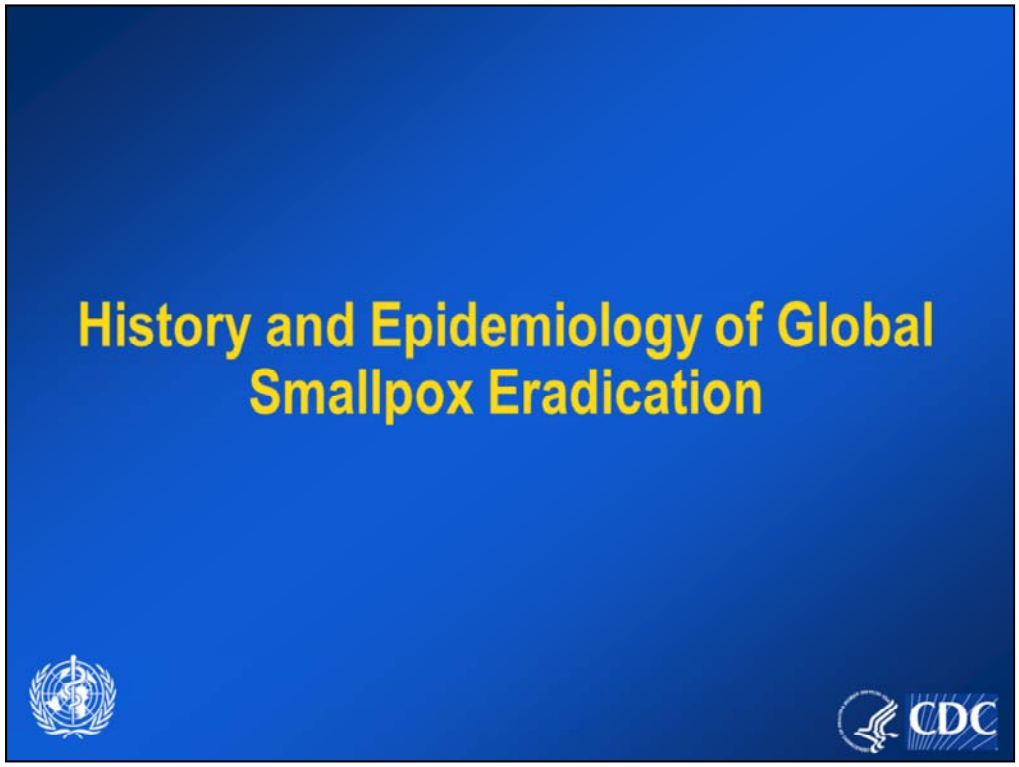
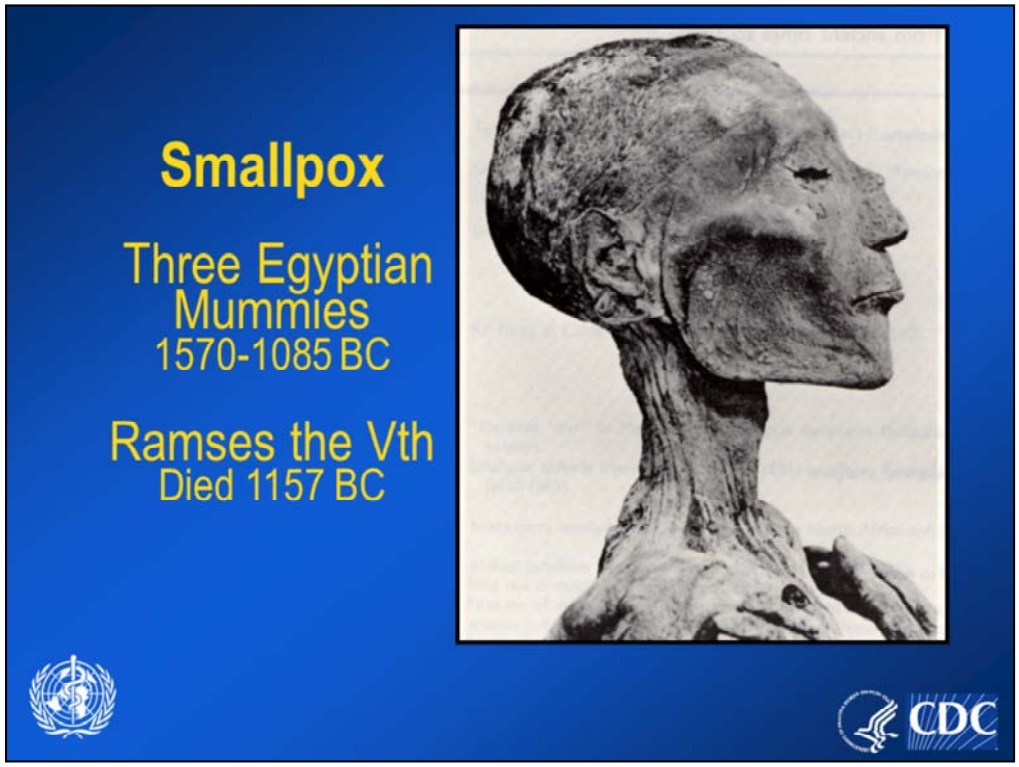
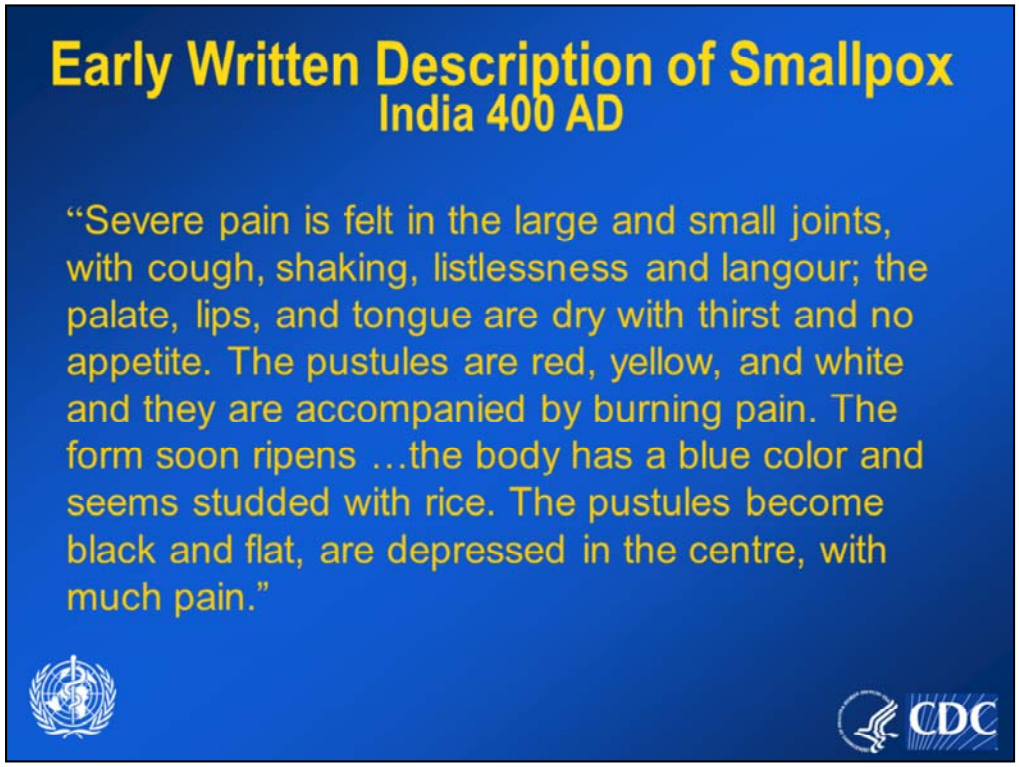


•Discuss history and epidemiology of smallpox eradication



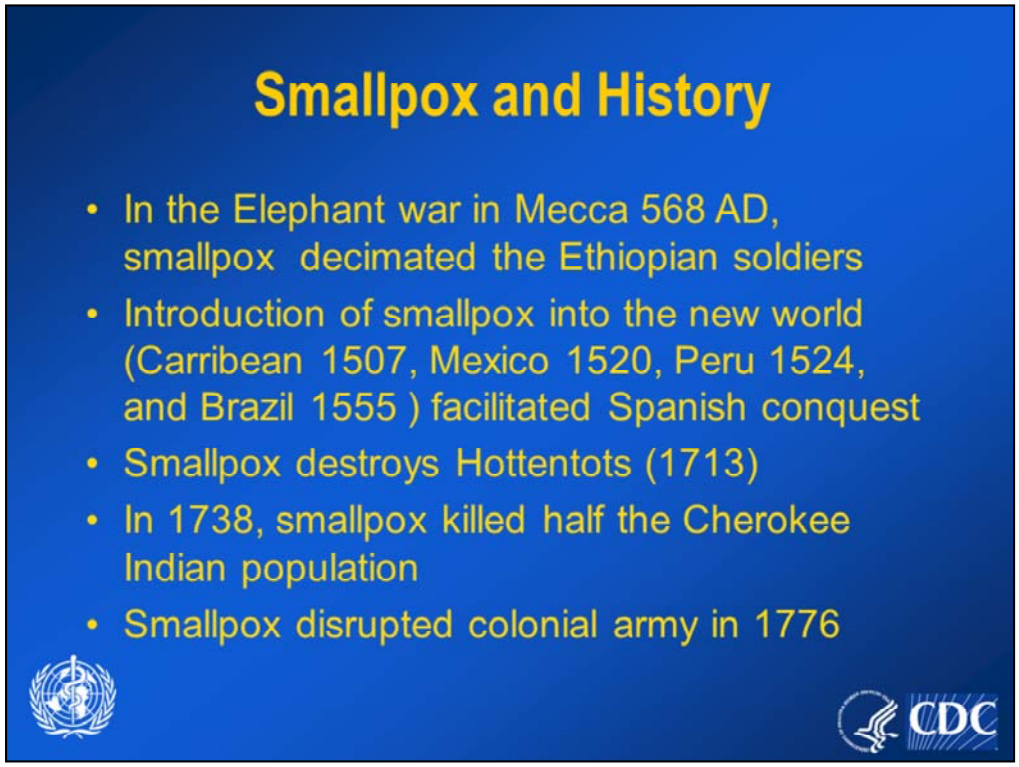
•Smallpox is thought to have emerged in human populations about 10 thousand years BC.

•The earliest evidence of smallpox is believed to be the vesicular skin lesions seen on the mummy of Ramses V, who died in Egypt in 1157 BC.



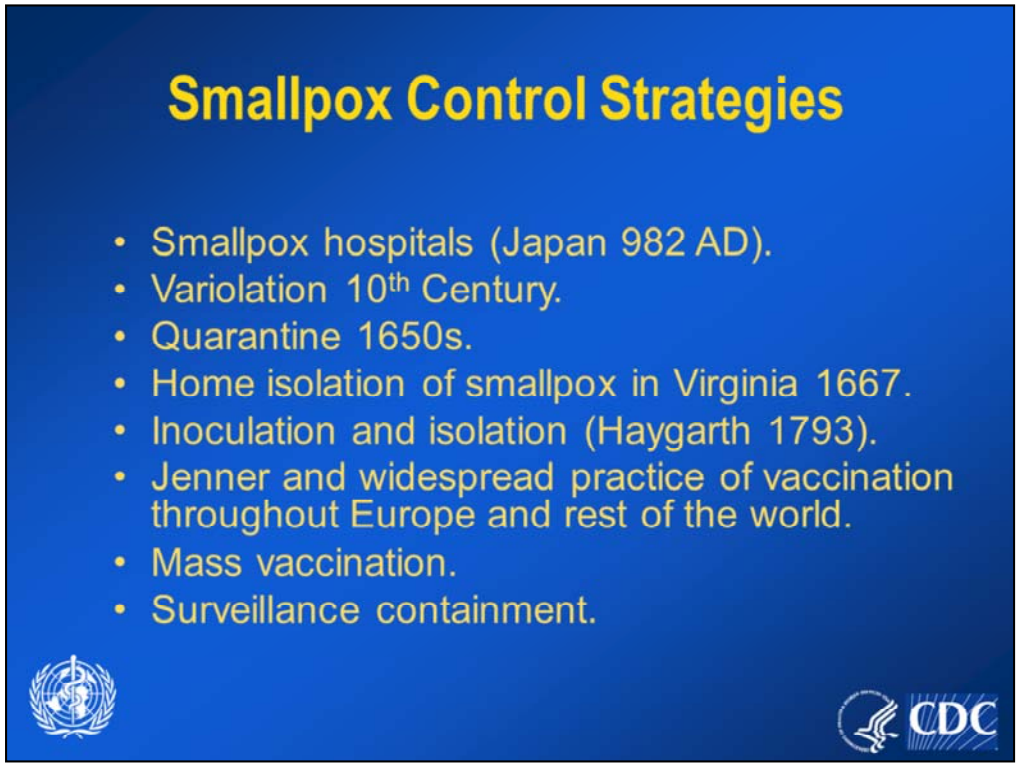
•Written descriptions occurred as early as 400 AD

•This is an early written description of smallpox from India, 400AD



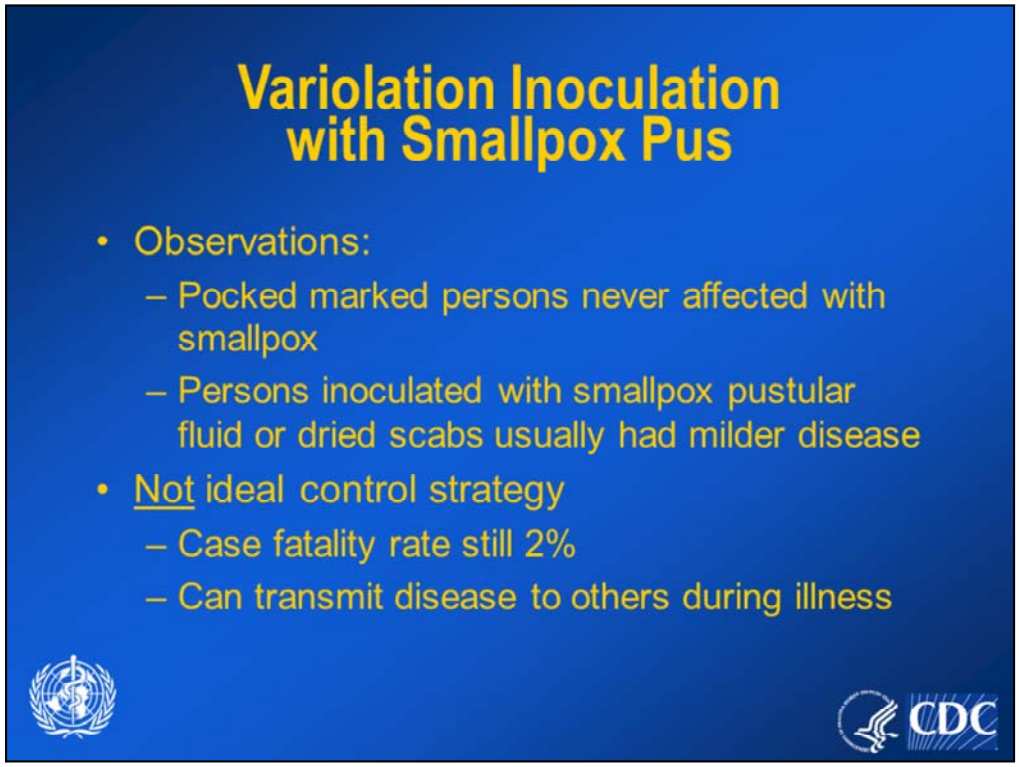
•Throughout the centuries, smallpox was directly responsible for many history changing events

