GUIDELINES AND RESOURCES

Updated Interim CDC Guidance for Use of Smallpox Vaccine, Cidofovir, and Vaccinia Immune Globulin (VIG) for Prevention and Treatment in the Setting of an Outbreak of Monkeypox Infections

This interim guidance updates the June 12, 2003, interim guidance on the use of smallpox vaccine, cidofovir, and vaccinia immune globulin (VIG) for purposes of monkeypox outbreak control in affected states. The principal changes include a revision of the definition of close contact with an ill animal, vaccination of clinical laboratory workers handling specimens from ill animals and persons infected with monkeypox virus, and instructions for reporting smallpox vaccine-related serious adverse events to the Vaccine Adverse Event Reporting System (VAERS).

In most instances, only limited data are available on which to directly base recommendations and thus the guidance is primarily based on expert opinion. This interim CDC guidance was developed using the best available information about the benefits and risks of smallpox vaccination, VIG, and cidofovir for prevention and management of smallpox, monkeypox and complications of vaccinia infection. Smallpox vaccine for controlling outbreaks of monkeypox would be available under an investigational new drug (IND) protocol sponsored by CDC.

Limited information is available on efficacy of smallpox vaccination for prevention of monkeypox. The data suggest that pre-exposure smallpox vaccination is highly effective ($\geq$85%) in protecting persons exposed to monkeypox from disease (1-5). No information is available on the efficacy of post-exposure vaccination. Data that suggest smallpox vaccination following exposure to smallpox is effective in preventing or ameliorating disease, suggest that post-exposure smallpox vaccination should have similar impact against monkeypox. Data from investigations in Africa in the 1980s suggested that in household setting, secondary transmission occurred to about 8 – 15% of contacts. Among infected human cases, reported mortality rates have ranged most frequently from 1-10% (1-8); the risk of death from smallpox vaccine is estimated to be 1-2 per million vacinees (9).

Available data on transmission from monkeypox cases are based on studies in Africa. Person-to- person transmission is thought to occur primarily by direct contact and may occur by respiratory droplet spread. Transmission of monkeypox within hospitals has been described, albeit rarely. In the absence of data, extrapolating from smallpox outbreaks where person-to-person airborne transmission has been clearly described, person-to-person airborne transmission from (human) monkeypox cases cannot be excluded as a possibility, especially in patients presenting with cough. Similarly, although the current outbreak investigation in the United States. has identified transmission of monkeypox from ill prairie dogs to persons by direct (intimate) contact, airborne transmission from ill prairie dogs with respiratory symptoms (e.g., cough) to persons cannot be excluded as a possibility. It is potentially possible, but unknown, if transmission can occur from ill prairie dogs to persons by contact with the ill animal's bedding or cages; monkeypox virus may be transmitted through fomites on contaminated surfaces.

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Because of the potential seriousness of this disease, CDC has developed interim guidance, which attempts to balance the risks of smallpox vaccination against the risks posed by exposure to monkeypox infection. This interim guidance will be re-evaluated as more information becomes available.

It is important that vaccinators, as currently occurs in the pre-event smallpox vaccination program, screen potential vaccinees for precautions and contraindications to smallpox vaccination and evaluate vaccination sites for a successful vaccination (i.e., a major reaction at the site 6-8 days after vaccination). Persons without a successful vaccine take should be revaccinated within 2 weeks of the most recent exposure to monkeypox. State and local health departments should provide information on how vaccinees should seek consultation on evaluation of vaccination sites for major reactions or for potential complications of vaccination.

