Smallpox disease

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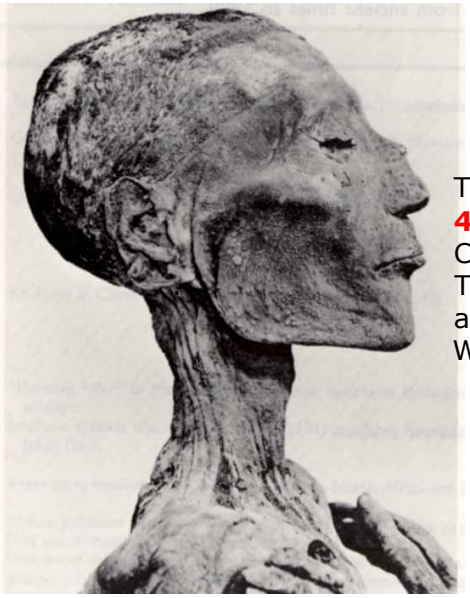
The History of smallpox

The history of the smallpox is still a mystery. It is speculated to have appeared among human population during the first agricultural settlements in northeastern Africa, around 10,000 BC . Perhaps the scars, which appear on Pharaoh Ramses V's delicately preserved mummy dating back to **1157 BC.**

may be the earliest signs of smallpox exposure was in **Egypt** .



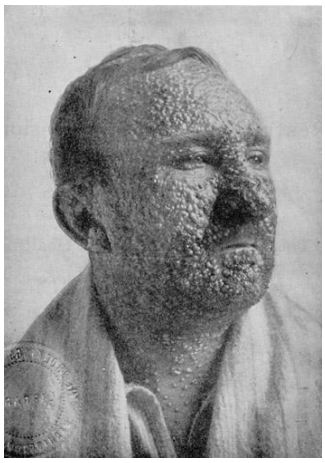
Then an early written description of smallpox from was in **India 400AD**, Severe pain is felt in the large and small joints, with Cough, shaking and and tongue are dry with thirst and no appetite. The pustules are red, yellow, and white and they are accompanied by burning pain.
With all this symptoms was describing the smallpox diseases .

In the Elephant war in **Mecca 568 AD**, smallpox decimated the Ethiopian smallpox decimated the Ethiopians soldiers**.**

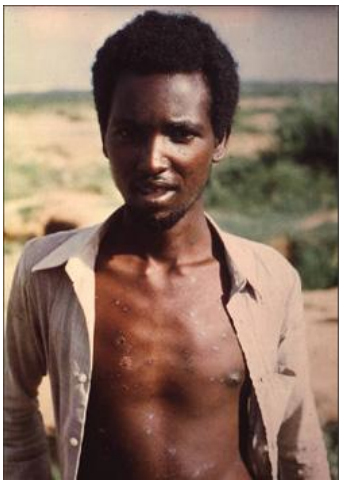
Then smallpox is spreaded all the world , Inoculation of healthy individuals by placing pus or powdered scab material from an infected individual, to the nose of the intended was recorded by the Chinese as early as tenth century . The procedure of inoculation a healthy individual with smallpox was widely used in England by 1740. Around 1765, English physicians noticed that milkmaids were immune to smallpox, as a result of being exposed to the less severe cowpox. As a result, in May of 1796 **Edward Jenner**, a brave scientist, inoculated an eight-year old boy, with the cowpox virus, and was exposed to smallpox. The boy became immune to smallpox, and **Jenner** was credited for creating the first smallpox vaccine .

Edward Jenner

This became the starting point of the attempt to eradicate smallpox on a global scale, which was eventually confirmed and declared by the World Health Organization in 1980. The last confirmed case of smallpox in the **United States** Occurred in **1949**, and the last naturally occurring case in the world was recorded in **Somalia in 1977**



Smallpox sufferer in the United States



Ali Maow Maalin of Somalia is the last known individual in the world to have contracted smallpox

--Biological

Why is Variola major considered an effective bioweapon?