•These are just a few examples



•Multiple methods have been used to try and control the spread of smallpox including:

- •Use of designated hospitals for care of smallpox cases
- •Quarantine and home isolation measures
- •Variolation with smallpox virus to try and induce milder disease leading to lifelong immunity
- •Larger scale vaccination initially utilizing the cowpox vaccine created by Jenner then vaccinia vaccine produced through other, more stable methods
- •And ultimately the addition of thorough surveillance for cases coupled with isolation and targeted vaccination to bring about the ultimate eradication of the disease



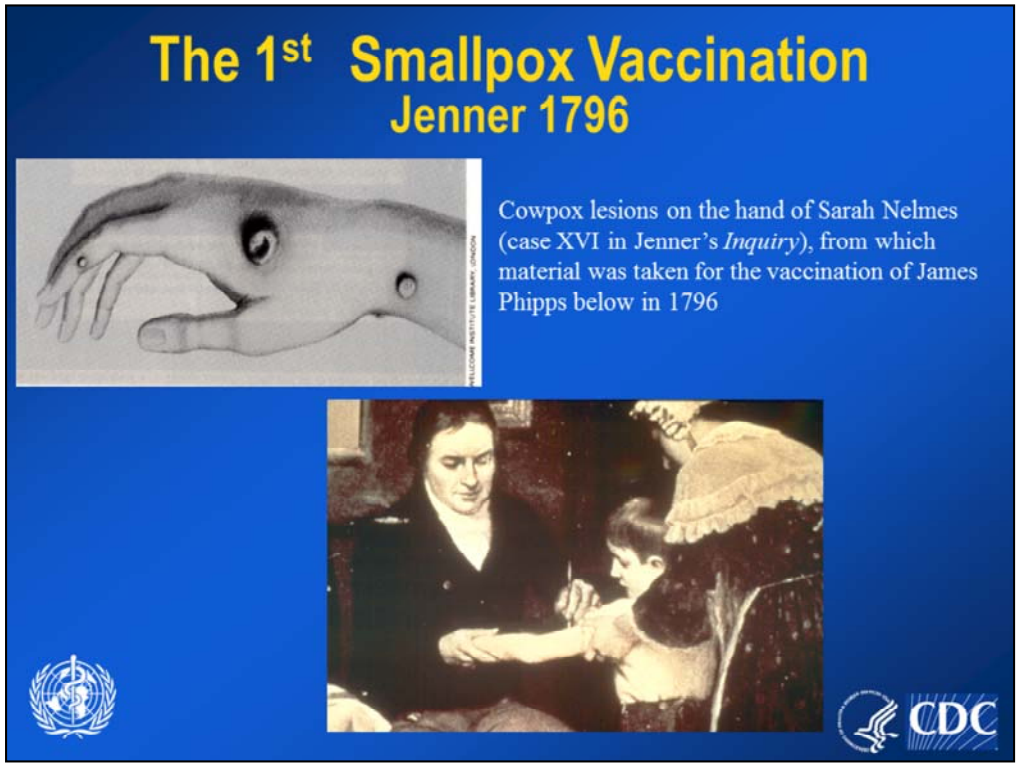
•One if the first attempts to induce immunity to smallpox was through variolation or the intentional inoculation of infected material from a smallpox scab into an individual's skin to produce a less severe infection than naturally acquired smallpox

•Several observations led to the use of variolation to try and prevent smallpox and control the spread of this disease

- •First, persons skin pock marks, evidence of previous smallpox disease, did not come down with the disease again
- •And second, person inoculated through the skin with smallpox material usually had a milder form of the illness compared to those who were infected naturally

•Was not an ideal control strategy as this still had a case fatality rate of 2% and people infected by this method could transmit the disease to others.

•A better method to induce immunity to this disease was needed.

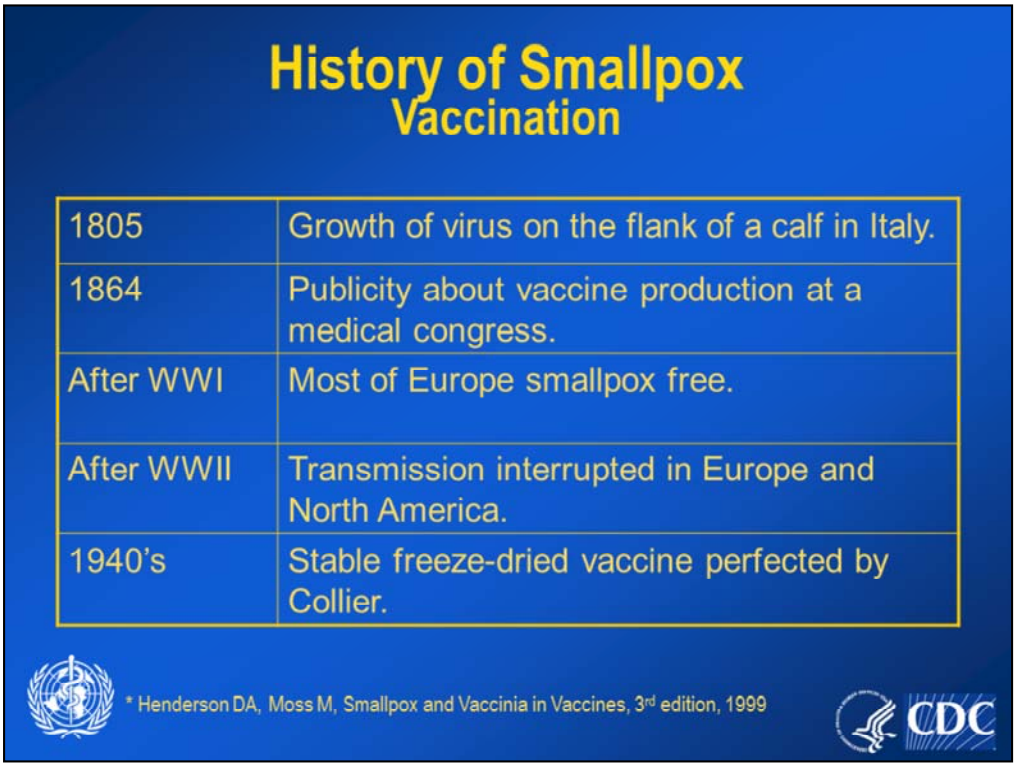


•Edward Jenner demonstrated that immunity to smallpox could be produced by inoculating a human with material from a lesion on the udder of a cow. Jenner called this infectious material vaccine, and the procedure came to be called vaccination.

•The material Jenner used for his vaccine probably contained cowpox virus, a virus related to variola but not as virulent.

•Taking pus from the lesions on the hands of a diary maid, Sarah Nelmes, Jenner inoculated James Phipps. Phipps was later challenged with smallpox and had no response.

•Jenner predicted the eradication of smallpox with his discovery.



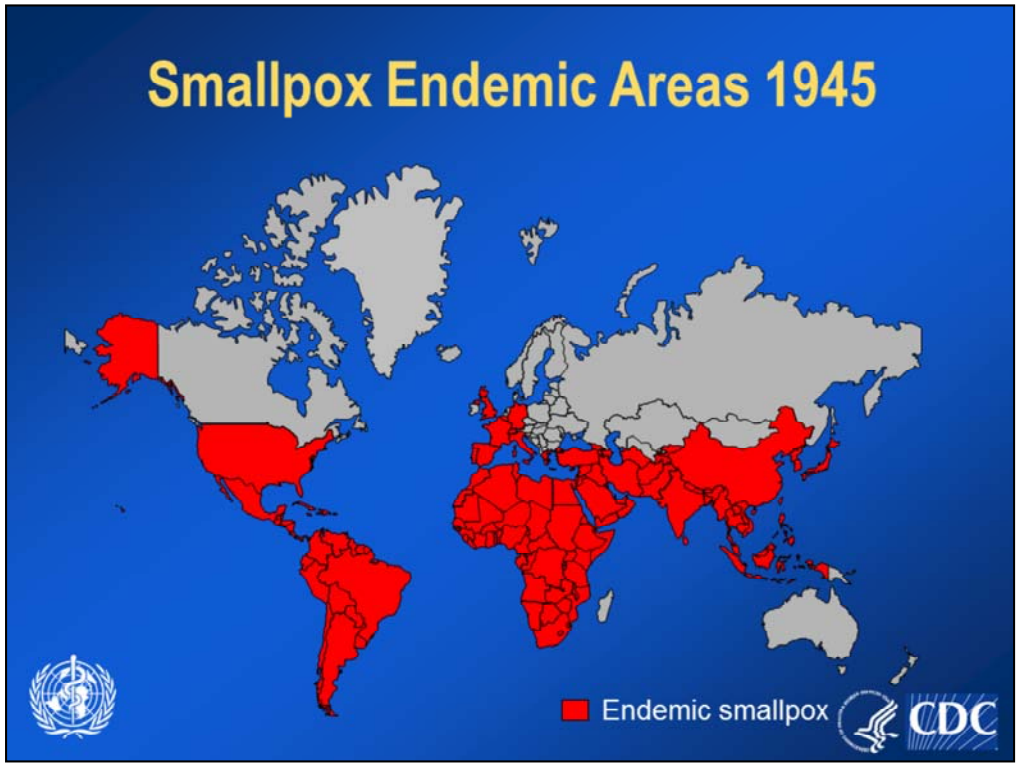
•Significant events in the history of smallpox vaccination include the growth of the vaccine virus on the flank of a calf in Italy, which led to the main method for vaccine production

•At some time during the nineteenth century, the virus used for vaccination changed from cowpox to vaccinia. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia, and how it came to replace cowpox virus in the vaccine is not known.

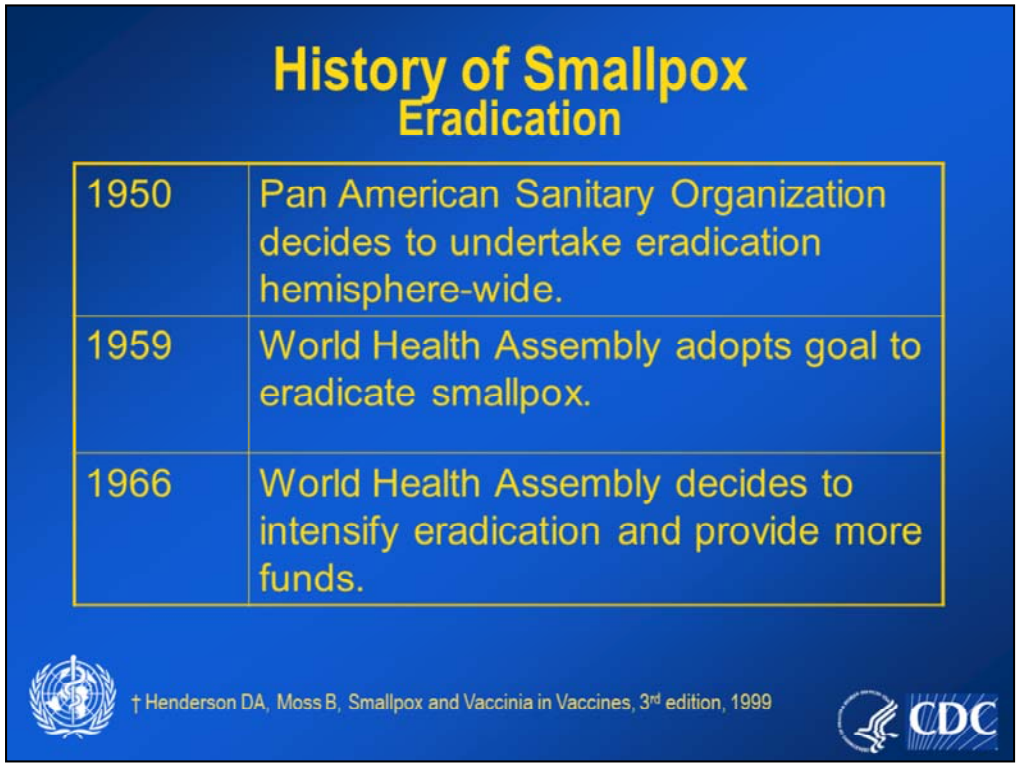
•With the use of vaccine produced from the flank of cows, most of Europe became smallpox free after WWI

•After WWII endemic transmission was completely interrupted in Europe and North America

•With the development of a freeze-dried vaccine that was more stable in higher temperature and humidity climates, vaccine was available for wider use throughout the world.



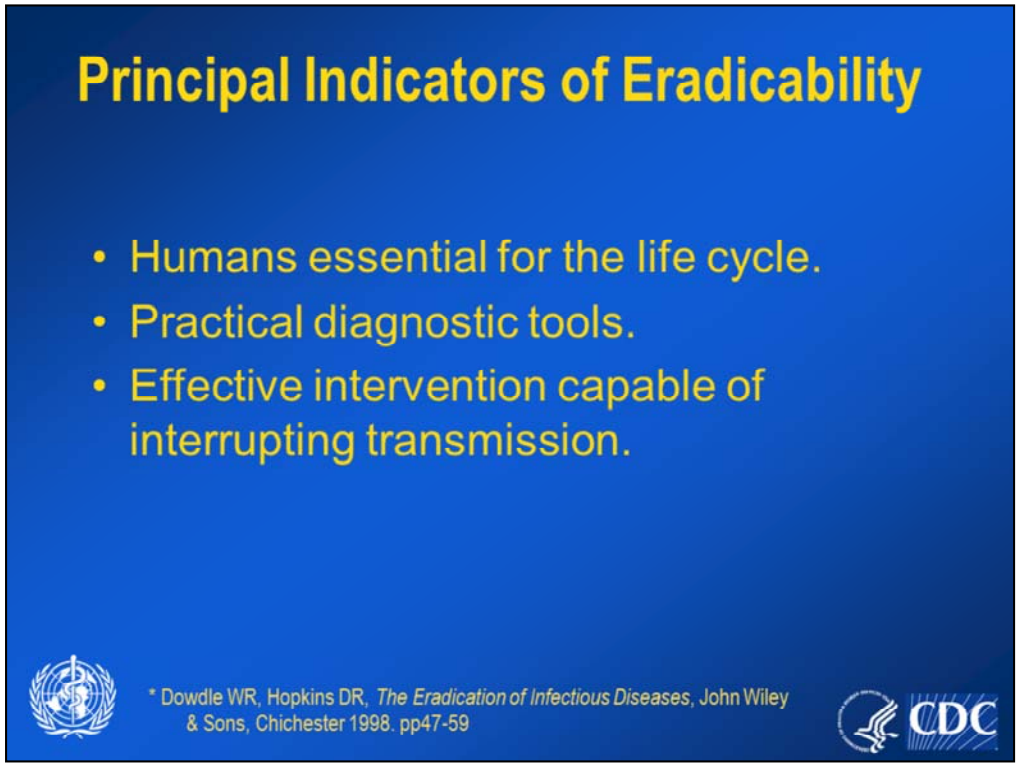
•In 1945, most of the countries in the world still had endemic smallpox cases.



•In 1950, the Pan American Sanitary Organization, the predecessor to the Pan American Health Organization, undertook a hemisphere-wide smallpox eradication program.

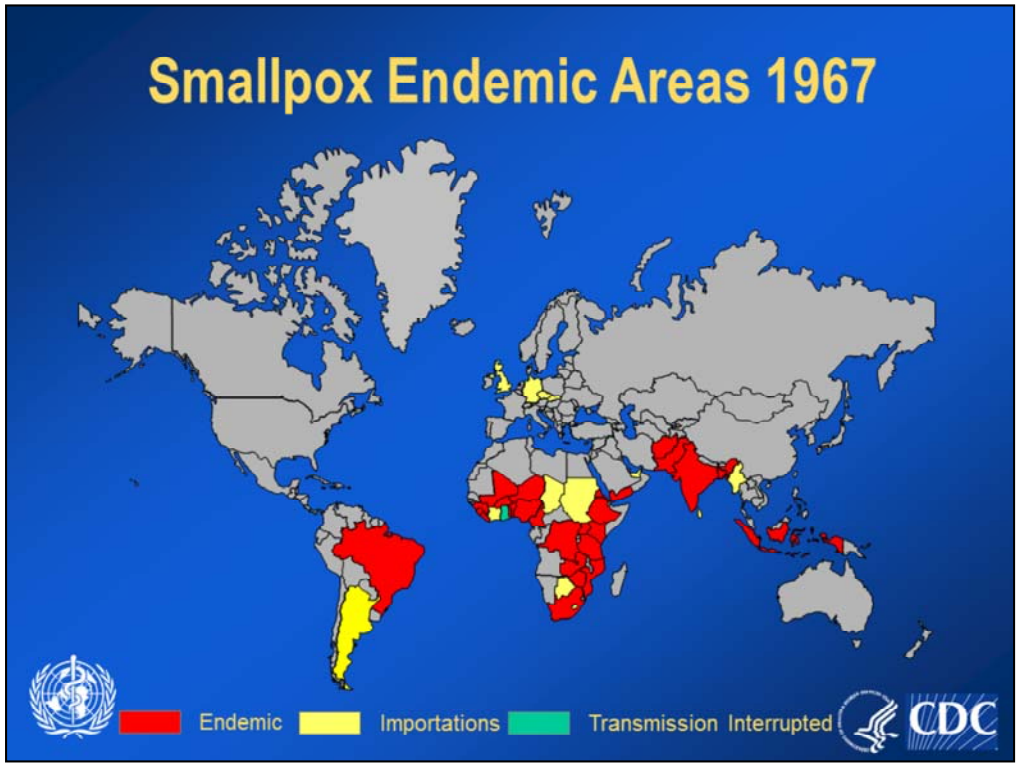
•The first proposal for global eradication was made to the World Health Assembly by the USSR in 1958. They proposed a worldwide vaccination program to be completed in a 3 to 5 year period. Some progress was made during the next 7 years, but the results overall were disappointing.

•Finally, in 1966, the World Health Assembly decided to intensify the eradication program by providing a special budget of $2.4 million per year specifically for this effort.



•The reasons that smallpox could be targeted for eradication when many other infectious diseases could not include:

- •Humans are the only known reservoir for the disease, therefore, if transmission from human to human could be stopped, the disease could be eliminated as there is no animal reservoir that would contribute to continued circulation.
- •Practical diagnostic tools were available to assist in the diagnosis and confirmation of smallpox cases
- •A vaccine was available that could effectively protect individuals from disease for several years (or longer if repeated), therefore, interrupting transmission was possible



•The Intensified Global Eradication program began in 1967

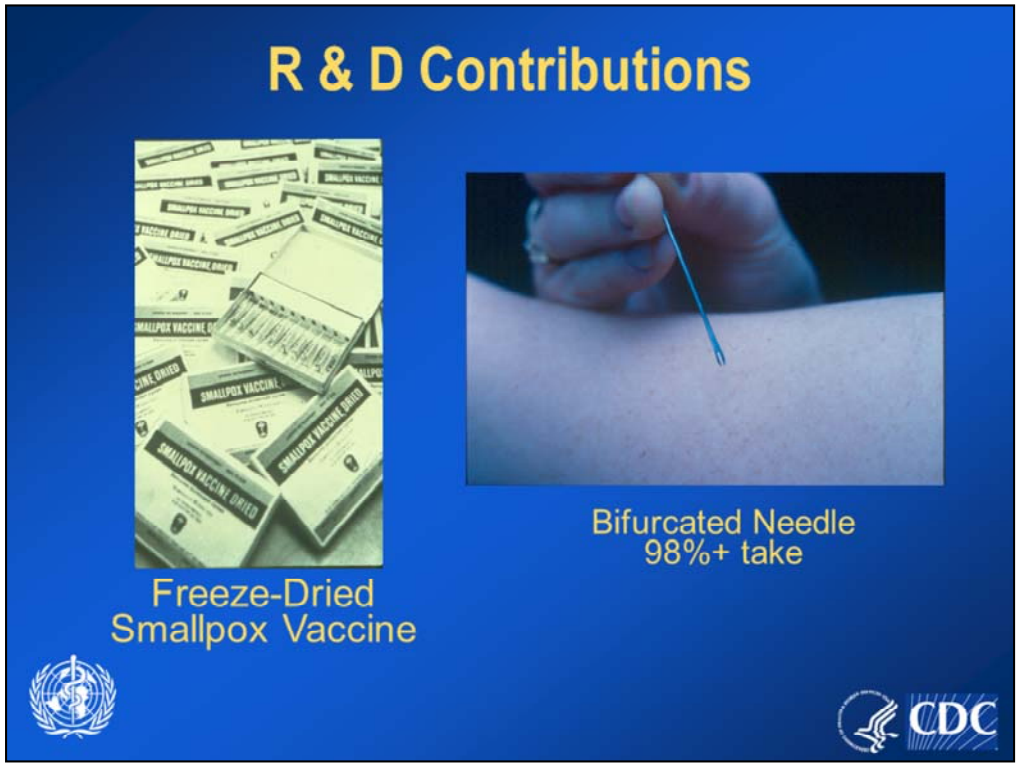
•An estimated 10 - 15 million smallpox cases still occurred in 31 countries where the disease was endemic. More than 1 billion people lived in these areas.

•A major reservoir was Africa, where most countries south of the Sahara were infected.

•A second major reservoir was in Asia, extending from Bangladesh through India, Nepal, Pakistan, and Afghanistan.

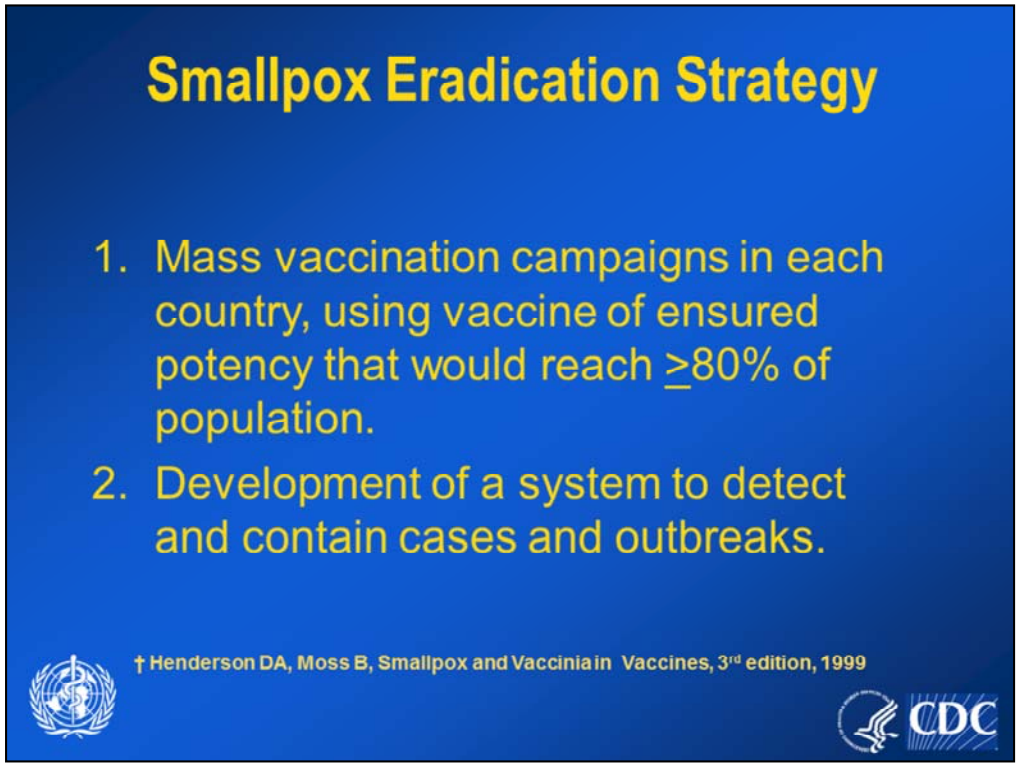
•The third was the Indonesian archipelago,

•The fourth was Brazil, which compromised half of South America.



- Two technical advances laid the foundation for smallpox eradication:
  - The development of a freeze dried vaccine which retained its potency at tropical temperatures, allowing use of the vaccine in more areas of the world.
  - The development of the bifurcated needled for vaccination.
- The bifurcated needle had a number of advantages over previous methods of vaccine administration:
  1. The method could be easily taught to almost any individual in 5-10 minutes.
  2. Vaccination using this technique resulted in nearly 100% successful vaccine takes

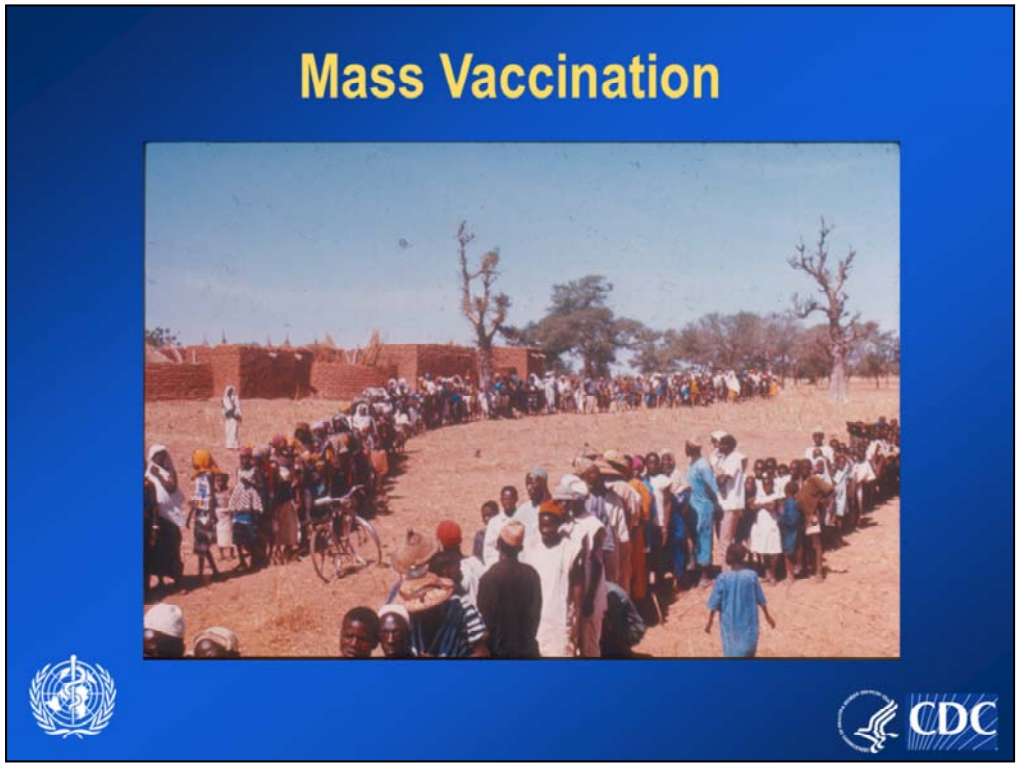
3. The dose held between the prongs was about 1/100 the the vaccine that was required by the previous methods of vaccination, therefore, more vaccine was available



•The initial eradication campaign was based on a two-fold strategy.

- First, mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population.
- Second, the development of surveillance systems to find cases and outbreaks so that more focused containment measures could be implemented.

•Of the two strategies, the second – case detection and containment – proved to be the more crucial. However, both strategies were necessary overall to bring about the eradication of smallpox.



