

Viral Agents (other than arboviruses)

Agent: Hantaviruses

Work with Hantaan virus (hemorrhagic fever with renal syndrome) and other hantaviruses (Puumala, Seoul, and Sin Nombre, whether or not they are registered in the *International Catalogue of Arboviruses and Certain Other Viruses*-1985, such as El Moro Canyon virus) in rats, voles, and other laboratory rodents, should be conducted with special caution because of the extreme hazard of aerosol infection, especially from infected rodent urine.

Hantavirus pulmonary syndrome (HPS) is a severe, often fatal new disease that is caused by Sin Nombre and/or related virus.⁽¹⁾ Most cases of human illness have resulted from exposures to naturally infected wild rodents. Arthropod vectors are not known to transmit hantaviruses. Person-to-person transmission has not been reported with any of the viruses associated with this disease.

Laboratory Hazards: Laboratory transmission of hantaviruses from rodents to humans via the aerosol route is well documented.⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾ Exposures to rodent excreta, fresh necropsy material, and animal bedding are presumed to be associated with risk. Other potential routes of laboratory infection include ingestion, contact of infectious materials with mucous membranes or broken skin, and, in particular, animal bites.

Four laboratory workers were infected while working with cell-culture-adapted Hantaan virus. Although the procedures associated with infection are unclear, all four persons worked repeatedly with hantavirus cultures and performed centrifugation of concentrated virus.⁽⁶⁾ Viral RNA has been detected in necropsy specimens and in patient blood and plasma obtained early in the course of the disease.⁽⁷⁾ The implications of these findings for the infectivity of blood or tissues are unknown.

Recommended Precautions: Biosafety level 2 practices and procedures are recommended for laboratory handling of sera from persons potentially infected with the agents of HPS. The use of a certified biological safety cabinet is recommended for all handling of human body fluids when potential exists for splatter or aerosol.

Potentially infected tissue samples should be handled in BSL-2 facilities following BSL-3 practices and procedures. Cell-culture virus propagation should be carried out in a BSL-3 facility following BSL-3 practices and procedures. Large-scale growth of the virus, including preparing and handling viral concentrates, should be performed in BSL-4 containment facilities.

Experimentally infected rodent species known **not** to excrete the virus can be housed in ABSL-2 facilities using ABSL-2 practices and procedures. BSCs and other primary physical containment devices should be used whenever procedures with high potential for generating aerosols are conducted. Serum or tissue samples from potentially infected rodents should be handled at BSL-2 using BSL-3 practices and procedures. All work

involving inoculation of virus containing samples into *P. maniculatus* or other permissive species should be conducted at ABSL-4.

Transfer of Agents: For a permit to import these agents, contact CDC. Contact the Department of Commerce for a permit to export these agents. Laboratory registration with CDC is required before sending or receiving these select agents.

Agent: Hendra and Hendra-like Viruses (includes virus formerly known as Equine Morbillivirus)

Outbreaks of a previously unrecognized paramyxovirus, at first called equine morbillivirus, later named "Hendra virus," occurred in horses in Australia in 1994 and 1995.⁽⁸⁾⁽⁹⁾⁽¹⁰⁾⁽¹¹⁾⁽¹²⁾ Three people in close contact with ill horses developed encephalitis or respiratory disease and two died. No associated outbreaks of human disease were recognized, but two piggery workers recalled an influenza-like illness at the time of the pig outbreak, and had neutralizing antibody titers to the Menangle virus. During 1998-99 an outbreak of illness caused by a similar but distinct Hendra-like virus occurred in Singapore and Malaysia.⁽¹³⁾ In Malaysia and Singapore, human illness, characterized by fever, severe headache, myalgia and signs of encephalitis has occurred in individuals in close contact with pigs (i.e., pig farmers and abattoir workers). Few patients developed a respiratory disease. Half of the people infected with this virus died. The natural host(s) for the Hendra and Hendra-like viruses has not been identified; however in Australia, bats are suspected of carrying the Hendra virus. Epidemiologic and laboratory studies are ongoing. No laboratory-acquired infections are known to have occurred as a result of Hendra or Hendra-like virus exposure. However, it should be noted that in both the Australia and Malaysia/Singapore outbreaks the virus has been recognized as a significant veterinary pathogen. Laboratory studies have been confined to high containment veterinary and/or human infectious disease laboratories and veterinary and public health officials have monitored all studies closely.