Variola major is considered an effective bioweapon for a number of reasons.

First, it is highly contagious; a single uncontrolled case would likely infect 3-6 more people, exponentially spreading the disease. It also has a low infectious dose and a relatively high fatality rate. In addition, V. major can be stable for hours as an aerosol (over 24 hours in optimal environmental conditions) and can be produced and stored in large quantities. The majority of the global population is unvaccinated against smallpox, making. The Soviet Union produced tons of weaponized Variola major per year during the Cold War, in violation of the 1975 Biological Weapons Convention. With the fall of the Soviet Union in 1991 and the disarray that followed, stocks of smallpox may exist outside of the designated research facility in Russia, and some may have been transferred to other state bioweapons programs.

--Classification of smallpox

How are viruses classified ?

Two classification systems exist:

1-The Hierarchical virus classification system

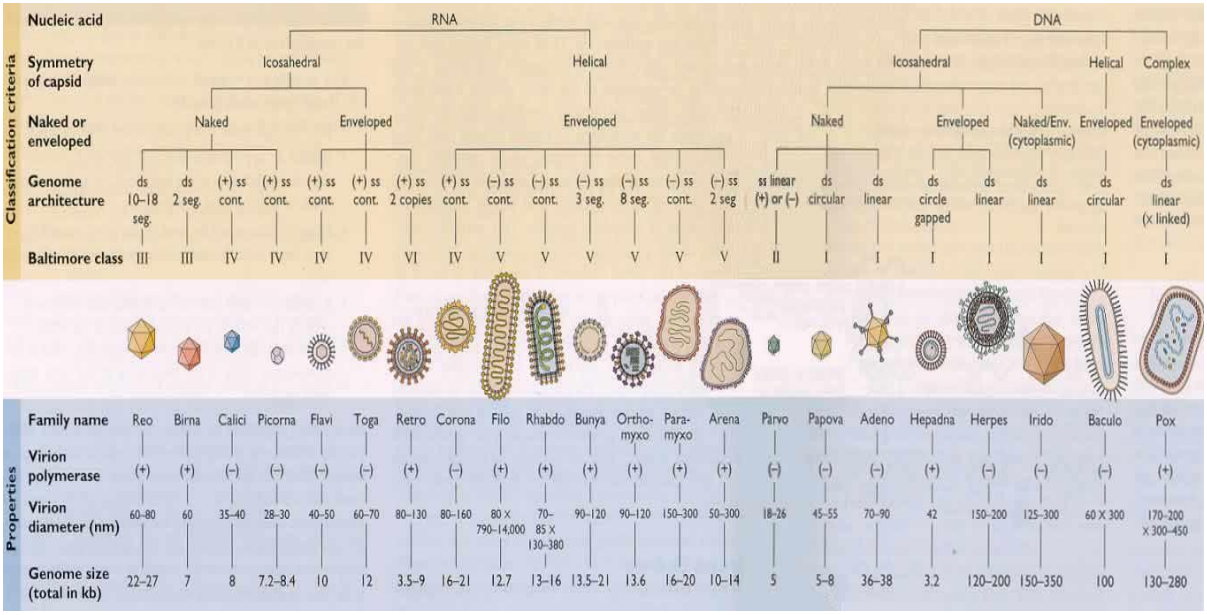
2-the Baltimore Classification System.

The Hierarchical virus classification system

Four main characteristics are used:

1. Nature of the nucleic acid: RNA or DNA
2. Symmetry of the capsid
3. Presence or absence of an envelope
4. Dimensions of the virion and capsid

Hierarchical virus Classification of Smallpox



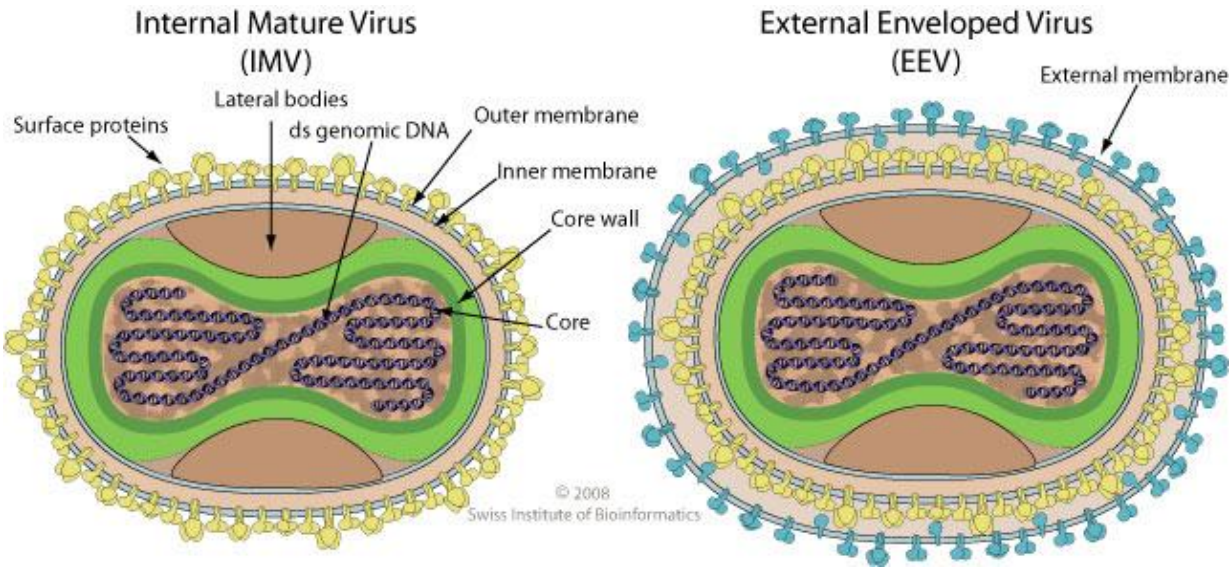
Baltimore Classification of smallpox

Class	Nucleic Acid	Examples	Envelope	Genome size (kb)
I	dsDNA	Herpes virus Poxvirus Adenovirus Papillomavirus	Yes Yes No No	120 - 220 130 - 375 3.0 - 4.2 5.3 - 8.0
II	ssDNA	Adeno-associated virus	No	5.0
III	dsRNA	Reovirus	No	18 - 31‡
IV	(+) ssRNA	Togavirus Poliovirus Foot-and-mouth disease virus Hepatitis A virus Hepatitis C virus	Yes No No No Yes	9.7 - 11.8 7.4 7.5 7.5 10.5
V	(-) ssRNA	Influenza virus	Yes	12 - 15‡
VI	(reverse) RNA	HIV	Yes	9.7
VII	(reverse) DNA	Hepatitis B virus	Yes	3.1

I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)

--The structure of smallpox "GENOME"

Orthopoxvirus



VIRION

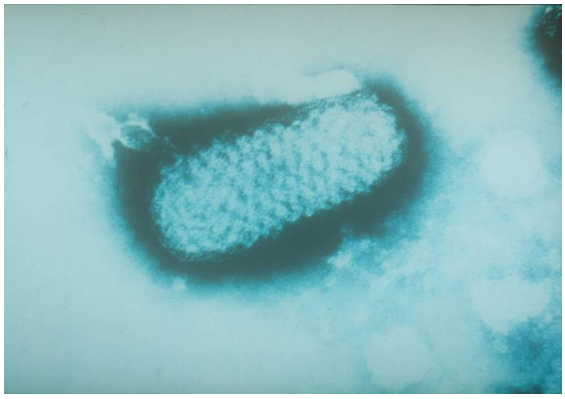
Enveloped, brick-shaped virion, 250nm long and 200nm wide. The surface membrane displays surface tubules or surface filaments. Two distinct infectious virus particles exists: the intracellular mature virus (IMV) and the extracellular enveloped virus (EEV).