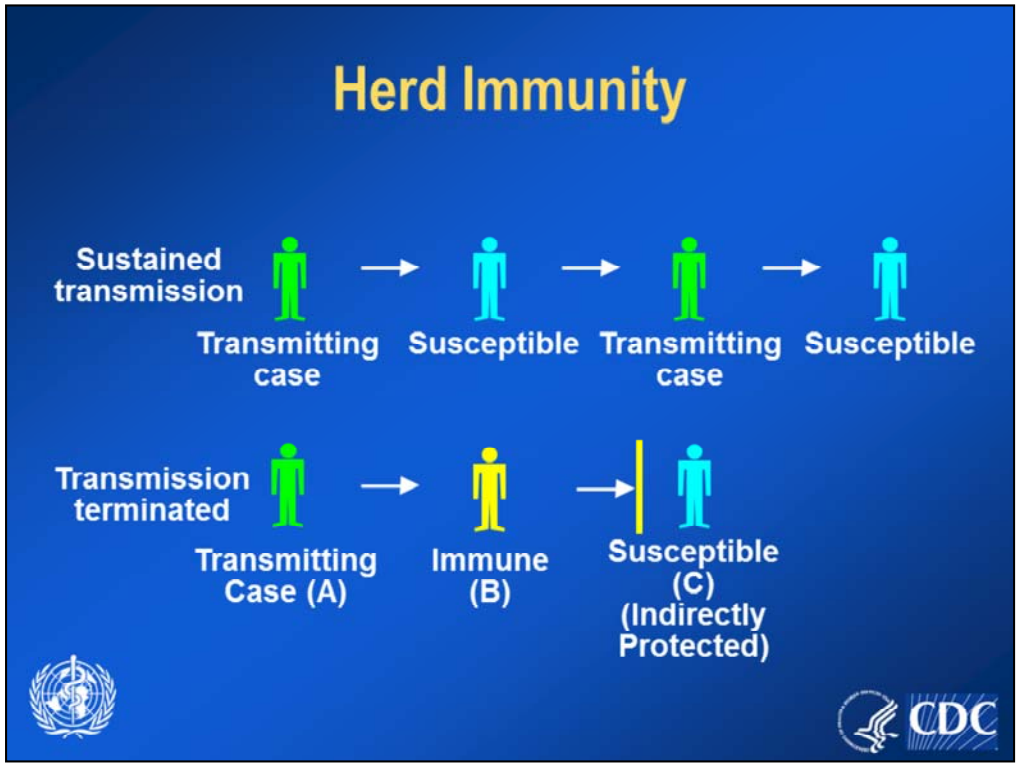
•In 1966, the Smallpox Eradication Measles Control Program was initiated in 18 West African Countries to move toward eradication in this endemic area. At that time, Sierra Leone, had the highest infection rates in the world.

•Using vaccination guns, government resources, and, most importantly, traditional health authorities, large numbers of people were vaccinated. The program administered over 100 million vaccinations in a 5 year period. Surveys showed that 90% of the population had been vaccinated. Smallpox rates fell as a result of these efforts.

•The program had to overcome numerous problems, including lack of organization in national health services; epidemic smallpox among refugees fleeing areas stricken by civil war and famine; shortages of funds and vaccine; and a host of other problems posed by difficult terrain,

climate, and cultural beliefs.

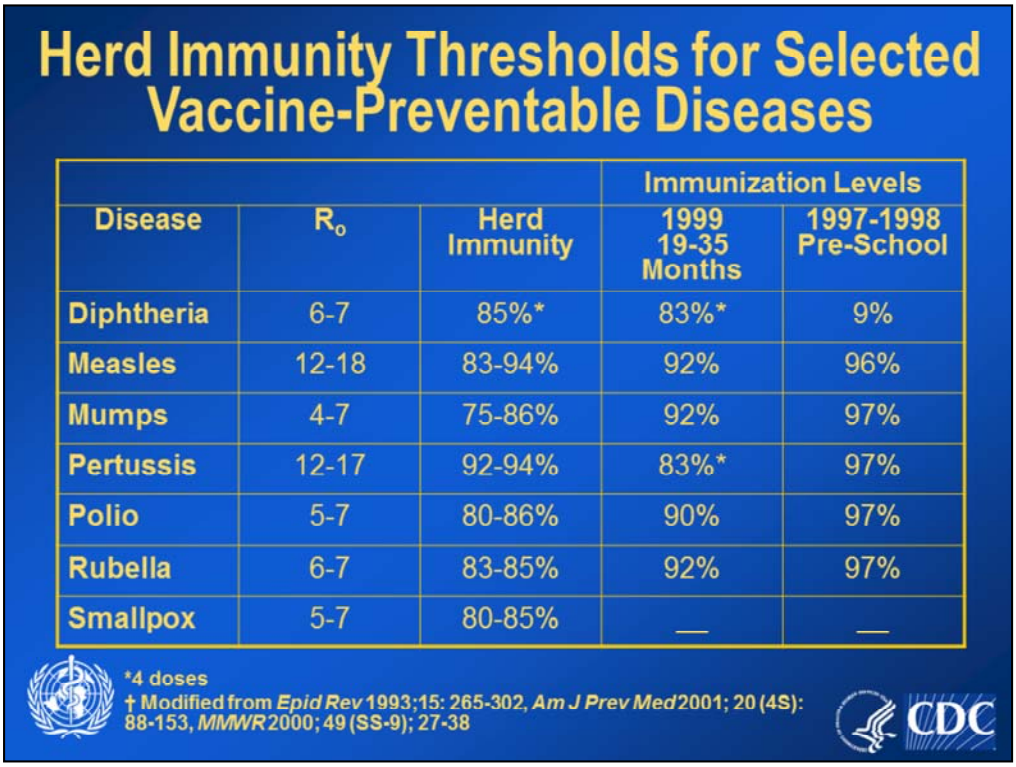
•Ultimately, this program taught us many things about smallpox and disease eradication



•The mass vaccination campaigns allowed health authorities to achieve “herd immunity”.

•The theory behind the development of “herd immunity” is: in diseases that can be passed from person to person, it is more difficult to pass that disease easily when there are those who are immune to it. The more immune individuals there are, the less likely it is that a susceptible person will come into contact with someone who has the disease

•For example, if “Person A” had smallpox and exposed “Person B” who was immune because of vaccination, “Person B” would not get ill and could not pass on the disease to “Person C.” when he comes into contact with him. So even if “Person C” is not vaccinated, he gets indirectly protection from the disease.



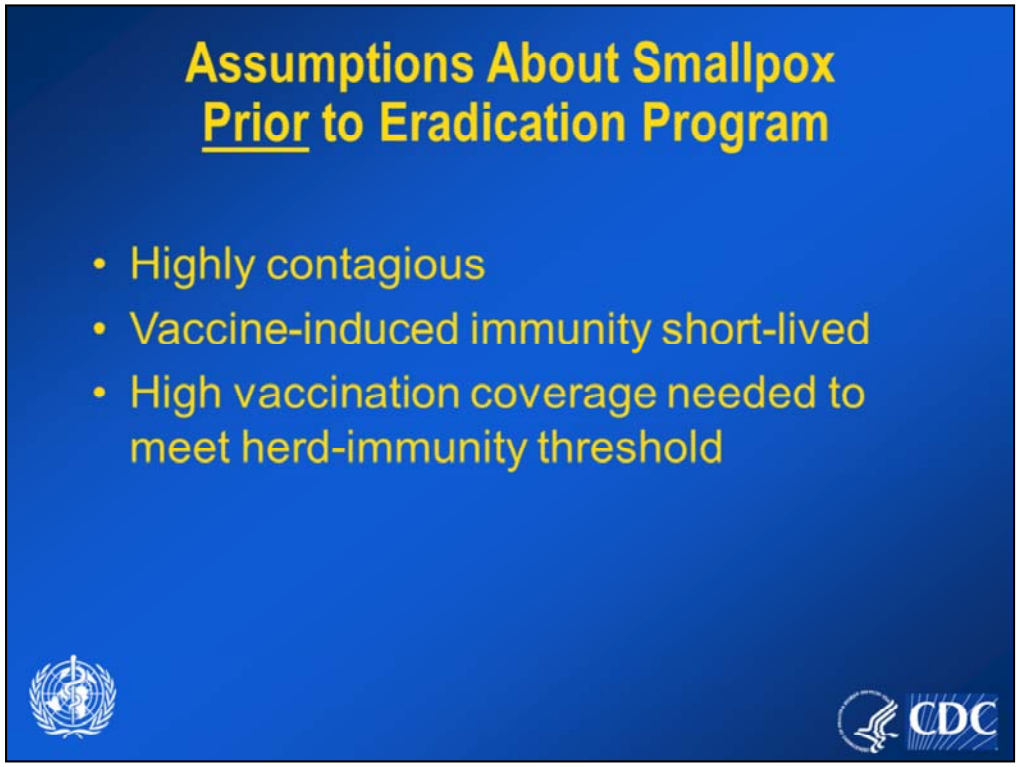
•This slide shows the estimated herd-immunity thresholds needed to stop transmission for several communicable diseases.

•The R_o , or the number of usual secondary transmissions from a single case of the disease, for several vaccine preventable diseases

•Notice that smallpox is actually less “transmissible” than measles and pertussis

•What this slide doesn’t show is the fact that even if desired herd immunity levels can be reached, outbreaks of the disease can and still do occur, though not to the extent they occurred before larger-scale immunity was achieved

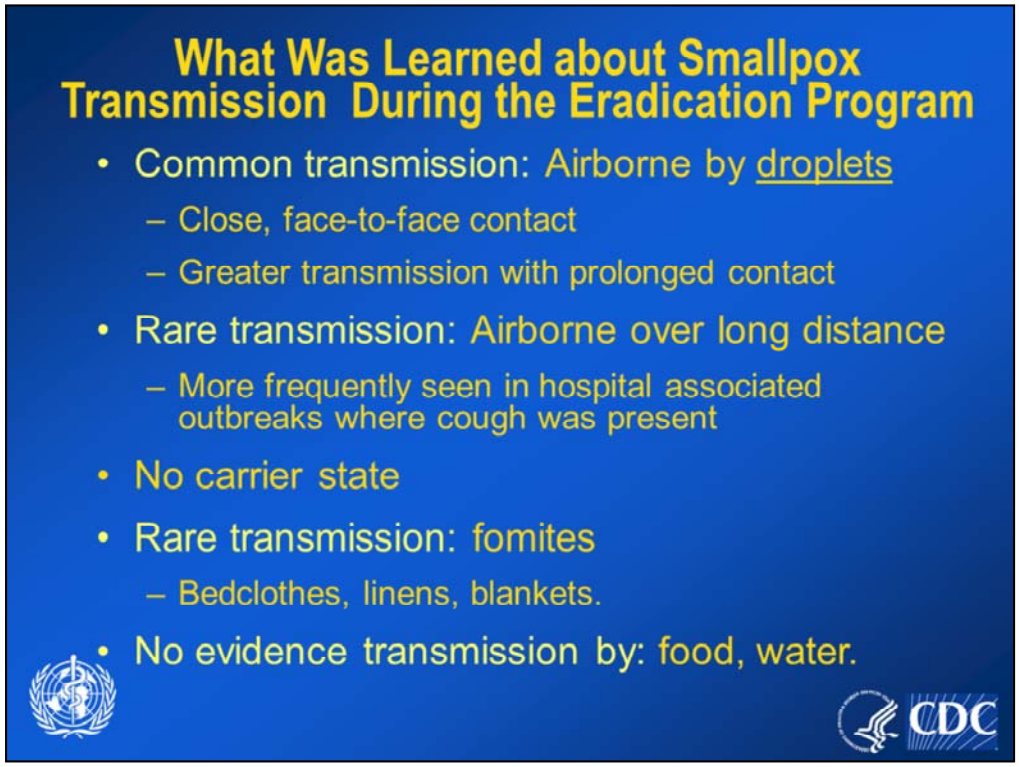
•Because outbreaks of disease can still occur even when a high level of herd immunity is achieved, other measures were ultimately also needed to accomplish the eradication of smallpox



•Prior to starting the eradication program, it was thought that smallpox was highly contagious

•It was also thought that any immunity provided by the vaccine would be short-lived

•Because of these assumptions, it was thought that a fairly high herd immunity level was needed in order to eliminate the disease

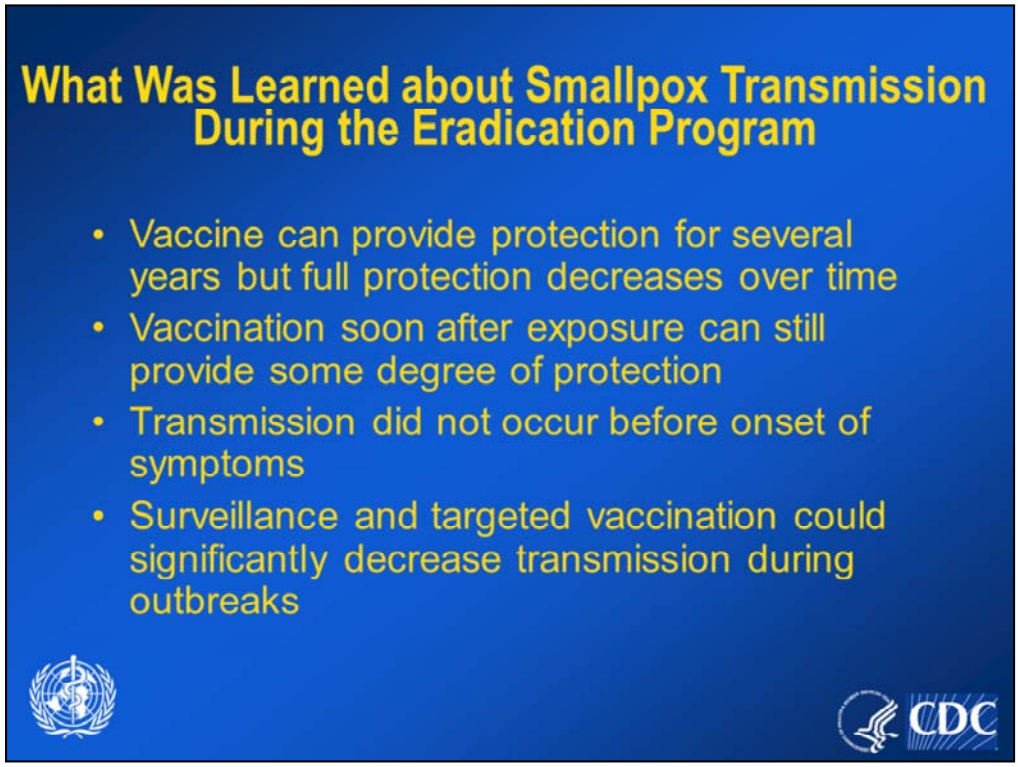


•We learned from studies done during the eradication program that smallpox wasn't quite as contagious as previously assumed.

•Other things that were confirmed included the fact that humans were the only natural host for variola virus, and there was no chronic carrier state.

•Studies on transmission of smallpox showed that the majority of transmission occured by the respiratory route through inhalation of respiratory droplets containing variola virus, expressed over short distances by an infected person.