Laboratory Hazards: The exact mode of transmission has not been established. All cases to date have been associated with close contact with horses, their blood or body fluids (Australia) or pigs (Malaysia/Singapore). Hendra and Hendra-like viruses have been isolated from tissues of infected animals in the outbreaks listed above. In the recent outbreak in Malaysia and Singapore, viral antigen has been found in central nervous system, kidney and lung tissues of fatal human cases.⁽¹⁴⁾

Recommended Precautions: Both because of the unknown risks to laboratory workers and the potential impact on indigenous livestock should the virus escape a diagnostic or research laboratory, health officials and laboratory managers should evaluate the need to work with the virus and the containment capability of the facility before undertaking any work with the Hendra, Hendra-like or suspected related viruses. Both human public health and veterinary disease experts should be involved in planning such laboratory studies, and the transport of specimens and isolates to the laboratory location. Until more information is available, handling of human clinical specimens or virus isolation attempts should be

performed in, at least, enhanced BSL-3 facilities by experienced personnel. BSL-4 (suit laboratory or Class III safety cabinet) should be used for any work with infected animals or involving large quantities of virus.⁽¹⁵⁾

Transfer of Agent: For a permit to import this agent, contact CDC. An importation or domestic transfer permit for this agent can be obtained from USDA/APHIS/VS. Contact the Department of Commerce for a permit to export this agent. Laboratory registration with CDC is required before sending or receiving this select agent.

Agent: Hepatitis A Virus, Hepatitis E Virus

Laboratory-associated infections with hepatitis A or E viruses do not appear to be an important occupational risk among laboratory personnel. However, the disease is a documented hazard in animal handlers and others working with chimpanzees and other nonhuman primates which are naturally or experimentally infected.⁽¹⁶⁾ Hepatitis E virus appears to be less of a risk to personnel than hepatitis A virus, except during pregnancy, when infection can result in severe or fatal disease. Workers handling other recently captured, susceptible primates (owl monkeys, marmosets) may also be at risk.

Laboratory Hazards: The agents may be present in feces, saliva, and blood of infected humans and nonhuman primates. Ingestion of feces, stool suspensions, and other contaminated materials is the primary hazard to laboratory personnel. The importance of aerosol exposure has not been demonstrated. Attenuated or avirulent strains of hepatitis A viruses resulting from serial passage in cell culture been described.⁽¹⁷⁾⁽¹⁸⁾

Recommended Precautions: Biosafety Level 2 practices, safety equipment, and facilities are recommended for activities with known or potentially infected feces from humans or nonhuman primates. Animal Biosafety Level 2 practices and facilities are recommended for activities using naturally or experimentally infected nonhuman primates. Animal care personnel should wear gloves and take other appropriate precautions to avoid possible fecal-oral exposure. A licensed inactivated vaccine against hepatitis A is available in Europe; it is available as an investigational vaccine in the U.S., and is recommended for laboratory personnel. Vaccines against hepatitis E are not available for use in humans.

Transfer of Agent: For a permit to import these agents, contact CDC.