Genome :

The Variola virus is a liner and double-stranded DNA virus. It has two envelopes: the outer envelope is present only in the extracellular state. The outer surface or the core membrane, which surrounds the core of the virus, contains lipids and proteins and has a complex symmetry.

The core, which has a dumbbell-shape, contains a large amount of the double-stranded DNA (186kbp), about 10 enzymes to mediate gene

expression and lots of nucleoproteins- both specific and common. These proteins are involved in DNA transcription, as well as inducing cross-reactive immunity (IOM, 1999). The space outside the core contains lateral bodies – which do not have any known functions.



Smallpox virion. Courtesy of US Centers for Disease Control and Prevention

--Clinical features

There are two clinical forms of smallpox. Variola major is the severe and most common form of smallpox, with a more extensive rash and higher fever. There are four types of variola major smallpox:

case fatality rates by case type

Type	Case fatality rate %
Hemorrhagic	**100%**
Flat	**> 90%**
Ordinary-confluent	**50-75%**
Ordinary-semiconfluent	**20-50%**
Ordinary-discrete	**<10%**
Vaccine-modified	**<10%**

ordinary (the most frequent type, accounting for 90% or more of cases); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic (both rare and very severe). Historically, variola major has an overall fatality rate of about 30%; however, flat and hemorrhagic smallpox usually are fatal. Variola minor is a less common presentation of smallpox, and a much less severe disease, with death rates historically of 1% or less.

Table: classification of clinical type of variola major

Type	Characteristics
Ordinary	Raised pustular skin lesions .Three subtypes: *confluent :rash on face and forearms. *semiconfluent :rash on face ,discrete elsewhere. *discrete :areas of normal skin between pusttules ,even on face.
Modified	Like ordinary type but with an

	accelerated course.
Flat type	Pustules remained flat ,usually confluent or semiconfluent usually fatal.
Haemorrhagl	Weldspreadhaemorrhages in skin and mucuosmembranes.Two subtypes: *early:purpuric rash, always fatal *late: with haemorrhages into base of pustules, usually fatal.

--Transmission:

Smallpox transmission can happen in one of several ways :

1) face to face contact : smallpox is a highly contagious disease. In most cases smallpox transmission occurs by inhaling droplets of saliva, which are full of virus during face to face contact.

2) Direct contact: It can also occur through direct contact with the infected bodily fluids, or contaminated objects such as bed or clothes.

3) Through the air: Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, busses, and trains.

Attachment of the virus to the host cell:

Variola virus usually enters through the respiratory tract.The cells comprising of the mucos membrane are not tightly packed therefore allowing it to penetrate and move into the saliva. Then it reaches the cell membrane and begin to enter the host cell to replicate in the cytoplasm of the host cell.

Variola virus replication (life cycle):

Variola virus replicates in the **cytoplasm** through the following steps:

--Replication of smallpox

The step	The exact mechamism
Binding to cell receptors and penetration of host cell.	The exact mechanisms involved in the binding to and penetration of the host cell are not known.
Uncoating of protein coat.	The virus loses its exterior membrane coat. once inside the cell the interior membrane layer is removed and the virus's proteins, enzymes, and DNA are released into the cytoplasm of the host cell where viral replication and assembly rakes place.
Genome replication (occurs in the cytoplasm)	The first step in replicating the virus DNA involves a particular set of virus enzymes . called Type 1 topiosomerase enzymes. Which uncoil the compressed strands of variola DNA and aid in replicated early genes. The second step of genome replication involves replication the late genes. During the replication of variola DNA, large concatamers are formed and subsequently cleaved to form individual virus genomes. Finally, the variola virus appears to be able to replicate itself without using any of the host cell's replication machinery.
Assembly and release of new virions	Individual viruses are assembled with the help of type 1 topiosomerase enzymes. New viruses are released from the host cell.

	Release occurs about 12 hours after initial infections. The production of variula virus by the host cell usually results in host cell death.

--Symptoms

Most significantly, the rash of smallpox is preceded by a prodrome consisting of 1 to 4 days of high fever, malaise, headache, muscle pain, prostration; sometimes nausea, vomiting, abdominal pain, and backache. In 90% of cases, smallpox *(variola major) presents* as an acute infectious disease*,* characterized by a maculopapular rash *,* which becomes vesicular on day 3 or 4 then slowly evolves into pustular lesions deeply embedded into the dermis, by day Fourteen days after the initial appearance of the rash, most of the lesions have developed scabs. The rash in smallpox usually appears as a single crop with all lesions progressing from the macular to the pustular stage at about the same time

Differential diagnosis:

Although there are other causes of generalized rash illness which present as vesicles and pustules, the severe prodrome along with the nature of the rash and its evolution distinguishes smallpox from other diseases. The diseases, which can look , similar to smallpox, include: varicella disseminated herpes simplex , enterovirus, molluscum contagiosum, secondary syphilis, drug rash. meningococcal sepsis, and monkeypox

Diagnosis

The clinical case definition for smallpox is: an illness with an acute onset of fever of 101°F or higher followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development on any body part, without other

apparent cause. Laboratory diagnosis is aided by a negative result on one of the rapid diagnostic tests for varicella (i.e., DFA, electron microscopy , and PCR). Laboratory diagnosis of smallpox can be made by PCR, culture of vesicular or pustular fluid, or culture of the scab; it should only be performed by the LAC Public Health Laboratory, California , Viral & Rickettsial Diseases Laboratory and Centers for Disease Control and Prevention (CDC). (After appropriate consultation to ensure safe packaging and handling, specimens can be sent to the local public health laboratory for forwarding to the state laboratory and then to CDC.)

Incubation:

Usually 12-14 days (range 7-17 days).

Source:

Macules, papules, vesicles pustules, and scabs of the skin and lesions in mouth and pharynx

Serologic Testing: Acute and convalescent serologic testing is available through the CDC. 10 cc of blood should be drawn into a plastic or glass marble-topped serum separator tube. Contact the LAC Public Health Laboratory prior to collection of serologic specimens from patients with suspected smallpox

Electron Microscopy:

Because of the distinct appearance of poxviruses, electron microscopy can be helpful in the rapid diagnosis of smallpox. This test is available through the CDC. Contact the Public Health Laboratory for information regarding this test .

Specimen Collection

Vesicular Material

1. Sanitize the patient's skin with an alcohol wipe and allow skin to dry.
2. Open the top of a vesicle or pustule with a scalpel, sterile 26-gauge needle, or slide. Collect the skin of the vesicle top in a dry, sterile 1.5- to 2-mL screw-capped tube. Label the tube.

3. Scrape the base of the vesicle or pustule with the wooden end of an applicator stick or swab and smear the scrapings onto a glass or plastic light microscope slide. Allow slide to dry for 10 minutes.

4. Label the slide and place it in a slide holder. To prevent cross-contamination, do not place slides from more than one patient in the same slide holder.

5. Take another slide, and touch it repetitively to the opened lesion using progressive movements of the slide in order to make a touch prep. Allow slide to dry for 10 minutes.

6. Label the slides as touch preps and place in the same slide holder. To prevent cross-contamination, do not place slides from more than one patient in the same slide holder.

7. If plastic-coated electron microscopic (EM) grids are available, lightly touch the shiny side of 3 EM grids to the base of the open lesion, allow EM grids to air-dry for 10 minutes, and place grids in an appropriately labeled grid box. Use varying degree of pressure (minimal, light, and moderately firm) in application of the 3 grids to the unroofed lesion. EM grids and collection materials will soon be available at Laboratory Response Network (LRN) sites.

8. If a slide or EM grid is not available, swab the base of the lesion with a polyester or cotton swab, place in screw-capped plastic vial, break off applicator handle, and seal.

9. Repeat this procedure for 2 or more lesions.

Scab Specimens

1. Sanitize the patient's skin with an alcohol wipe and allow skin to dry.

2. Use a 26-gauge needle to remove 2 to 4 scabs.

3. Place 1 or 2 scabs in each of 2 dry, sterile screw-capped plastic tubes.

4. Wrap parafilm around the juncture of the cap and vial.

5. Label the tube.

Biopsy Lesions
(At least 2 specimens obtained by using a 3.5- or 4-mm punch biopsy kit.)

1. Use sterile technique and appropriate anesthetic.
2. Place 1 sample in formalin for immunohistochemical or histopathologic evaluation and store at room temperature.
3. The second specimen should be placed dry (do not add transport medium) in a sterile 1.5- to 2-mL screw-capped container (do not add transport medium).
4. Refrigerate if shipment occurs within 24 hours; otherwise, the specimen should be frozen.

Serum Specimens

1. Draw 10 mL of blood for serum separation and collection.
2. Send serum, stored refrigerated.

--Epidemiological:

Despite a dramatic decline in smallpox during the nineteenth century, the disease still posed a threat at the beginning of the twentieth century. Expanding trade networks as well as the rise of immigration and leisure travel meant that smallpox could spread more easily and more rapidly than ever before

--Vaccination

Vaccination administered within 3-4 days postexposure can prevent disease or severe illness caused by variola virus. Presently, smallpox (vaccinia) vaccine is available in the U.S. Vaccinia human immunoglobulin (VIG), which is licensed to treat certain postvaccinia-vaccination adverse effects.

Length of Protection

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. In addition, the vaccine was proven to prevent or substantially lessen infection when given within a few days of exposure. It is important to note, however, that at the time when the smallpox vaccine was used to eradicate the disease, testing was not as advanced or precise as it is today.

Receiving the Vaccine

The smallpox vaccine is not given with a hypodermic needle. It is not a shot as most people have experienced. The vaccine is given using a bifurcated (two-pronged) needle that is dipped into the vaccine solution. When removed, the needle retains a droplet of the vaccine. The needle is used to prick the skin a number of times in a few seconds. The pricking is not deep, but it will cause a sore spot and one or two droplets of blood to form. The vaccine usually is given in the upper arm.

Post-Vaccination Care

After vaccination, it is important to follow care instructions for the site of the vaccine. Because the virus is live, it can spread to other parts of the body, or to other people. The vaccinia virus (the live virus in the smallpox vaccine) may cause rash, fever, and head and body aches. In certain groups of people.

Benefit of Vaccine Following Exposure

Vaccination within 3 days of exposure will prevent or significantly lessen the severity of smallpox symptoms in the vast majority of people. Vaccination 4 to 7 days after exposure likely offers some protection from disease or may modify the severity of disease.

Smallpox Vaccine Safety

The smallpox vaccine is the best protection you can get if you are exposed to the smallpox virus. Anyone directly exposed to smallpox, regardless of health status, would be offered the smallpox vaccine because the risks associated with smallpox disease are far greater than those posed by the vaccine.

Smallpox Vaccine Availability

Routine smallpox vaccination among the American public stopped in 1972 after the disease was eradicated in the United States. Until recently, the U.S. government provided the vaccine only to a few hundred scientists and medical professionals working with smallpox and similar viruses in a research setting.

Who should NOT get the smallpox vaccine?

People most likely to have side effects are people who have, or even once had, skin conditions, (especially eczema or atopic dermatitis) and people with weakened immune systems, such as those who have received a transplant, are HIV positive, or are receiving treatment for cancer. Anyone who falls within these categories, or lives with someone who falls into one of these categories, should NOT get the smallpox vaccine unless they are exposed to the disease.

