. Vaccination Campaign

- December 2002-January 2004
- 578,286 military vaccinees
  - 71% primary vaccinees
- 30 suspected cases of contact transfer to other people
  - Mostly minor skin infections
  - No eczema vaccinatum
  - No progressive vaccinia

Data as of Feb 13, 2004; MMWR

Center for Food Security and Public Health
Iowa State University - 2004

As mentioned previously, our nation's military began receiving smallpox vaccinations as part of a pre-event vaccination program. From December 2002 until January 2004, 578,286 military personnel had received a dose. 71% of this population were primary vaccinees (received the smallpox vaccination for the first time). Contact transfer of vaccinia was identified among 30 persons: spouses, adult friends, adult intimate contacts, and children from the same household as the vaccinee. Sixteen of the 30 cases involved minor skin infections, two involved the eye, and there were no cases of eczema vaccinatum or progressive vaccinia. Secondary transmission involves transmission between persons for example, sharing a bed; tertiary transmission involved the wife of a vaccinee becoming infected and then exposing their infant through breastfeeding. Source: MMWR February 13, 2004 / 53(05);103-105.

Slide 56

2003 U.S. Vaccination Campaign

- January 24-December 31, 2003
- 39,213 civilian vaccinees
  - 11 cases of inadvertent inoculation
  - 1 case of generalized vaccinia
  - 97 serious events
  - 712 nonserious events
    - Rash, fever, pain, headache, fatigue
  - Myocarditis/pericarditis
    - 16 suspected, 5 probable cases

Data as of Feb 13, 2004; MMWR

Center for Food Security and Public Health
Iowa State University - 2004

With all the concerns over vaccine reactions as described in previous slides, you may be wondering how the 2003 vaccination campaign compared. For the civilian population, as of 31 December 2003, out of 39,213 vaccinees, there were 11 total cases of inadvertent inoculation (ocular and non-ocular), 1 case of generalized vaccinia, no cases of postvaccinal encephalitis and 97 other serious events. Serious events are those that result in hospitalization, permanent disability, life-threatening illness or death. These events occurred around the time of vaccination, but it is unknown whether they were caused by smallpox vaccine. There were 712 nonserious adverse events reported and these included self-limiting responses to the vaccination, such as fatigue, headache, itching, redness and swelling at the vaccination site, swollen and/or sore lymph nodes, fever, muscle aches and chills, and nausea. Source: MMWR February 13, 2004 / 53(105); 106-107. There were two deaths and both were attributed to ischemic heart disease and unrelated to the vaccine. The one adverse reaction that appeared that was not described in earlier slides was myocarditis or pericarditis (inflammation of the heart/membrane around the heart ranging from mild to life-threatening in severity). There were 16 suspected and 5 probable cases. No fatalities occurred, and although all patients have since recovered, it is now strongly recommended that those at risk for heart disease do not undergo vaccination unless they become exposed. For more information, please see MMWR May 30, 2003 / 52(21);492-496.

Slide 57

2003 U.S. Vaccination Campaign

- 2003, more cardiac related reactions than expected
- 1947, compared to NYC vaccinations
  - Data indicated no relationship to vaccine
- Defer vaccine with 3 or more cardiac risk factors
  - Current smoker/tobacco user, high blood pressure, high cholesterol or triglycerides, high blood sugar, heart condition before age 50 in a parent, brother or sister

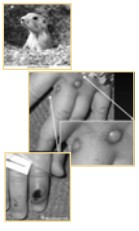
Center for Food Security and Public Health
Iowa State University - 2004

Concerns arose in 2003 when there were a higher number of myocarditis/pericarditis cases and 7 deaths in people receiving smallpox vaccines than what history had shown. In 1947, over 6 million people were vaccinated in New York City in a 4-week period with the same strain of vaccine. Data from death certificates in NYC were retrospectively analyzed and there were no increase in cardiac, atherosclerotic, or all-causes of death. This indicated the ischemic cardiac deaths in 2003 might have been unrelated to vaccine. Each of the 2003 vaccinees with cardiac fatalities had multiple risk factors for cardiac disease, including hypertension, hyperlipidemia, and smoking, and each had been vaccinated for smallpox in childhood. However, due to the higher number of cases of myocarditis/pericarditis, it is now recommended that people with three or more cardiac risk factors defer the smallpox vaccine unless exposed. Those risk factors include being a current smoker or tobacco user, having high blood pressure, high cholesterol or triglycerides, high blood sugar and a heart condition before age 50 in a parent, brother or sister.