Rash illnesses suspected to be monkeypox should be confirmed by laboratory evaluation, which, in addition to determining the presence of monkeypox, should have the capability to detect varicella, vaccinia and other relevant viruses. Laboratory confirmation of monkeypox cases is particularly important before recommending vaccination to persons with close or intimate contact with a monkeypox case and considered to have contraindications to smallpox vaccination in the pre-event smallpox vaccination (e.g., pregnant women, persons with eczema, and children aged <1 year). Intimate contact refers to contact resulting in exposure to body fluids or lesions of ill persons or ill animals. The period of communicability (i.e., exposure period for contacts) for humans may be from 1 day before onset of rash up to 21 days after rash or illness onset or when all rash lesions have scabbed over. The period of communicability (i.e., exposure period for contacts) for animals may be from 1 day before onset of illness up to 21 days after rash or illness onset or when the ill animal is removed from possible exposure with the contact, or when the animal's clinical illness ends and all rash lesions have scabbed over. As general guidance, for purposes of smallpox exposure (for human-to-human transmission), close contact has been defined as $\geq$3 hours of direct (face-to-face) exposure within 6 feet; this is reasonable guidance for exposure to monkeypox from humans as well. In animal care settings, close contact has been defined as direct exposure within 6 feet of an animal suspected to have monkeypox with respiratory symptoms such as nasal discharge, cough, or conjunctivitis in a setting where the animal has been manipulated (e.g., an exam room). However, judgment must be applied to determine the significance of contact in individual exposure situations.

1 - Should persons investigating suspected human and animal monkeypox cases receive smallpox vaccination? If so, should a prior recent history of smallpox vaccination with a confirmed take be required or is it acceptable to vaccinate these individuals as they depart for the investigation?

Ideally investigators of suspected monkeypox cases should have received smallpox vaccination within the past 1-3 years. When possible, priority should be given to using investigators, veterinarians, and animal control personnel who previously were vaccinated and who had a confirmed take. Ideally the vaccination site should have crusted over before deployment. However, if this is not feasible these individuals may be vaccinated immediately before deploying for the field investigation. Unvaccinated investigators currently involved in field investigations or who have been recently involved in such work should be vaccinated as soon as possible, preferably within 4 days from initial direct exposure. Any investigator with an active vaccination site that is not healed should follow the precautions advised for health care workers (HCWs) with regard to vaccination site care to avoid potential contamination of field samples or transmission of vaccinia to others (9).

Field investigators of suspected cases of monkeypox should observe recommended standard, contact, and air-borne infection control precautions even if vaccinated. These include the use of recommended personal protection equipment (currently N95 or comparable respirator) when

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appropriate. Interim guidance for infection control and exposure management in the health-care and community setting for patients with possible monkeypox virus infection is available at: www.cdc.gov/ncidod/monkeypox/infectioncontrol.htm

2 - Should HCWs who care for suspected cases of monkeypox be vaccinated?

A. Previously or currently exposed HCWs

HCWs currently caring for confirmed monkeypox cases or who have been recently involved in such care should be vaccinated. Vaccination should occur as soon as possible after confirmed exposure. Vaccination is recommended for persons who are within 4 days of initial direct (intimate or close) exposure and should be considered only for persons who are within 2 weeks of most recent exposure. Vaccination sites should be managed as recommended for HCWs in the pre-event smallpox vaccination program (9). Persons without a vaccine take by day 7 should only be revaccinated if within 2 weeks of most recent exposure.

B. HCWs who may be asked to care for monkeypox patients in the future

Ideally, HCWs selected to care for suspected monkeypox cases should not have any of the contraindications to smallpox vaccination in the pre-event smallpox vaccination setting (10, 11). When possible, priority should be given to having HCWs who were previously vaccinated, with confirmed takes, care for patients with suspected monkeypox. When such workers are unavailable, HCWs may be vaccinated immediately prior to beginning their clinical care duties. Vaccination sites should be managed as recommended for HCWs in the pre-event vaccination program (9).

HCWs who care for suspected cases of monkeypox should continue to observe recommended standard, contact, and air-borne infection control precautions including use of personal protective equipment (currently N95 or comparable respirator) (10) when appropriate, even if vaccinated.

C. Clinical laboratory workers

Interim guidance on vaccination and appropriate handling of routine clinical laboratory specimens from animals or persons suspected to be infected with monkeypox is available at: www.cdc.gov/ncidod/monkeypox/lab.htm

3 – Should smallpox vaccination of contacts of human monkeypox cases be recommended? If so, how is contact defined (e.g., family, classroom etc.) and what is the recommended interval for vaccination following exposure?