- •The overwhelming majority of secondary transmissions could be traced to close, prolonged contact with a smallpox case
- •Rarely, transmission occurred from contact with infected fomites or from travel of infected airborne droplets over greater distances.
- •No cases of smallpox were linked to food or water transmission

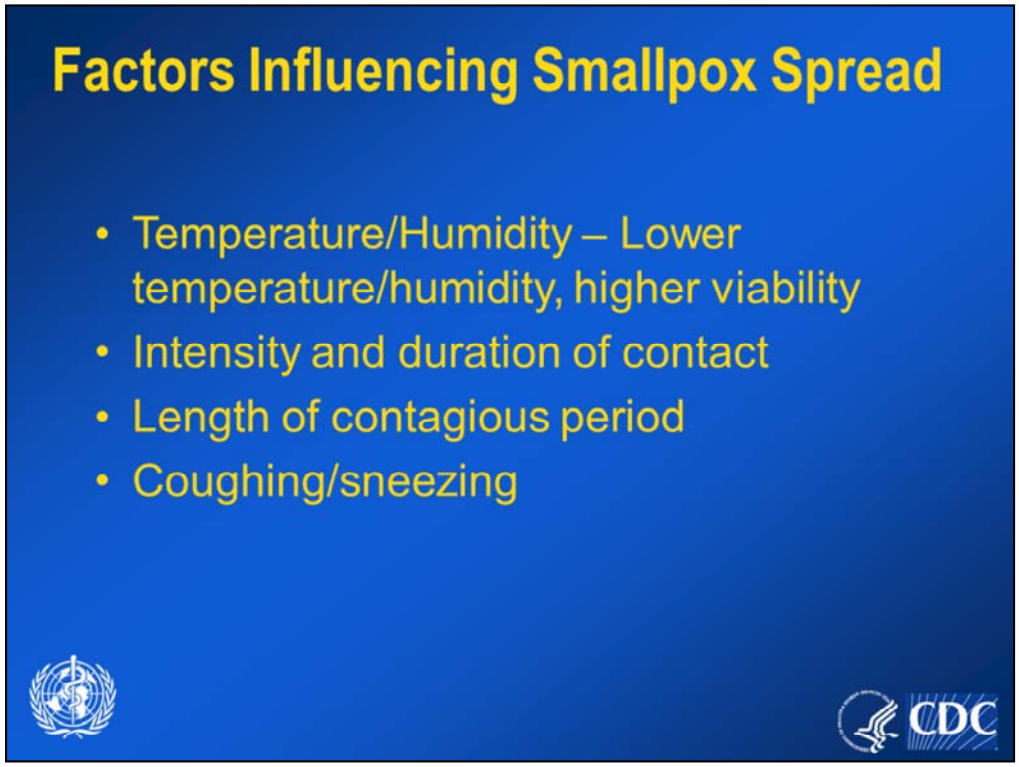


•Studies showed that vaccine can provide full protection against smallpox but that the degree of protection decreases over time

•Because more was learned about the incubation period of smallpox and the immune response to vaccine, we learned that vaccination even a few days after exposure may still prevent disease or can at least decrease the severity of the illness

•Transmission of smallpox did not occur during the incubation period, before the onset of symptoms, like it can for other transmissible diseases

•Good surveillance for cases with targeted vaccination of those around the cases significantly decreased the transmission of disease, even in areas with low herd immunity rates from vaccination



•Discovered that several factors can influence how well smallpox spreads.

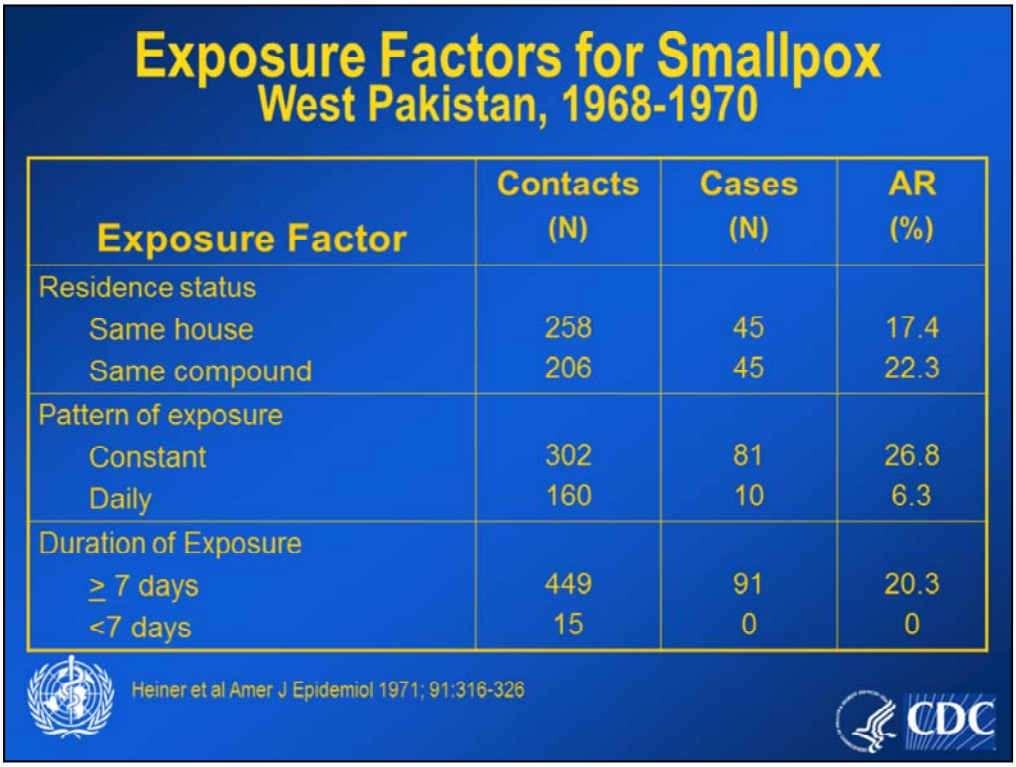
•Experiments show that the viability of variola and vaccinia viruses was less prolonged at higher temperatures and higher humidity.

> •Outbreaks of smallpox seemed to follow a seasonal pattern that supported this finding, higher transmission of the disease occurred during the cooler months of the year

•The intensity and duration of contact and the severity of the illness in the case also contributed to higher rates of secondary transmission

•Also learned that although a person is contagious until the rash of smallpox was completely resolved, which could be several weeks, they were much more contagious in the early part of their illness than they were during the later part

•In outbreaks where airborne transmission over greater distances occurred, the initial case exhibited a greater degree of coughing or sneezing which contributed to the creation and distribution of airborne particles

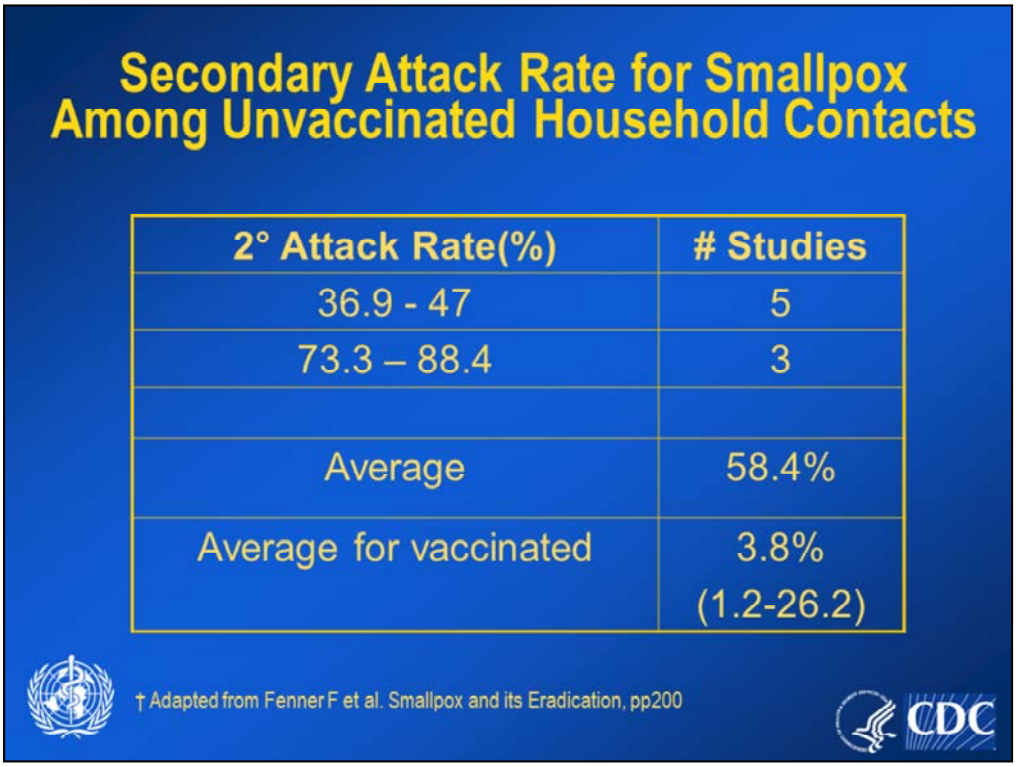


•Comparisons of how smallpox spread demonstrated that closeness and duration of contact were very important in the transmission pattern of the disease

•Highest attack rates occurred in close family contacts of overt cases of smallpox that had constant exposure (e.g. mothers of young children with smallpox) as opposed to those whose exposure was only daily.

• Residents of the same house or people who lived in the same compound also had higher attack rates. Those who lived in the same compound would often have visited the house of the patient, increasing their risk of contracting the disease.

•Those who had contact over a 7 or greater day period had a much higher attack rate than those who had some degree of contact over less than 7 days

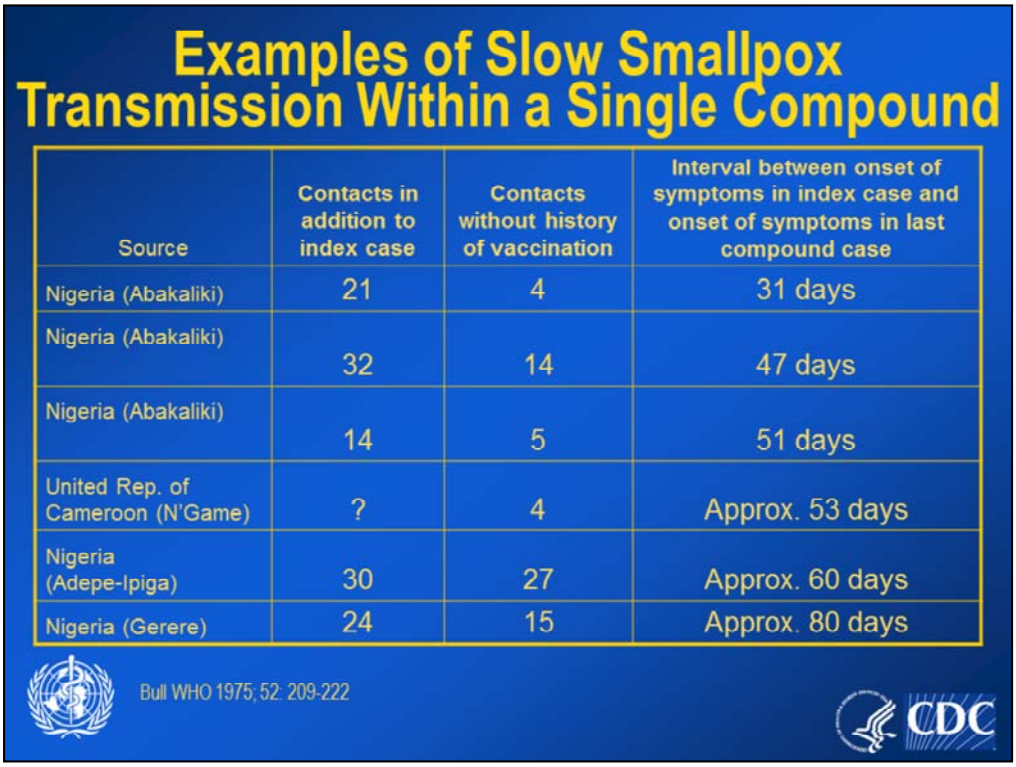


•Studies during the eradication period also demonstrated that smallpox may not be as easily transmitted as originally believed as the overall attack rate was less than 60% in unvaccinated household members

•Attack rates in previously unvaccinated household members were less than 50% in 5 of 8 studies

•3 studies had unvaccinated household transmission rates of greater than 70% which may have been related to more favorable environmental conditions (low temperature, low humidity) that existed during the time periods for these studies

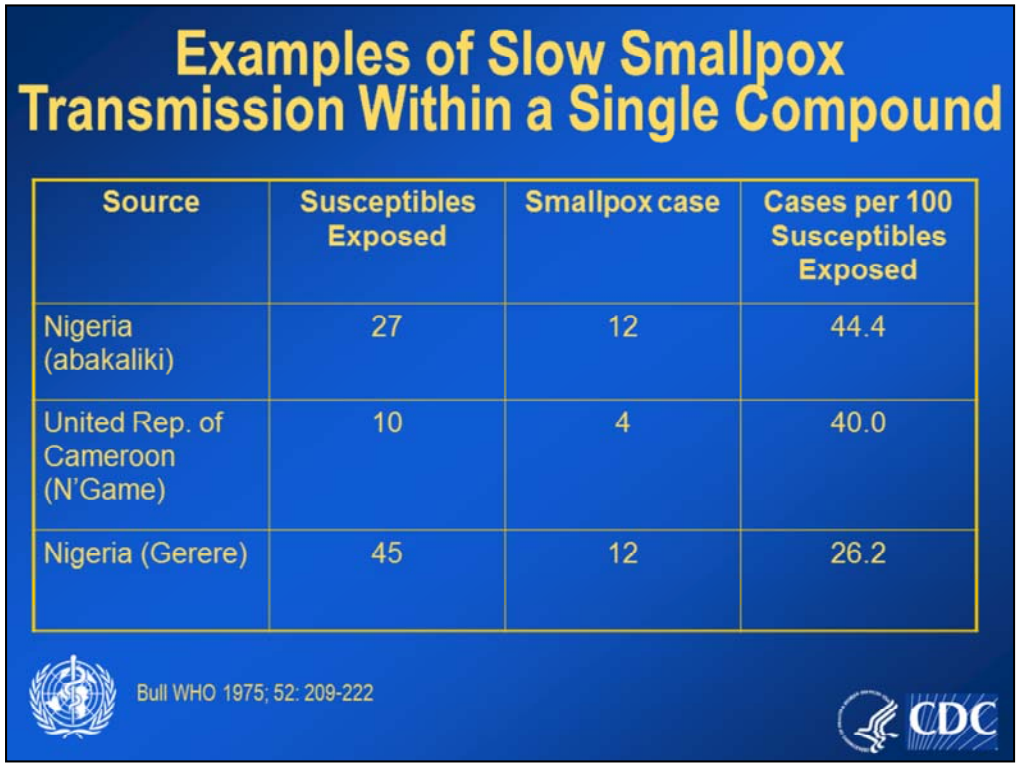
•The average attack rate for previously vaccinated household contacts was 3.8%, demonstrating the efficacy of vaccination



•Other outbreaks of smallpox in close, defined populations demonstrated that the disease didn't spread as rapidly through the population as might be expected if smallpox were as easily transmitted as previously believed.