--Treatment

The smallpox vaccine is the only known way to prevent smallpox in an exposed person. If given within 4 days of viral exposure, the vaccine can prevent or significantly lessen the severity of smallpox symptoms. Vaccination 4-7 days after exposure may offer some protection from the disease and may lessen its severity.

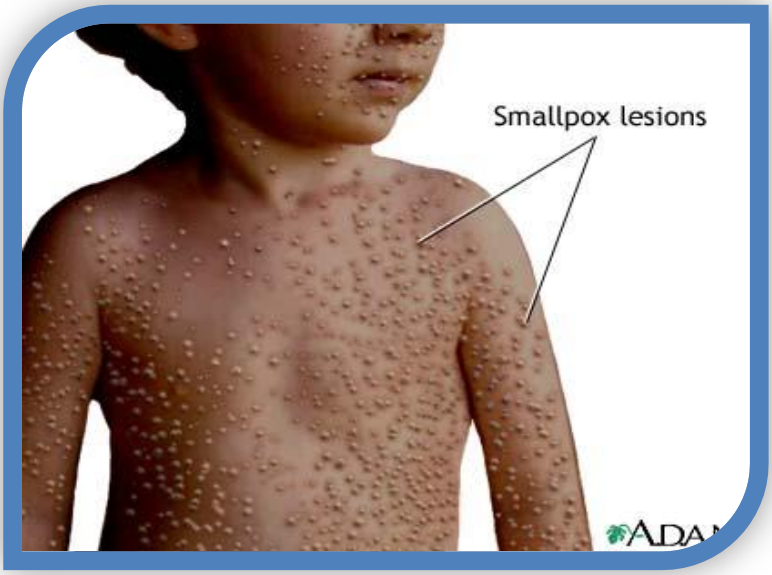
Vaccinia immunoglobulin (VIG) does not appear to offer a survival benefit when given to patients during the incubation or active-disease stages of smallpox. However, new drugs are under investigation. For example, cidofovir may be beneficial if given in the early stages of illness, although the effectiveness of this treatment has not been proven in humans.

*** cidofovir**

Belongs to a class of drugs known as antivirals. It works by stopping the growth of the virus.

Nausea may occur. Headache, nausea, and vomiting may occur with probenecid use.

Smallpox Prevention and Control:



How can I keep from Getting Smallpox?

To lower your risk of getting sick if terrorists release smallpox virus on purpose:

- Stay informed. Listen to the news to learn how the emergency is affecting your community and what actions recommend people to take.
- If you were exposed to a suspicious substance or if you were in an area thought to containsmallpox virus, it may help to wash your skin and hair thoroughly with soap and water. It may also help to change and wash your clothing, or if you cannot wash your clothes immediately, to put them in a plastic bag to keep them separate from your other things.
- Stay away from, and keep your children away from, anyone who might have smallpox.
- Avoid being in enclosed areas with others who may be sick, such as buses and trains.
- Do not touch the skin area where someone had a smallpox vaccine placed.
- Wash your hands regularly and avoid touching your eyes, nose, and mouth.

- **If you were vaccinated as a child :**

- It's not known how long immunity lasts after a smallpox vaccine. Studies to answer that question have had conflicting results. The duration of protection can be affected by the type of vaccine used and how it was administered.
- It's likely that vaccination is most effective for about three to five years, with immunity decreasing after that. Partial immunity may last much longer.

Engineering Controls :

To control the spread of the virus, people who have smallpox would be kept in isolation at a hospital. All the people they've had contact with would receive the smallpox vaccine, which can prevent or lessen the severity of the disease if given within three days of exposure to the smallpox virus.

The vaccine uses a live virus that's related to smallpox, and it can occasionally cause serious complications, such as infections affecting the heart or brain. That's why a general vaccination program for everyone isn't recommended at this time. The potential risks of the vaccine outweigh the benefits, in the absence of an actual smallpox outbreak.

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