Agent: Hepatitis B Virus, Hepatitis C Virus, Hepatitis D Virus

Hepatitis B has been one of the most frequently occurring laboratory-associated infections,⁽¹⁹⁾ and laboratory workers are recognized as a high risk group for acquiring such infections.⁽²⁰⁾ Individuals who are infected with hepatitis B virus are at risk of infection with hepatitis D (delta) virus, which is defective and requires the presence of hepatitis B virus for replication. Hepatitis C infection can occur in the laboratory situation. The prevalence of antibody to hepatitis C is slightly higher in medical care workers than in the

general population. Epidemiologic evidence indicates that hepatitis C is spread predominantly by the parenteral route.⁽²¹⁾⁽²²⁾⁽²³⁾

Laboratory Hazards: Hepatitis B virus may be present in blood and blood products of human origin, in urine, semen, cerebrospinal fluid, and saliva. Parenteral inoculation, droplet exposure of mucous membranes, and contact exposure of broken skin are the primary laboratory hazards. The virus may be stable in dried blood or blood components for several days. Attenuated or avirulent strains have not been identified. Hepatitis C virus has been detected primarily in blood and serum, less frequently in saliva and rarely or not at all in urine or semen. It appears to be relatively unstable to storage at room temperature, repeated freezing and thawing, etc.

Recommended Precautions: Biosafety Level 2 practices, containment equipment and facilities are recommended for all activities utilizing known or potentially infectious body fluids and tissues. Additional primary containment and personnel precautions, such as those described for Biosafety Level 3, may be indicated for activities with potential for droplet or aerosol production and for activities involving production quantities or concentrations of infectious materials. Animal Biosafety Level 2 practices, containment equipment and facilities are recommended for activities utilizing naturally or experimentally infected chimpanzees or other nonhuman primates. Gloves should be worn when working with infected animals and when there is the likelihood of skin contact with infectious materials. Licensed recombinant vaccines against hepatitis B are available and are highly recommended for and offered to laboratory personnel.⁽²⁴⁾ Vaccines against hepatitis C and D are not yet available for use in humans.

In addition to these recommended precautions, persons working with HBV, HCV, or other bloodborne pathogens should consult the OSHA Bloodborne Pathogen Standard.⁽²⁵⁾ Questions related to interpretation of this Standard should be directed to federal, regional or state OSHA offices.

Transfer of Agent: For a permit to import these agents, contact CDC.

Agent: Herpesvirus simiae (Cercopithecine herpesvirus [CHV-1], B-virus)

CHV-1 is a naturally occurring alphaherpesvirus infecting free-living or captive macaques including *Macaca mulatta*, *M. fascicularis*, and other members of the genus. In macaques it is associated with acute vesicular oral lesions, as well as latent and often recrudescent infection.⁽²⁶⁾ Human infection has been documented in at least 50 instances, usually with a lethal outcome or serious sequelae from encephalitis.⁽²⁷⁾⁽²⁸⁾⁽²⁹⁾⁽³⁰⁾⁽³¹⁾⁽³²⁾⁽³³⁾ Twenty-nine fatal cases of human infections (at a 58% fatality rate) with CHV-1 have been reported.⁽³⁴⁾⁽³⁵⁾⁽³⁶⁾⁽³⁷⁾

Although CHV-1 presents a potential hazard to laboratory personnel working with the agent, laboratory-associated human infections with CHV-1 have, with rare exceptions, been limited to those having direct contact with macaques. Primary macaque cell cultures,

including commercially-prepared rhesus monkey kidney cells, occasionally may be asymptotically infected with CHV-1 and have been implicated in one human case.⁽³⁸⁾ Specific periodic training in risk assessment, understanding the modes of CHV-1 transmission and exposure, and proper use of personal protective equipment is highly recommended for all persons working with or having contact with macaques, their tissues, and their potentially-contaminated environments (including cages, enrichment toys, and waste materials). Appropriate immediate first-aid training and supplies and emergency medical support is necessary.

Laboratory Hazards: Asymptomatic shedding accounts for most transmission among monkeys and to human workers, although the highest risk of acquiring CHV-1 from macaques is through the bite of an infected monkey with active lesions. Contamination of broken skin or mucous membranes with oral, ocular, or urogenital secretions from infected macaques during their primary or recedescant infections is also dangerous and has caused at least one occupational fatality.⁽³⁹⁾ Stability of viral particles on cages and other surfaces is not known, but the potential hazard must be recognized for cuts or abrasions from these potentially-contaminated surfaces. Other alphaherpesviruses are not thought to persist in the environment for any duration. Experimental work with animals indicates that the importance of aerosol exposure of CHV-1 is likely to be minimal. Attenuated or avirulent strains have not been identified. The agent also may be present in thoracic and abdominal viscera and nerve tissues of naturally infected macaques. These tissues, and the cultures prepared from them, are potential hazards.⁽⁴⁰⁾

Recommended Precautions: Biosafety Level 2 practices and facilities are recommended for all activities involving the use or manipulation of tissues, body fluids, and primary tissue culture materials from macaques. Additional practices and personnel precautions, such as those detailed for Biosafety Level 3, are recommended for activities involving the use or manipulation of any material known or suspected to contain CHV-1, including *in vitro* propagation of the virus for diagnosis. It would be prudent to confine manipulations of positive cultures which would contain high-titered virus to a BSL-4 facility (Class III BSC or suit laboratory; see Section III), depending on the judgement of the laboratory director. Biosafety Level 4 practices and facilities are recommended for activities involving the propagation and manipulation of production quantities or concentrates of CHV-1.

All macaque colonies, even those thought to be free of CHV-1 antibody, should be presumed to be naturally infected. Animals with oral lesions suggestive of active B-virus infection should be identified and handled with extreme caution. Studies with animals experimentally infected with CHV-1 should be conducted at ABSL-3. Guidelines are available for safely working with macaques and should be consulted.⁽⁴¹⁾⁽⁴²⁾ The wearing of gloves, masks, and laboratory coats or coveralls is recommended for all personnel while working with non-human primates - especially macaques and other Old World species - and for all persons entering animal rooms where non-human primates are housed. To minimize the potential for mucous membrane exposure,⁽⁴³⁾ some form of barrier must be utilized to prevent droplet splashes to eyes, mouth, and nasal passages. Types and use of personal protective equipment (e.g., goggles, glasses with solid side shields, or wrap-around face shields worn in conjunction with masks or respirators) must be determined

with reference to the institutional hazard assessment. The specifications of the equipment must be balanced with the work to be performed so that the barriers selected do not increase work place risk by obscuring vision and contributing to increased risk of bites, needle sticks, or animal scratches.

Antiviral drugs have shown promise in the therapy of rabbits infected with *H. simiae*, and limited clinical experience⁽⁴⁴⁾⁽⁴⁵⁾ suggest that this may extend to man.⁽⁴⁶⁾⁽⁴⁷⁾ Because of the seriousness of infection with this virus, experienced medical personnel should be available for consultation to manage incidents involving exposure to the agent or suspected infections. Human-to-human transmission has been documented in one case, indicating that precautions should be taken with vesicle fluids, oral secretions, and conjunctival secretions of infected persons.⁽⁴⁸⁾ Vaccines are not available for use in humans.

Transfer of Agent: For a permit to import this agent, contact CDC.

Agent: Human Herpesviruses

The herpesviruses are ubiquitous human pathogens and are commonly present in a variety of clinical materials submitted for virus isolation. While few of these viruses are demonstrated causes of clinical laboratory-associated infections, they are primary as well as opportunistic pathogens, especially in immunocompromised hosts. Herpes simplex viruses 1 and 2 and varicella virus pose some risk via direct contact and/or aerosols; cytomegalovirus and Epstein-Barr virus pose relatively low infection risks to laboratory personnel. The risk of laboratory infection from herpesviruses 6 and 7 is not known. Although this diverse group of indigenous viral agents does not meet the criteria for inclusion in agent-specific summary statements (i.e., demonstrated or high potential hazard for laboratory-associated infection; grave consequences should infection occur), the frequency of their presence in clinical materials and their common use in research warrants their inclusion in this publication.

Laboratory Hazards: Clinical materials and isolates of herpesviruses may pose a risk of infection following ingestion, accidental parenteral inoculation, droplet exposure of the mucous membranes of the eyes, nose, or mouth, or inhalation of concentrated aerosolized materials. Clinical specimens containing the more virulent *Herpesvirus simiae* (B-virus) may be inadvertently submitted for diagnosis of suspected herpes simplex infection. This virus has also been found in cultures of primary rhesus monkey kidney cells. Cytomegalovirus may pose a special risk during pregnancy because of potential infection of the fetus.

Recommended Precautions: Biosafety Level 2 practices, containment equipment, and facilities are recommended for activities utilizing known or potentially infectious clinical materials or cultures of indigenous viral agents that are associated or identified as a primary pathogen of human disease. Although there is little evidence that infectious aerosols are a significant source of laboratory-associated infections, it is prudent to avoid the generation of aerosols during the handling of clinical materials or isolates, or during the

necropsy of animals. Primary containment devices (e.g., biological safety cabinets) constitute the basic barrier protecting personnel from exposure to infectious aerosols.

Transfer of Agent: For a permit to import these agents, contact CDC.

Agent: Influenza

Laboratory-associated infections with influenza are not normally documented in the literature, but by informal accounts and published reports are known to have occurred, particularly when new strains showing antigenic drift or shift are introduced into a laboratory for diagnostic/research purposes. ⁽⁴⁹⁾ Laboratory animal-associated infections are not reported; however, there is a high possibility of human infection from infected ferrets and vice-versa.

Laboratory Hazards: The agent may be present in respiratory tissues or secretions of humans or most infected animals, and in the cloaca of many infected avian species. The virus may be disseminated in multiple organs in some infected animal species. The primary laboratory hazard is inhalation of virus from aerosols generated by infected animals, or by aspirating, dispensing, or mixing virus-infected samples. Genetic manipulation has the potential for altering the host range, pathogenicity, and antigenic composition of influenza viruses. There is unknown potential for introducing into man transmissible viruses with novel antigenic composition.

Recommended Precautions: Biosafety Level 2 practices and facilities are recommended when receiving and inoculating routine laboratory diagnostic specimens. Autopsy material should be handled in a biological safety cabinet using Biosafety Level 2 procedures.

Activities Utilizing Noncontemporary Virus Strains: Biosafety considerations should take into account the available information about infectiousness and virulence of the strains being used, and the potential for harm to the individual or society in the event that laboratory-acquired infection and subsequent transmission occurs. Research or production activities utilizing contemporary strains may be safely performed using Biosafety Level 2 containment practices. Susceptibility to infection with older noncontemporary human strains, with recombinants, or with animal isolates warrant the use of Biosafety Level 2 containment procedures. However, there is no evidence for laboratory-acquired infection with reference strains A/PR/8/34 and A/WS/33, or its commonly used neurotropic variants.

Transfer of Agent: For a permit to import this agent, contact CDC. An importation or domestic transfer permit for this agent can be obtained from USDA/APHIS/VS.

Agent: Lymphocytic Choriomeningitis Virus

Laboratory-associated infections with LCM virus are well documented in facilities where infections occur in laboratory rodents - especially mice, hamsters and guinea pigs. ⁽⁵⁰⁾⁽⁵¹⁾⁽⁵²⁾

Nude and SCID mice may pose a special risk of harboring silent chronic infections. Cell cultures that inadvertently have become infected represent a potential source of infection and dissemination of the agent. Natural infections are found in nonhuman primates, including macaques and marmosets (*Callitrichid* hepatitis virus is a lymphocytic choriomeningitis virus) and may be fatal to marmoset monkeys. Swine and dogs are less important vectors.