Close contacts, defined as household contacts as well as others who have had close or intimate contact with confirmed human cases, and who are within 4 days of initial direct exposure to a monkeypox case should be vaccinated. Vaccination should be considered for persons who are within 2 weeks of most recent exposure. As general guidance, for purposes of smallpox exposure, close contact has been defined as $\geq$3 hours of direct exposure within 6 feet and this is reasonable guidance for monkeypox exposure as well. Intimate contact refers to contact resulting in exposure to body fluids or lesions of affected persons. However, judgment must be applied to determine the significance of contact in individual exposure situations. State and local health departments should be consulted regarding decisions about vaccination of contacts, and in particular be consulted for contacts who may not meet the strict definitions of close or intimate contact above, especially in child care, school, or health care settings.

Vaccination sites should be managed as recommended for HCWs in the pre-event smallpox vaccination program (9). Persons who care for recently vaccinated children should be particularly

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vigilant to observe recommended standard and contact infection control precautions with the vaccination site. Persons without a vaccine take by day 7 should only be revaccinated if within 2 weeks of most recent exposure.

4 – Should smallpox vaccination be recommended for persons who have been exposed to a recently acquired prairie dog or other small mammals from implicated distributors?

Smallpox vaccination should be recommended for persons who have, within the past 4 days, had direct physical (intimate) contact with ill prairie dogs or other ill small mammals meeting the probable or confirmed case definitions for monkeypox from implicated distributors acquired since April 15 within the affected areas. The interim case definition for animal cases of monkeypox is available at: www.cdc.gov/ncidod/monkeypox/animalcasedefinition.htm. Vaccination should be considered for persons who are within 2 weeks of most recent exposure. In addition, vaccination can be considered for persons who have close contact with an ill animal that meets the probable or confirmed animal case definition. Close contact is defined as direct exposure within 6 feet of a probable or confirmed monkeypox case in an animal with respiratory symptoms such as nasal discharge, cough, or conjunctivitis in a setting where the animal has been manipulated (e.g., an exam room). Smallpox vaccination is not recommended for persons exposed to a healthy animal.

These recommendations may change should evidence show that other symptomatically ill small mammals pose significant risk for human monkeypox.

Vaccination sites should be managed as recommended for HCWs in the pre-event smallpox vaccination program (9). Persons who care for recently vaccinated children should be particularly vigilant to observe recommended standard and contact infection control precautions with the vaccination site. Persons without a vaccine take by day 7 should only be revaccinated if within 2 weeks of most recent exposure.

Veterinary health care workers should observe recommended infection control practices available at: www.cdc.gov/ncidod/monkeypox/animalguidance.htm including use of personal protective equipment when appropriate, even if vaccinated. It is anticipated that fit-tested N95 respirators will not be available in most veterinary facilities; when currently N95 or comparable respirators are unavailable, surgical masks should be worn to protect against transmission through contact or large droplets. Exposed veterinarians and staff without N95 (or comparable) respirator protection who have direct or close contact to animals with monkeypox should be vaccinated according to the guidelines. Interim guidance for infection control and exposure management in the health-care and community setting for patients with possible monkeypox virus infection is available at: www.cdc.gov/ncidod/monkeypox/infectioncontrol.htm

Interim guidance on appropriate handling of routine clinical laboratory specimens from animals suspected or confirmed to be infected with monkeypox is available at: www.cdc.gov/ncidod/monkeypox/labbiosafetyguide.htm

5 – What contraindications to smallpox vaccination should be observed for persons exposed to monkeypox infections?

The nature of exposure should be assessed carefully for HCWs, household, close or intimate contacts who have been exposed within the past 2 weeks to a probable or confirmed animal case or confirmed human case of monkeypox, but who have contraindications to smallpox vaccine receipt in the pre-event smallpox setting (10, 11). If there are difficulties in obtaining rapid laboratory confirmation, the state health department should be urgently consulted. The risk of

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monkeypox disease for persons with a close or intimate exposure to confirmed monkeypox cases is believed to be greater than the risk of adverse events resulting from vaccinia exposure for most persons for whom smallpox vaccination would be otherwise contraindicated in the pre-event smallpox vaccination setting. In the post-exposure setting, the benefit of vaccination outweighs the risk of vaccination. In this setting, most contraindications are considered precautions to vaccination. In persons with close or intimate exposure within the past 2 weeks to a confirmed human case or probable or confirmed animal case of monkeypox, neither age, pregnancy, nor a history of eczema are contraindications to receipt of smallpox vaccination. These conditions are precautions and not contraindications. Active eczematous disease is more concerning, but in instances when the potential vaccinee has had true close or intimate exposure, the risk of contracting monkeypox would likely still be greater than the risk of complications of smallpox vaccination. Appropriate site care should be used to prevent transmission of smallpox vaccine (vaccinia virus) from vaccinated persons to other non-vaccinated household members (9).