Slide 58

Monkeypox: The Agent

- Orthopoxvirus, related to smallpox
- Transmission
  - Reservoir may be African squirrel
  - Bites, aerosol, direct contact
  - Zoonotic, animal-to-animal, person-to-person
- Animals: Fever, rash, pustules conjunctivitis
- Humans: Flu-like, rash, pustules, lymphadenopathy

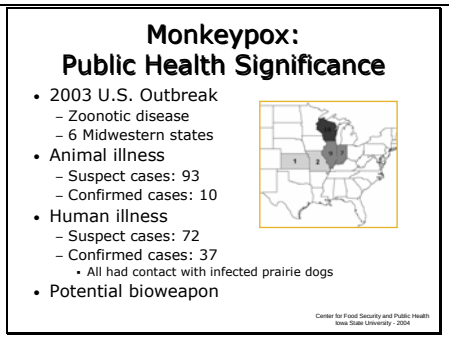


Center for Food Security and Public Health
Iowa State University - 2004

Monkeypox virus is a naturally occurring relative of variola (smallpox) virus and is endemic in central and western Africa. Monkeypox disease is clinically indistinguishable from smallpox, with the exception that monkeypox is less severe and there is often notable enlargement of cervical and inguinal lymph nodes. The virus was first identified and named when it was isolated from laboratory monkeys in 1958. The first isolation of the monkeypox virus from humans in Africa was in 1970. The reservoir for monkeypox virus may be an African squirrel. Many different rodents, rabbits, and primates are susceptible to infection. The virus is transmitted through bites, aerosols, or direct contact with lesions or body fluids from infected animals or humans. Fomite transmission is also possible. Transmission can be from animal to person, animal to animal or person to person. Epidemiological evidence in Africa indicates a rate of person-to-person transmission of 3.3 to 30%. The incubation period is approximately 12 days for humans and 6-7 days for animals. In rodents symptoms include fever, conjunctivitis, cough, lethargy and a blister-like rash. The disease in non-human primates is usually fever followed by a self-limiting rash. In humans, flu-like symptoms occur in the first 10 days, followed by the development of the rash (macular, papular, vesicular or pustular) and enlarged lymph nodes. An infected animal or person is contagious one day before clinical symptoms and

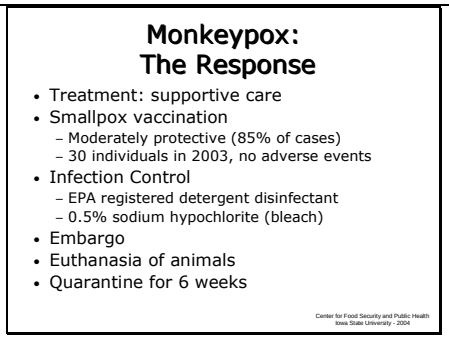
for 21 days after symptoms or until scabs heal. Case-fatality rates reported from a rural African outbreak ranged from 1-10% with higher death rates among children. Images courtesy of CDC and USDA APHIS.

Slide 59



In June 2003, monkeypox was diagnosed for the first time in humans in the United States. Trace back investigations identified that the virus was introduced into the U.S. in a shipment of 800 small mammals which arrived in Texas on April 9 from Ghana, Africa. It appears that infected rodents (dormice, Gambian giant pouched rats, rope squirrels) from this shipment were placed in contact with prairie dogs at an animal distribution facility in Illinois. The prairie dogs were then sold and went to 6 states [Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin]. There have been 93 prairie dogs suspected of being infected with monkeypox virus. The CDC confirmed 4 of those cases. The CDC has also confirmed monkeypox in 1 Gambian rat, 3 dormice, and 2 rope squirrels from the original shipment. In 2003, 72 human suspect cases of monkeypox were reported to CDC. Thirty seven were confirmed and 35 were investigated. The majority of human cases reported some contact with an infected prairie dog. To date there are no confirmed cases of transmission between humans. In addition, there are no reports of human cases due to contact with animals other than prairie dogs or cases of transmission to other animal species in contact prairie dogs or African rodents. Monkeypox has not been reported in dogs or cats, and their susceptibility is unknown. Weaponization of monkeypox has raised concern as to whether or not it would constitute a threat similar to that posed by variola virus (smallpox). “Nevertheless, (a) the pathogenicity of monkeypox for humans, (b) the potential morbidity of an aerosolized monkeypox virus attack, and (c) the theoretical potential that genetic recombination could produce a modified animal poxvirus with enhanced virulence for humans have raised the specter that another poxvirus besides variola might constitute either a serious biowarfare threat or a reemergent public health problem.” From: Textbook of Military Medicine: Medical aspects of chemical and biological warfare, 1997. The map shows the distribution and number of human cases confirmed in the US as of July 11, 2003.

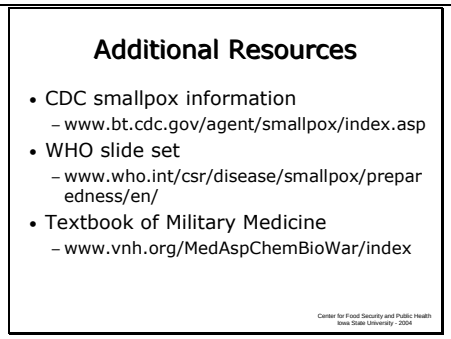
Slide 60



Treatment for monkeypox is primarily supportive care and the illness typically lasts between 2 to 4 weeks. Vaccination with the vaccinia virus (smallpox vaccine) affords approximately 85% protection against monkeypox. It is recommended that individuals exposed to monkeypox be vaccinated with the smallpox vaccine, up to 14 days post-exposure. In the 2003 outbreak in the U.S., 30 people were vaccinated (23 post-exposure) with vaccinia and there were no adverse events. Biosafety precautions should be adhered to when dealing with suspected or confirmed cases, including hand washing and personal protective equipment (i.e., mask, gown, gloves, and eye protection). Recommended guidelines for the decontamination and handling of environment and soiled bedding should be followed. [see Monkeypox Infections In Animals: Updated Interim Guidance for Veterinarians at http://www.cdc.gov/ncidod/monkeypox/animalguidance.htm]. Any EPA-registered hospital detergent-disinfectant or 0.5% sodium hypochlorite (bleach) will be effective against the virus. A joint order issued by the FDA and CDC in July 2003 restricted the importation of any rodents from Africa and banned transportation of prairie dogs and 6 species of African rodents within the US. The only allowable transportation of these animals is to veterinarians or animal control officers or as directed by state, local, or federal authorities. The CDC

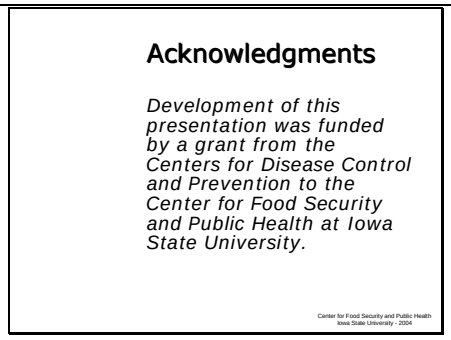
recommended euthanasia of all African rodents from the original April 9, 2003 shipment. Also, any prairie dog in contact with any of the animals from that shipment or any prairie dog housed at an infected premise should be euthanized. Only people who were recently vaccinated for smallpox should perform necropsies on animals infected with monkeypox. Other animal species in contact with infected rodents or prairie dogs should be quarantined for 6 weeks.

Slide 61



For additional information on smallpox, please view the CDC's website at http://www.bt.cdc.gov/agent/smallpox/index.asp. The World Health Organization also has a set of slides (in multiple languages) that photographically describe the disease from its onset through the various stages of pox lesion development at http://www.who.int/csr/disease/smallpox/preparedness/en/. Finally, the Textbook of Military Medicine describes more of the history of smallpox and goes into greater detail if you are interested. It can be accessed at http://www.vnh.org/MedAspChemBioWar/index.html.

Slide 62



Slide 63