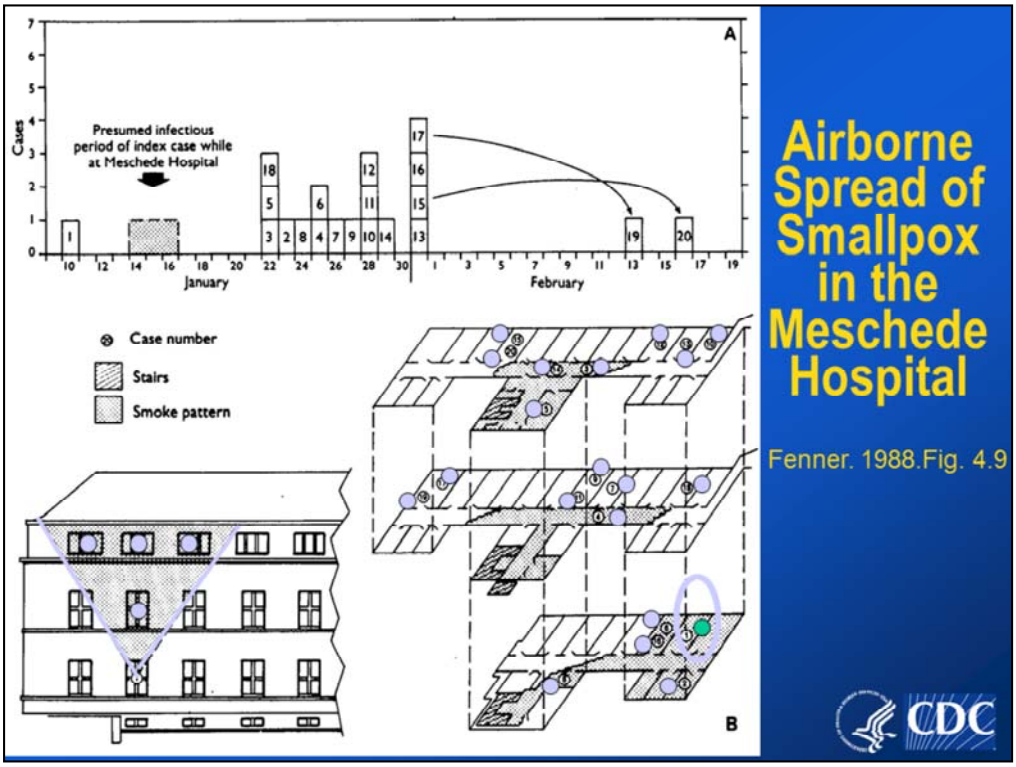
•These studies show the long interval between the onset of symptoms in the initial case and the onset of symptoms in the last case of the outbreak.

•Also notice the relatively low number of secondary cases over the long interval which often spanned several incubation periods and generations of cases. If smallpox were easily transmitted, one would expect there to be more cases appearing during these longer periods from the beginning to the end of the outbreaks



•Even when smallpox cases had close contact, as in these outbreaks occurring in close-knit compounds, transmission was not always that easy to achieve in susceptible individuals

•Transmission rates in the outbreaks reported here were less than 50% in contacts thought to be susceptible to disease (no previous history of smallpox or not protected by previous vaccination)



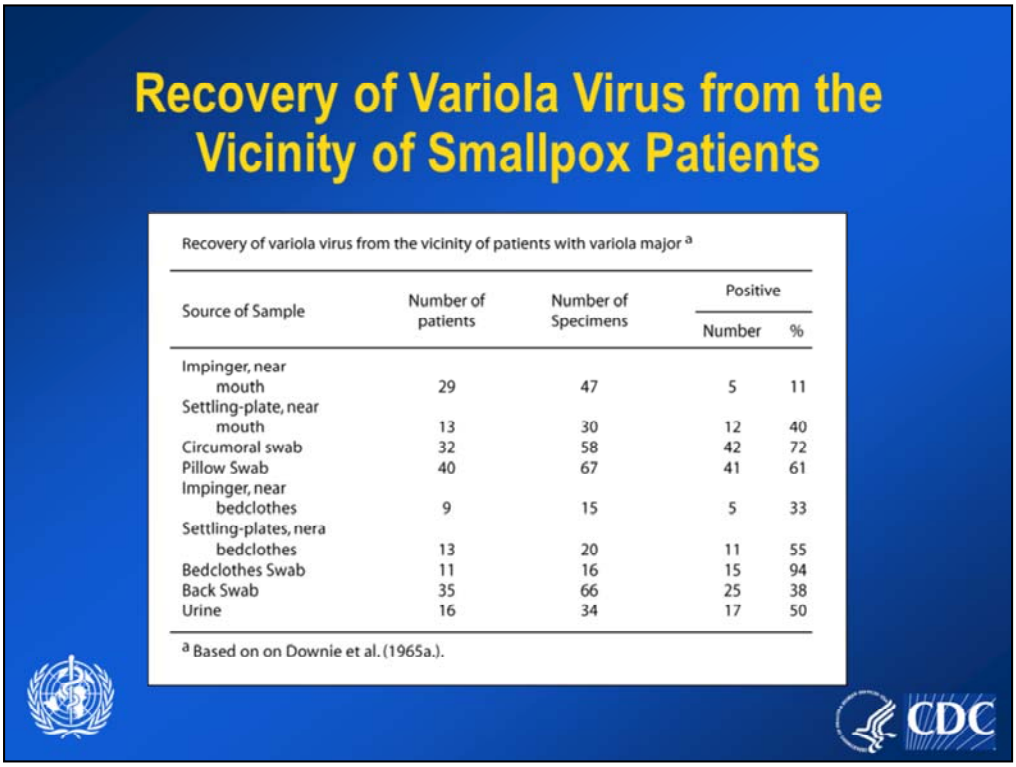
•Even though it is very rare, airborne infection over longer distances did sometimes occur.

•Two hospital outbreaks in Germany seem to have secondary cases arising from airborne spread.

•In this hospital associated outbreak in Meschede, Germany, a case of smallpox had been confined to his room before being diagnosed with smallpox and later transferred to the smallpox hospital. In spite of his isolation 19 further cases of smallpox occurred on all three floors of the building in which the index case had been housed before transfer to the smallpox hospital.

- •Confined to private room as a suspected typhoid fever case
- •Smoke studies showed fairly brisk air currents created by heating currents within the hospital that may have contributed to the distribution of air from the patient's room
- •Patient had prominent cough

•Today's infection control practices and hospital ventilation engineering controls are more strict and should prevent transmission by preventing circulation of air from an isolation room to other areas of the hospital if implemented appropriately.

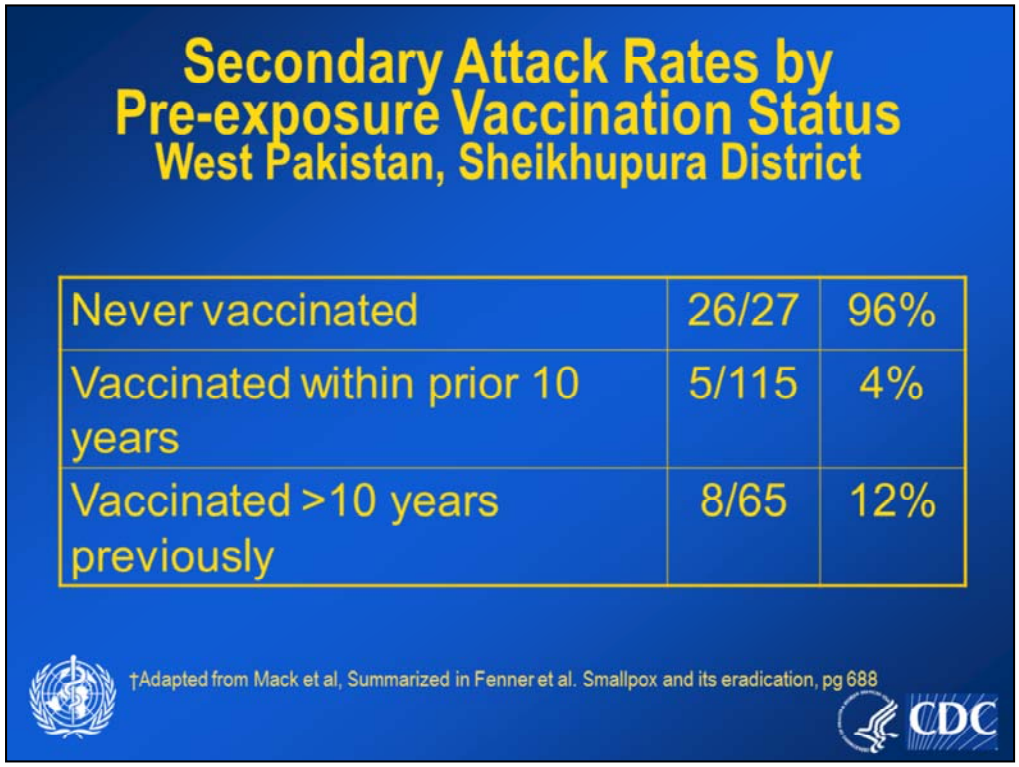


•Smallpox was occasionally transmitted by other means

•Transmission to laundry workers by infected bedding has been reported during several outbreaks by Dixon and others.

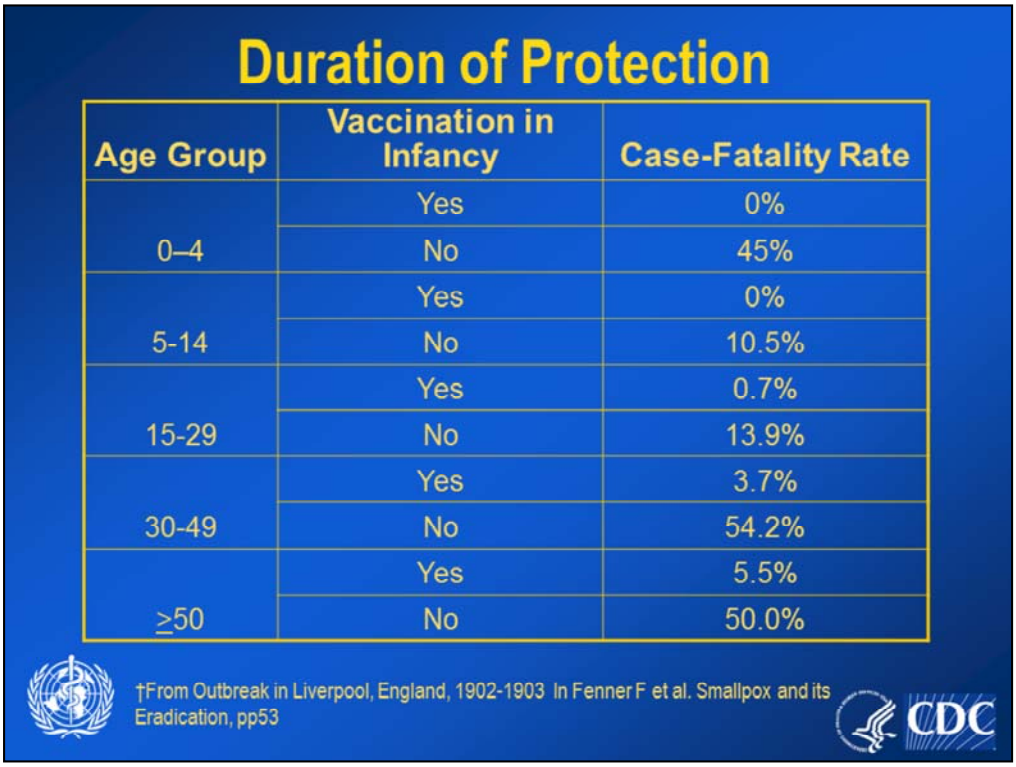
•Although the vast majority of smallpox cases can be traced back to close, face-to-face contact and not to fomite contact, this study by Downie et al. demonstrated that live variola virus could be recovered from bedding and clothing used by smallpox patients and therefore could serve as a possible source of infection

•The environment immediately around the patient (e.g. pillow, bedclothes) had the highest percentage of positive cultures. This would correspond to areas where respiratory droplets would be most likely to settle and where pustule drainage contamination would be the greatest.



•Also learned that vaccine could provide protection for several years, but the protection decreased over time

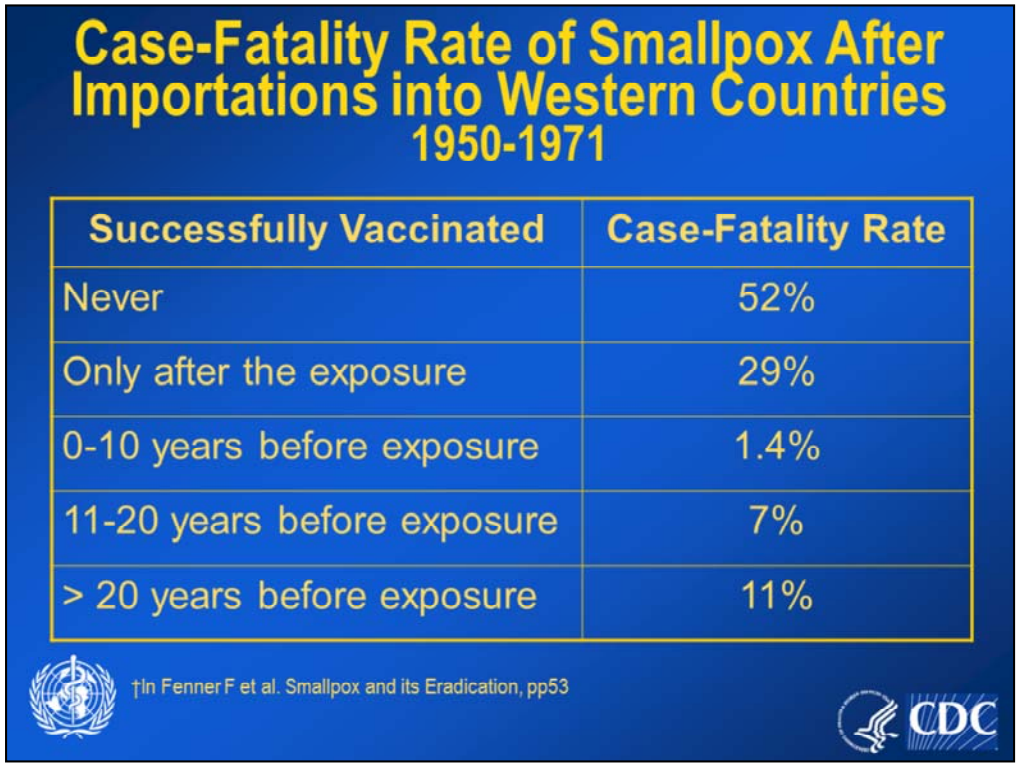
•A study by Mack, et al. on the secondary attack rates based on time interval since vaccination showed that individuals that were never vaccinated had a much higher attack rate when compared to persons vaccinated within 10 years of their exposure. Even those vaccinated more than 10 years previous had a significantly lower attack rate.