Smallpox vaccination is still contraindicated for:

1. Persons who have severe immunodeficiency in T-cell function, defined as:
    - HIV-infected adults with CD4 lymphocyte count less than 200 (or age appropriate equivalent counts for HIV infected children);
    - Solid organ, bone marrow transplant recipients or others currently receiving high dose immunosuppressive therapy (i.e. 2 mg/kg body weight or a total of 20 mg/day of prednisone or equivalent for persons whose weight is > 10 kg, when administered for > 2 weeks); and
    - Persons with lymphosarcoma, hematological malignancies, or primary T-cell congenital immunodeficiencies.
2. Persons with life-threatening allergies to latex or to smallpox vaccine or any of its components (polymyxin B, streptomycin, chlortetracycline, neomycin).

These persons have a risk of severe complications from smallpox vaccination that may approach or exceed the risk of disease from monkeypox exposure. Consultation with state and local health departments and CDC should be sought regarding judgments about vaccination of such persons in the post-exposure setting.

6 - What is the role of cidofovir and vaccinia immune globulin (VIG) in treatment and prophylaxis of these cases?

No data are available on the effectiveness of VIG in treatment of monkeypox complications. VIG has no proven benefit in the treatment of smallpox complications (9). It is unknown whether a person with severe monkeypox infection will benefit from treatment with VIG, however, its use may be considered in such instances. VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for whom smallpox vaccination following exposure to monkeypox is contraindicated.

No data are available on the effectiveness of cidofovir in treatment of human monkeypox cases. However, cidofovir has proven anti-monkeypox viral activity in *in vitro* and in animal studies (12,13). It is unknown whether a person with severe monkeypox infection will benefit from treatment with cidofovir, however, its use may be considered in such instances. Cidofovir has significant toxicity and should only be considered for treatment of severe monkeypox infections, not for prophylactic use.

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Clinical consultation on the use of VIG and cidofovir is available from staff at each state health department in the affected states. In addition, clinical consultation is available from staff at the CDC at 877-554-4625.

7 - Should pre-exposure smallpox vaccination be offered to veterinarians, veterinary staff, and animal control officers in the affected states?

Similar to health care workers, at this time pre-exposure smallpox vaccination is not recommended for unexposed veterinarians, veterinary staff, and animal control officers in the affected areas, but routine use of appropriate standard, contact and air-borne infection control measures should be stressed.

Persons who may be involved in field investigations involving potentially infected animals should be vaccinated in advance (see question 1). This recommendation will be re-evaluated as more information becomes available.

Laboratory workers (e.g., veterinary pathologists) at designated reference laboratories who handle specimens from ill prairie dogs or other ill small mammals meeting the probable or confirmed case definitions for monkeypox from implicated distributors acquired since April 15 within the affected states should be vaccinated as recommended for field investigators or health care workers anticipated to have future contact with suspected monkeypox cases.

8 –Reporting of adverse events associated with smallpox vaccination:

Serious adverse events after smallpox vaccination (14) should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted through a secure Internet-based system at https://secure.vaers.org/VaersDataEntryintro.htm. Printable VAERS forms are located online at www.vaers.org/pdf/vaers_form.pdf, or postage-paid forms can be obtained by calling 800-822-7967 (toll-free). Submission of VAERS reports by Internet is encouraged to expedite processing and data entry.

Completed forms can be faxed to 877-721-0366 (toll-free) or mailed to P.O. Box 1100, Rockville, MD 20894-1100. Additional information related to VAERS reporting can be obtained by calling 800-822-7967 or by e-mail at info@vaers.org.

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For more information, visit www.cdc.gov/ncidod/monkeypox or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY)