SMALLPOX

1. **Agent**: Variola virus, a member of the poxviridae family. (This is the agent for both variola major—classic smallpox—and variola minor, a less serious form of the disease.)

2. **Identification**:

   a. **Symptoms**: Smallpox occurs in two clinical forms: variola major and variola minor. Variola major causes a more severe form of smallpox, with a more extensive rash and higher fever. Variola major has four distinct syndromes: ordinary (the most frequent type, accounting for 90% or more of cases); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic (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.

   Onset: The rash of smallpox is preceded by a prodrome consisting of 1 to 4 days of high fever (101°F-105°F), malaise, head and body aches, prostration; sometimes nausea, vomiting, abdominal pain, and backache.
   As the fever subsides a maculopapular rash develops (usually starts as small red spots on the tongue and in the mouth), followed by lesions on face spreading to the extremities, and then trunk, palms and soles. Lesions become vesicular on day 3 or 4, then slowly evolves into pustular lesions, deeply embedded into the dermis, by day 6. Fourteen days after the initial appearance of the rash, most of the lesions have developed scabs. Lesions develop uniformly throughout the disease with all lesions progressing from the macular to the pustular stage at about the same time.

   In a minority of instances, smallpox can present as “flat type” smallpox where lesions remain flush with the skin, never becoming elevated even during the pustular stage. This type of presentation is seen in 5% to 10% of cases and results in very severe disease. Another severe form of smallpox is “hemorrhagic smallpox” which involves extensive bleeding into the skin and almost always results in death. This form of disease, which can be seen in less than 3% of cases, can easily be mistaken for meningococcal sepsis.

   Milder disease with a less severe prodrome and a more rapid evolution of lesions can be seen in previously vaccinated individuals.

   b. **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, disseminated herpes zoster, impetigo (*Streptococcus pyogenes, Staphylococcus aureus*), drug eruptions, contact dermatitis, erythema multiforme minor, erythema multiforme major (Stevens-Johnson syndrome), enterovirus infection (Hand, Foot, and Mouth Disease), scabies, molluscum contagiosum, and mpox.

   c. **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. Clinically consistent cases are those presentations of smallpox that do not meet this classical clinical case definition: a) hemorrhagic type, b) flat type, and c) *variola sine eruptione*. 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 (PHL), California Viral & Rickettsial Diseases

Laboratory (VRDL), 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.)

Electron microscopy of vesicular or pustular fluid, or of the scab, as well as acute and convalescent serologic testing through CDC, can also be performed for diagnosis.

CSTE CASE CLASSIFICATION

Clinical Description
An illness with acute onset of fever ≥101°F (≥38.3°C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause. Clinically consistent cases are those presentations of smallpox that do not meet this classical clinical case definition:

a) hemorrhagic type
b) flat type
c) *variola sine eruptione*

Laboratory Criteria for Diagnosis
Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, OR
Isolation of smallpox (variola) virus from a clinical specimen (CDC only; confirmed by variola PCR).

Diagnostic testing for variola virus is conducted in select Laboratory Response Network (LRN) laboratories that meet variola testing facility requirements. LAC Public Health Laboratory is an LRN laboratory and is capable of testing variola PCR.

Suspected Case
A case with a generalized, acute vesicular or pustular rash illness with fever preceding development of rash by 1-4 days.

Probable Case
A case that meets the classical clinical case definition, or a clinically consistent case that does not meet the clinical case definition and has an epidemiological link to a confirmed case of smallpox.

Confirmed Case
A case of smallpox that is laboratory confirmed, or a case that meets the classical clinical case definition that is epidemiologically linked to a laboratory confirmed case.

Exclusion Criteria:
A case may be excluded as a suspect or probable smallpox case if an alternative diagnosis fully explains the illness or appropriate clinical specimens are negative for laboratory criteria for smallpox.

Please refer to CDC National Notifiable Diseases Surveillance System (NNDSS) website for details

3. **Incubation**: Usually 10-14 days (range 7-19 days).

4. **Reservoir**: Officially, only in designated laboratory repositories in USA and Russia. Humans are the only natural host.

   Naturally occurring smallpox no longer exists, although the threat of smallpox release remains due to concerns that variola virus might exist outside the two official repositories.

5. **Source**: Macules, papules, vesicles, pustules, and scabs of the skin and lesions in mouth and pharynx.

6. **Transmission**: Human to human transmission occurs by inhalation of large, virus-containing airborne droplets of saliva from an infected person. Infectious virus particles are released from the sloughing off of oropharyngeal lesions. 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. Transmission may more easily occur in a

hospital setting if isolation of the case is not implemented immediately. The virus is most likely to be disseminated in an aerosol cloud if used in biological warfare. Smallpox is not known to be transmitted by insects or animals.

7. **Communicability**: A smallpox case is most infectious to others when rash lesions first appear in the mouth and throat/pharynx, which usually occurs 24 hours before the rash is noted on the skin. Patients can transmit the virus throughout the course of the rash illness until all smallpox scabs fall off. A smallpox case may be infectious when they are experiencing febrile prodrome, though they are not as infectious as when they have lesions.

8. **Specific treatment**: Tecovirimat (TPOXX) and brincidofovir (TEMBEXA) are the only medications approved by U.S. Food & Drug Administration to treat smallpox.

9. **Immunity**: Infection is felt to confer lifelong immunity. Immunity from vaccination with the smallpox vaccine (vaccinia virus) gradually wanes over time beginning 5 years after vaccination. Usually, no protection against disease is observed for persons 30 or more years post-vaccination, although they can have less severe illness if infected. Vaccination of the U.S. general public ceased in 1972 after the disease was eradicated in the U.S.

REPORTING PROCEDURES

1. **Report any case or suspect cases by telephone immediately** (Title 17, Section 2500. *California Code of Regulations*).

   A. Call Acute Communicable Disease Control Program (ACDC) during working hours; after working hours, contact Administrative Officer of the Day (AOD) through County Operator.

   B. Any laboratory that receives a specimen for smallpox testing is required to report to the State Microbial Diseases Laboratory immediately (Title 17, Section 2505, *California Code of Regulations).*

   C. ACDC must notify the CA Dept. of PH Division of Communicable Disease Control (CDPH DCDC) immediately upon receiving notice of a case of suspected smallpox by calling the Duty Officer at (916) 328-3605 (available 24 hours).

ACDC will supervise investigation and control measures.

Report Form:

A. Smallpox Case Report Form**(For Internal ACDC Use)**

B. Smallpox Contact Tracing Form **(For Internal ACDC Use)**

CONTROL OF CASE, CONTACTS & CARRIERS

ACDC will coordinate all investigations for smallpox. Personnel designated for case interviews and contact investigation must be vaccinated prior to initiating face-to-face interviews OR be vaccinated within 72 hours after contact with a smallpox patient.

CASE MANAGEMENT:

1. Place case immediately into airborne, contact and standard isolation precautions; maintain isolation for the duration of disease until all scabs have separated from skin lesions. Refer to LAC Smallpox Response Plan for details.

2. Interview case (if in person, interviewer must be wearing coverall or impervious gown, gloves, eye protection, and N95 respirator or Power Air-Purifying Respiratory (PAPR)) to obtain:
   - Symptoms and onset date for both fever and rash
   - Measured temperature
   - Distribution of rash
   - Vaccination status
   - Travel History for previous 2-3 weeks.
   - Sites visited by the case since onset of fever including health care provider offices, clinics, and emergency departments, work, school, gym or other social sites and regular, as well as occasional activities. (If case is unable to answer questions because of age or illness, obtain information from case's close family members and friends.)

   Case Contacts:

- Obtain detailed name and contact information for all:
  - Highest Priority: Household family members of case and others spending ≥3 hours in the household since onset of rash.
  - Second Priority: Non-household contacts with contact < 6 feet with case with rash for ≥ 3 hours
  - Third Priority: Non-household contacts with contact < 6 feet with case with rash for < 3 hours
  - Fourth Priority: Non-household contacts with contact ≥ 6 feet with case with rash for ≥ 3 hours
  - Last Priority: Non-household contacts with contact ≥ 6 feet with case with rash for < 3 hours

CONTACTS:

1. Locate and interview each case contact to confirm exposure to the case, determine the presence or absence of symptoms and obtain list of household members to the case contact (including those who work full time in the residence).

2. List and prioritize all case contacts for urgency of vaccination based on duration and intimacy of exposure, and prior immunization history for smallpox

3. Plan for the immediate vaccination of asymptomatic case contacts and case contact household members. (If household members cannot be vaccinated due to contraindications, ensure that they avoid exposure to the contact until the end of the contact's surveillance period).

4. If contact is symptomatic with fever or rash, make immediate arrangements (with appropriate safety precautions to prevent transmission of possible disease to others) for transportation of contact to an LAC designated facility for evaluation of smallpox.

5. Conduct active monitoring of vaccinated case contacts for 14 to 18 days. Contacts should monitor their temperature twice a day (every 12 hours) and assess for symptoms for 18 days after their last exposure to the case, or until 14 days after successful vaccination (whichever comes first).

6. Contacts who do not receive vaccine should monitor their temperature twice a day (every 12 hours) and assess for 18 days after their last exposure to a case.

7. Asymptomatic case contacts and household members may continue their usual daily activities if no temperatures ≥ 101°F are measured.

8. Case contacts should isolate at home for a temperature ≥ 101°F and call ACDC.

9. ACDC and Health Officer will determine appropriate isolation and quarantine measures.

CARRIERS: Not applicable.

PREVENTION-EDUCATION

Stress the importance of immunizing all contacts and their household contacts as soon as possible. In a smallpox emergency, all contraindications to vaccination would be reconsidered considering the risk of smallpox exposure.

Educate all cases and contacts regarding the transmission and communicability of smallpox and the actions required to prevent further transmission including precautions for the handling of case's clothing, bedding, linens, and eating utensils.

Educate case contacts and their household members about symptoms of smallpox and who to call if they become symptomatic.

CDC provides prevention strategies (e.g. decontamination and other infection control measures) for healthcare facilities that may be applied to household setting: CDC: Smallpox health-care facility response

OUTBREAK DEFINITION

A single case of smallpox is a public health emergency and warrants an immediate investigation, in consultation with ACDC.

DIAGNOSTIC PROCEDURES

1. **Real-Time PCR Testing**: Variola virus-specific PCR testing

2. **Culture**: Culture of vesicular or pustular fluid or scabs is available through the CDC. Contact the LAC Public Health Laboratory for specific procedures prior to any attempt to obtain specimens from patients with suspected smallpox.

Serologic Testing: Acute and convalescent serologic testing is available through the CDC. 7-10 cc of blood should be drawn into a red/gray (marbled), gold, or red topped serum separator tube. Contact the LAC Public Health Laboratory prior to collection of serologic

3. specimens from patients with suspected smallpox.

4. **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.

SMALLPOX VACCINE

When responding to smallpox investigation (e.g. in-person case interview, etc.), if previously unvaccinated, staff must not have contraindications for vaccination (refer to CDC website for details) as they would require immediate vaccination if the diagnosis of smallpox is confirmed. Initial investigation will be conducted immediately upon notification by the LAC Public Health Smallpox Response Team.

Note: In a smallpox emergency, the risk for adverse events from smallpox vaccination is outweighed more often by the risk for severe smallpox disease. Consequently, contraindications that would apply in a pre-event vaccination program might no longer apply in a post-event vaccination program. Because of the high case-fatality rate and severity of smallpox, no clear absolute contraindications exist for the use of smallpox vaccines for persons exposed to smallpox virus or at high risk for smallpox infection.

CDC: Smallpox Vaccine

The Strategic National Stockpile (SNS) has 3 smallpox vaccines: ACAM2000® and JYNNEOS™ which are licensed and Aventis Pasteur Smallpox Vaccine (APSV) which is investigational and may be used in a smallpox emergency under the appropriate regulatory mechanism.

ACAM2000® is a replication-competent vaccine containing vaccina virus and is administered as a single dose by the percutaneous route using the multiple puncture technique.

JYNNEOS is a replication-deficient smallpox vaccine, for the prevention of smallpox and mpox. Unlike ACAM200® it is an attenuated live virus vaccine. JYNNEOS™ is administered subcutaneously as two doses separated by 4 weeks for primary vaccinees. Individuals previously vaccinated against smallpox receive one dose.

APSV is another replication-competent vaccinia virus vaccine in the Strategic National Stockpile, with a safety profile anticipated to be similar to ACAM2000®. It is an investigational vaccine.

SMALLPOX VACCINE ADVERSE EVENTS MONITORING

Timely recognition of and response to smallpox vaccine adverse events are important in protecting the public from unnecessary risk and to maintain confidence during an immunization effort.

Adverse events that are serious or unexpected may require expert consultation or IND (investigational new drug) therapeutics.

Healthcare workers should report any unexpected or serious event occurring after smallpox vaccination as well as adverse events occurring in persons following close contact with a vaccine recipient to the Vaccine Adverse Event Reporting System (VAERS). An adverse event is any clinically significant medical event that occurs following administration of a vaccine. Refer to Side Effects of Smallpox Vaccination on CDC website for details.

REFERENCES:

SMALLPOX CLINICAL DESCRIPTION
https://www.cdc.gov/smallpox/hcp/clinical-signs/

DIAGNOSIS AND EVALUATION
https://www.cdc.gov/smallpox/hcp/diagnosis-testing/