•Although full immunity from vaccination does not last forever, some degree of protection against death from the disease may last for many years.

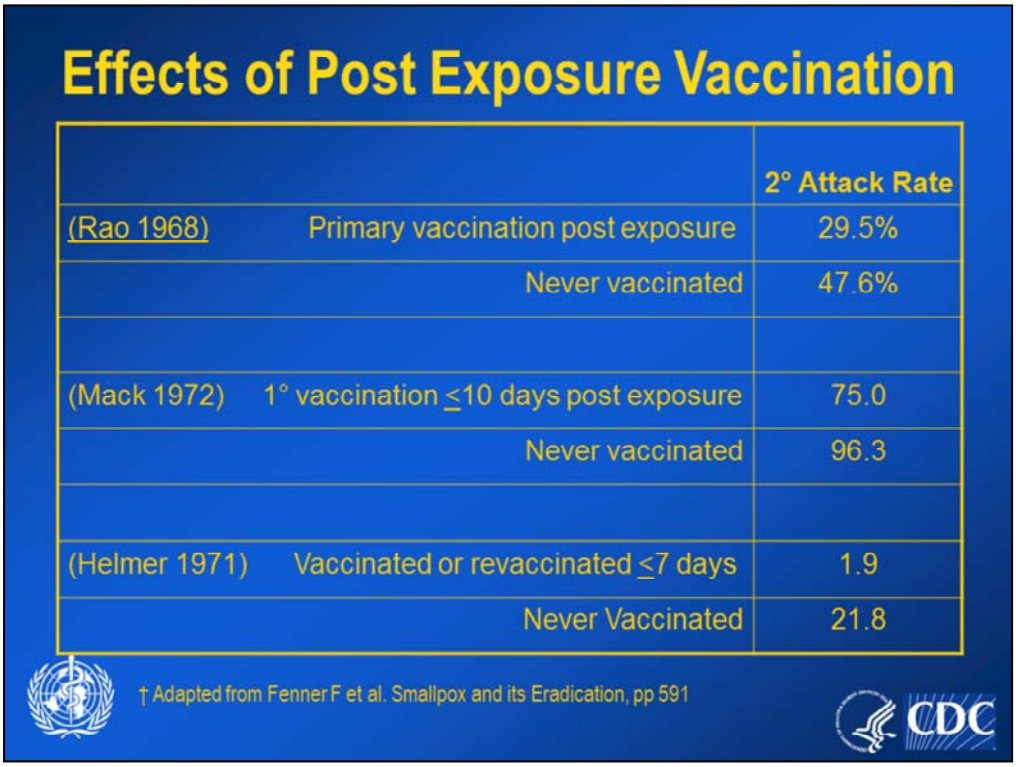
•This data published by Hanna in 1913 from an outbreak of smallpox in Liverpool, England, in 1902 to 1903, illustrated the ameliorating effect of childhood vaccination on the severity of smallpox.

- •There was a striking difference between vaccinated and unvaccinated patients in all age groups, both in the spectrum of severity and in case-fatality rates.
- •Protection decreased with age –with increasing intervals since vaccination – but was substantial even in those aged more than 50 years.



•Other studies supported that vaccination had a longer lasting effect than originally thought

•Data collected by Mack from Western countries with importations of smallpox between 1950 and 1971 showed the case-fatality rate was 52% in never vaccinated individuals, 1.4% in those vaccinated 0-10 years before exposure, and still only 11% in those vaccinated over 20 years before exposure.



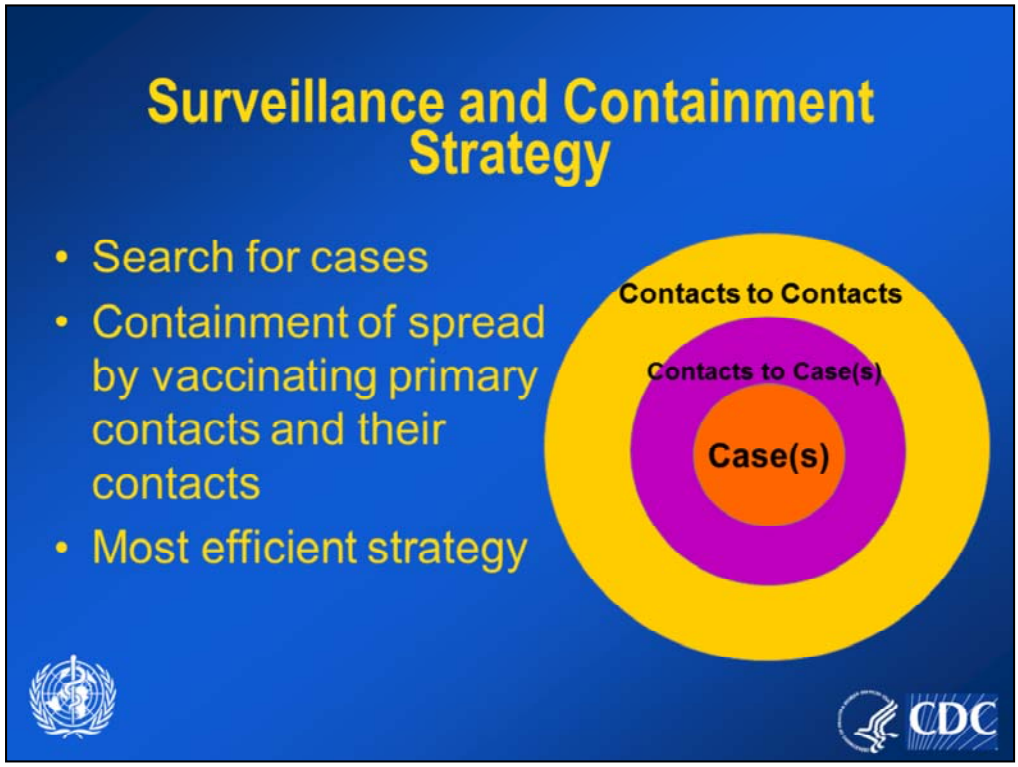
•Even during the Intensified Smallpox Eradication Programme, it was difficult to obtain accurate and reliable data on the level of protection against smallpox provided by vaccination. Immunity was determined by the presence of a scar. And many of these scars were caused by bacterial infections, rather than the vaccine.

•The best available information, which probably underestimated the protection afforded by post-exposure vaccination, came from several sets of data on secondary attack rates among vaccinated and unvaccinated family contacts of smallpox cases in Bangladesh, India and Pakistan.

•Although the numbers are small and not statistically significant in the individual studies, all the analyses showed a lower rate of occurrence of smallpox in previously unvaccinated family contacts who were vaccinated after exposure when compared to contacts who were not vaccinated at all following exposure.

• The level of protection was even greater when previously vaccinated subjects were included (Helmer 1971).

•Even when post-exposure vaccination did not prevent the occurrence of smallpox, it often mitigated its severity.



•It was possible to have an great impact on smallpox transmission even in areas where overall vaccination coverage was low by using a strategy called surveillance and containment

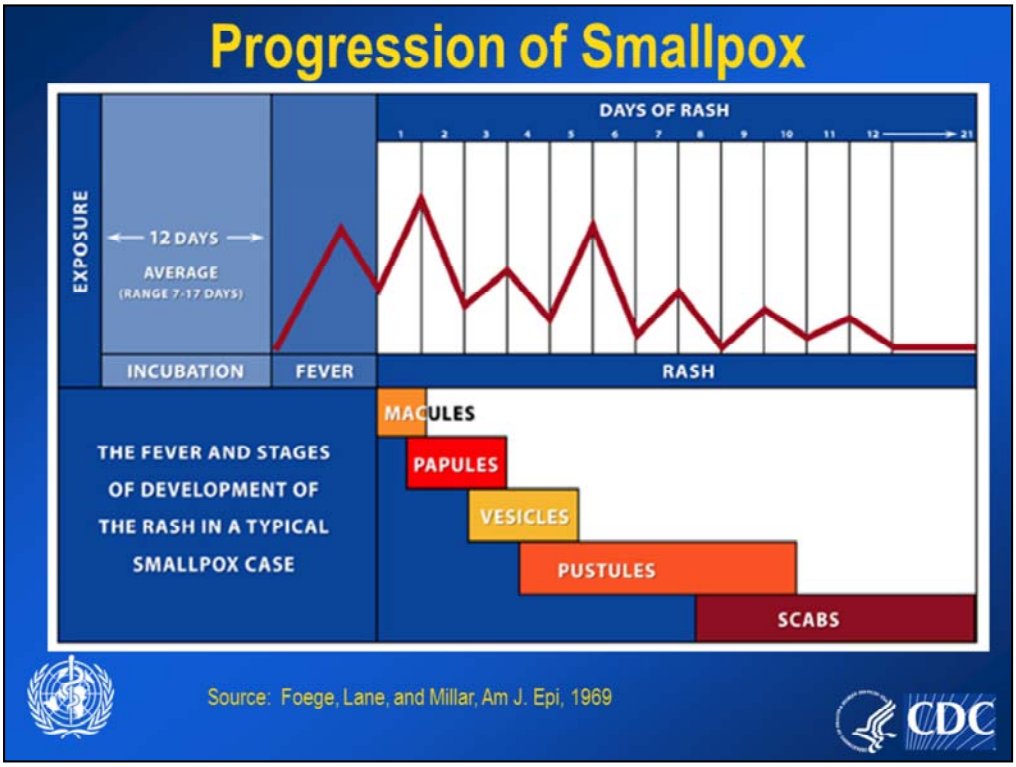
•This strategy became the key strategy in the global eradication program

•The principle behind this strategy is to identify cases of smallpox, vaccinate their household and other close contacts, then also vaccinate the close contacts of the primary household and close contacts to the case. Then, if the primary contacts developed smallpox despite vaccination, their close contacts would already be protected and the chain of transmission would have been broken,

•Special surveillance teams were recruited and trained to search for smallpox cases and vaccinate their contacts. They visited each health unit in an area of endemic smallpox to ensure that each week the health officer submitted a report indicating the number of cases seen

•When cases were reported, the teams worked with local health staff to find additional cases and to contain the outbreaks by vaccinating the contacts.

•A special WHO smallpox recognition card was printed and distributed to help in the search for cases

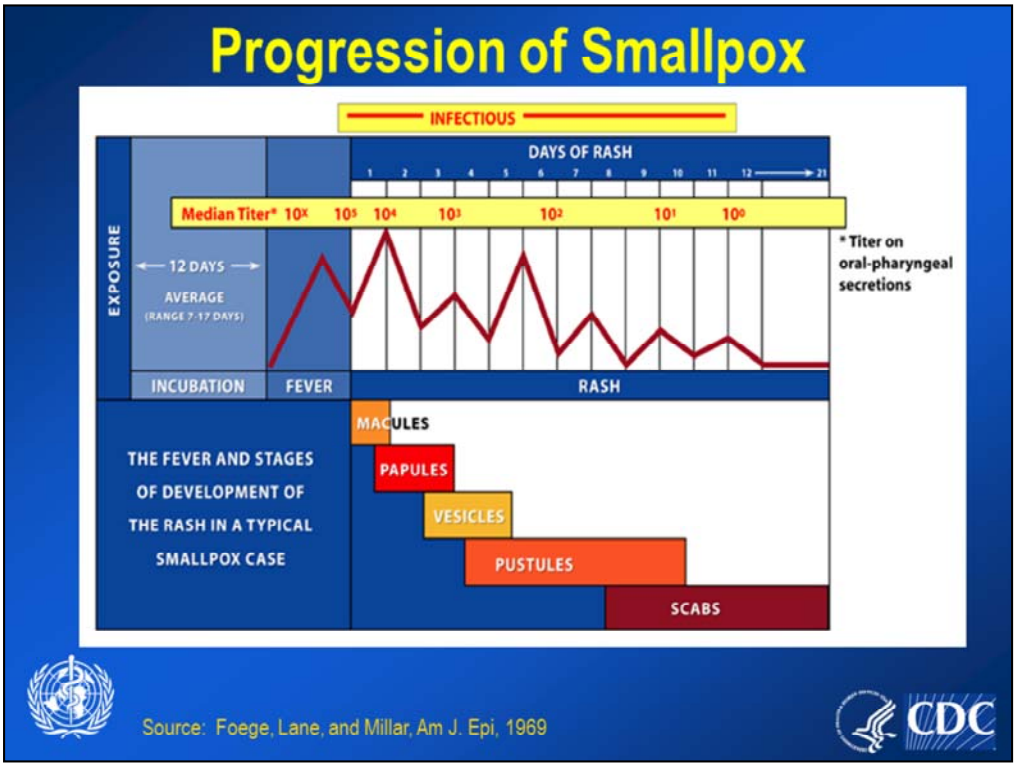


•We also learned a more about the pathogenesis and progression of the disease

•Following an incubation period of about 12 days, an average of 7 to 17 days, the first symptoms of illness – the prodrome, characterized by fever and other symptoms, begins

•In the skin, the virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. The result is the characteristic rash that appears 1-4 days after the onset of the prodromal period.

•This graph shows the timing of the fever and rash phases of smallpox infection and the progression of the rash stages

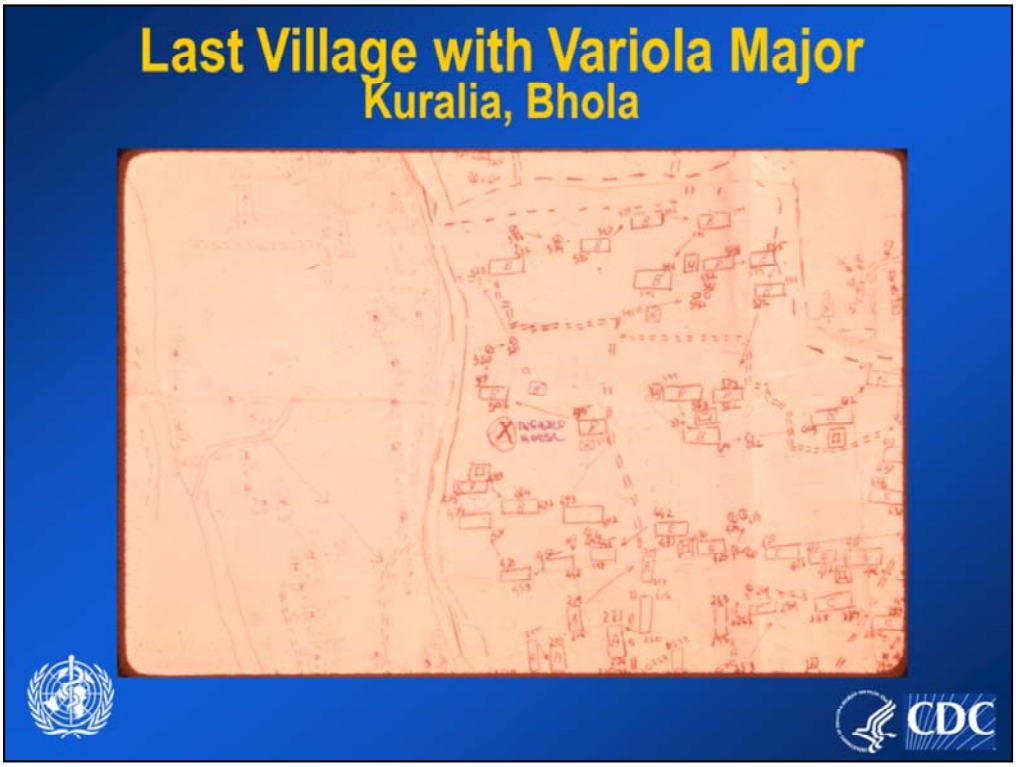


•Studies showed that viremia began at about the 8th day of the incubation period and then lead to the first symptoms of illness – the prodrome on about day 12.

•Virus localized to the skin and mucosal blood vessels during this time

•Virus titers in saliva were highest during the first week of the skin rash when oral mucosal lesions were present and shedding virus, this corresponded to the period where patients are most infectious

•Viral titers in the saliva decreased as the oral mucosal lesions healed over and were much lower after the first week of the rash, although the other skin lesions were still in the pustular or scab stages and contained infectious material



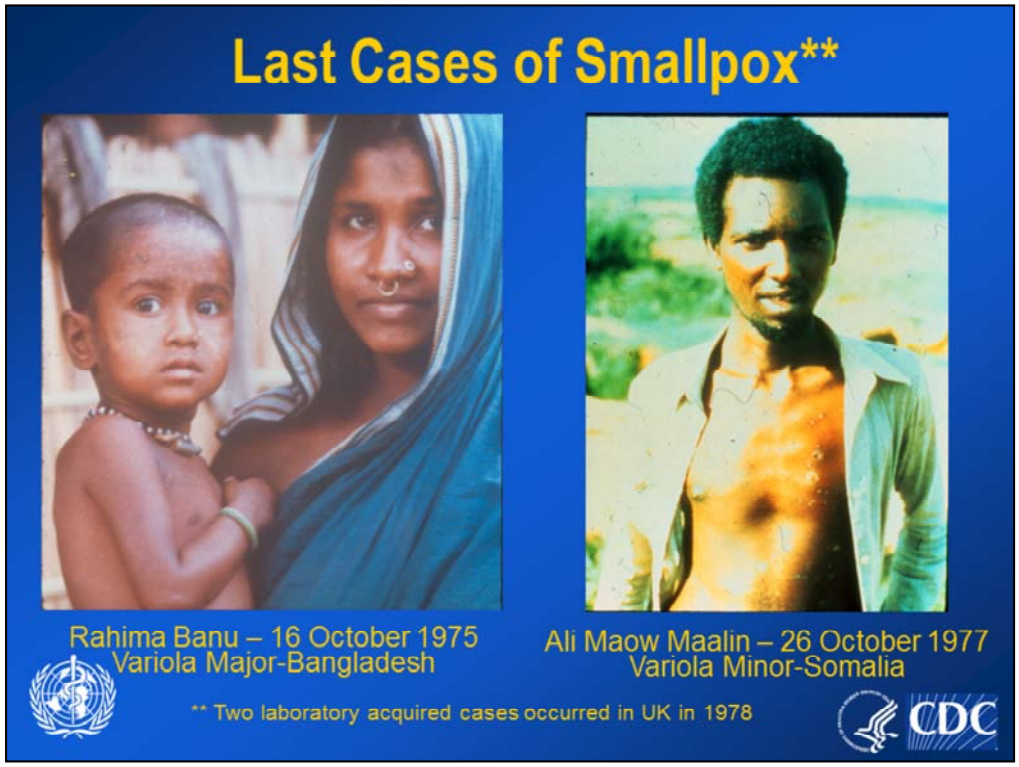
•Although setbacks occurred, the surveillance and containment strategy proved to be the strategy that finally brought about the eradication of smallpox throughout the world.

•By the end of 1975, smallpox persisted only in the Horn of Africa.

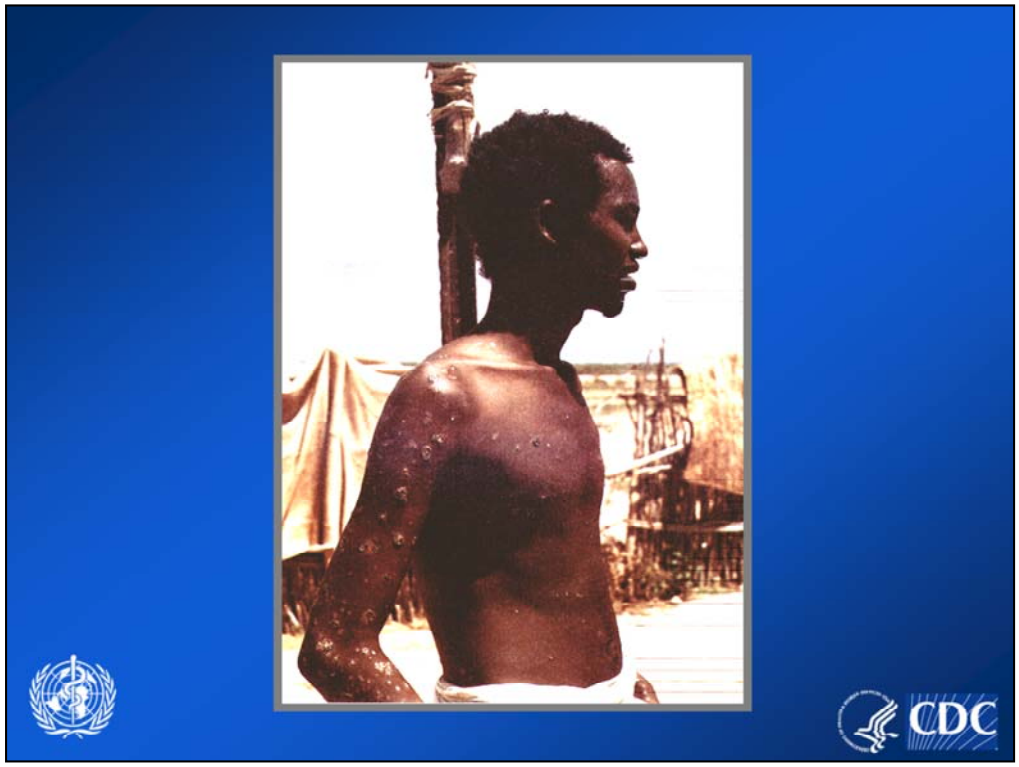
•Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult.

•With the interruption of smallpox transmission in Asia, more resources were made available in Africa, including more staff and transport.

•Just as it seemed that the last outbreak had been controlled, nomads in Somalia disseminated the disease throughout the southern part of that country.

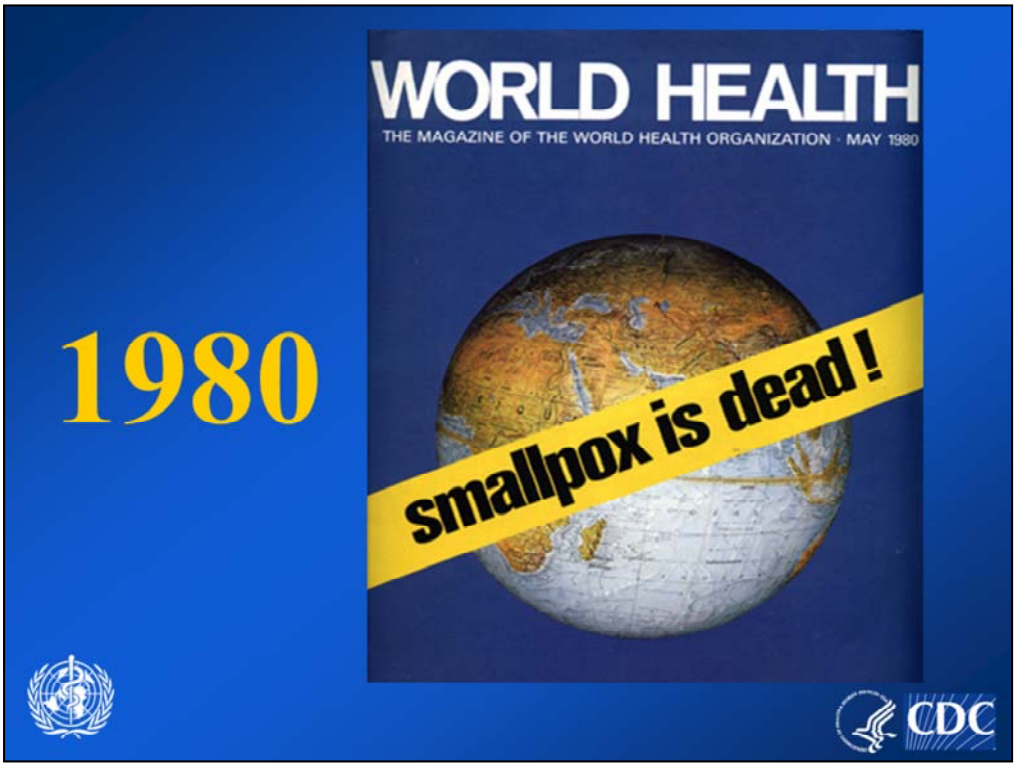


•An even more intensive surveillance and containment and vaccination program was initiated in the spring and summer of 1977. As a result, the world's last indigenous patient with smallpox on earth was a hospital cook in Merka, Somalia, on October 26, 1977 with variola minor.



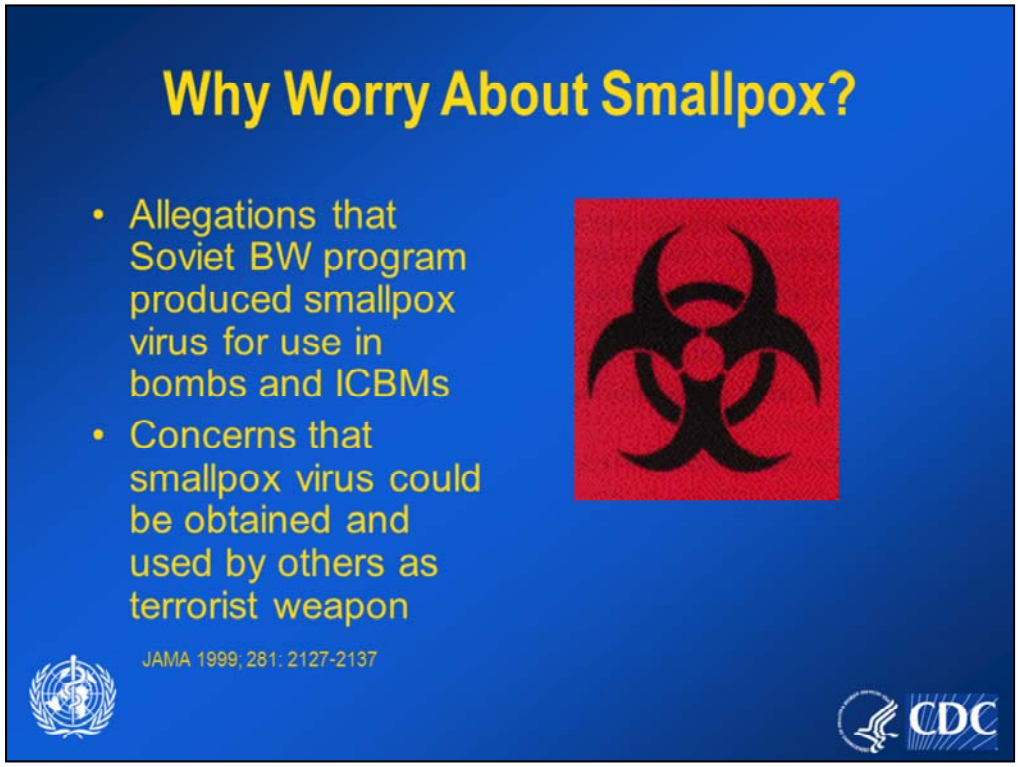
•Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox.

•Although 2 cases of smallpox occurred in England in 1978 as a result of a laboratory accident, smallpox was gone as a naturally transmitted disease.



•The World Health Organization officially certified that smallpox had been eradicated on December 9, 1979, 2 years after the last case in Somalia.

•In 1980 the World Health Assembly recommended that all countries cease routine vaccination.



•Following eradication, the World Health Organization also requested that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories – the Institute of Viral Preparations in Moscow, or the Centers for Disease Control and Prevention in Atlanta. All laboratories were believed to have complied with this request.

•In 1993, the former deputy director of the civilian branch of the Soviet Union's Bioweapons program reported that his government had produced large quantities of variola virus for use as a biologic weapon.

•With the breakup of the Soviet Union and unemployment of many of the program's scientists, there is concern that both the virus and expertise to produce it may have become available to other governments or terrorist groups who might wish to use this virus as a weapon.

•The deliberate reintroduction of smallpox into the world community would be an international crime of unprecedented proportions. Although this has not occurred, we can not afford to ignore this possibility.

•Smallpox is a devastating disease that can kill up to 30% of its victims and leave numerous others scarred for life.

•It is critical that physicians and other front line health care providers become, once again, familiar with the disease. Vigilance for suspected cases must be maintained as long as there is a threat of its possible use as a weapon of terrorism.

•It is also critical that public health and medical response plans be in place should a case occur. Such planning should occur now, not after an outbreak has occurred.

•The global eradication of smallpox ranks as one of the greatest triumphs in medicine. The outbreak control strategies identified and successfully used in that program would be essential once again should smallpox re-emerge.

•Although we hope the need to respond to a smallpox emergency never arises, current day planning efforts should incorporate these successful outbreak control strategies and still maintain the flexibility that is paramount to all emergency response plans.