Laboratory Hazards: The agent may be present in blood, cerebrospinal fluid, urine, secretions of the nasopharynx, feces and tissues of infected animal hosts and possibly man. Parenteral inoculation, inhalation, contamination of mucous membranes or broken skin with infectious tissues or fluids from infected animals are common hazards. Aerosol transmission is well documented.⁽⁵³⁾ The virus may pose a special risk during pregnancy because of potential infection of the fetus.

Recommended Precautions: Biosafety Level 2 practices and facilities are suitable for activities utilizing known or potentially infectious body fluids, and for cell culture passage of laboratory-adapted, mouse brain-passaged strains. Animal Biosafety Level 2 practices and facilities are suitable for studies in adult mice with mouse brain-passaged strains. However, additional primary containment and personnel precautions, such as those described for Biosafety Level 3, are indicated for activities with high potential for aerosol production, or involving production quantities or concentrations of infectious materials; and for manipulation of infected transplantable tumors, field isolates and clinical materials from human cases. Animal Biosafety Level 3 practices and facilities are recommended for work with infected hamsters. Vaccines are not available for use in humans.⁽⁵⁴⁾

Transfer of Agent: For a permit to import this agent, contact CDC.

Agent: Poliovirus

Laboratory-associated infections with polioviruses are uncommon and have been limited to unvaccinated laboratory personnel working directly with the agent.⁽⁵⁵⁾ There have been at least 12 documented laboratory associated poliovirus infections, including two deaths, between 1941 and 1976.⁽⁵⁶⁾ However, since only ~1% of infections with poliovirus result in disease, without laboratory confirmation it is impossible to estimate reliably the numbers of laboratory-acquired infections. With the available effective vaccines and vastly improved laboratory facilities, technologies and procedures, it is likely that such infections are now rare among laboratory workers. However, if laboratory workers do become infected, they provide a source of virus to exposed unvaccinated persons in the community.⁽⁵⁷⁾ Laboratory animal-associated infections have not been reported,⁽⁵⁸⁾ however, naturally or experimentally infected nonhuman primates could provide a source of infection to exposed unvaccinated persons. Transgenic mice expressing the human receptor for polioviruses can be experimentally infected by injection with virulent polioviruses and may be a potential source of human infection.

Laboratory Hazards: The agent is present in the feces and in throat secretions of infected persons. Ingestion or parenteral inoculation of infectious tissues or fluids by non-immunized personnel are the primary risks of infection in the laboratory. The importance of aerosol exposure is not known; it has not been reported as a hazard. Laboratory exposures pose negligible risk to appropriately immunized persons.

Recommended Precautions: Biosafety Level 2 practices and facilities are recommended for all activities utilizing known or potentially infectious culture fluids and clinical materials involving known or suspected wild-type strains. All laboratory personnel working directly with the agent must have documented polio vaccination or demonstrated serologic evidence of immunity to all three poliovirus types.⁽⁵⁹⁾ Animal Biosafety Level 2 practices and facilities are recommended for studies of virulent viruses in animals. Unless there are strong scientific reasons for working with virulent polioviruses (which have been eradicated from the United States), laboratories should use the attenuated Sabin oral poliovirus vaccine strains. These pose no significant risk to immunized laboratory personnel.

The World Health Organization (WHO) has issued guidance documents⁽⁶⁰⁾ related to work with wild poliovirus in the near and long-term future. Starting in 1999, BSL-2/polio laboratories should be established for all workers wishing to manipulate wild poliovirus. BSL-2/polio follows traditional BSL-2 requirements for facilities, practices, and procedures, with the following additions: 1) all poliovirus stocks and potentially infectious materials are disposed of when there are no programmatic or research needs for retention; 2) all persons entering the laboratory are fully immunized against polio; 3) access to the laboratory is restricted; 4) all wild poliovirus retained in the laboratory is inventoried and stored in a separate secure area with limited access; 5) only viruses that are readily identifiable by molecular methods are used if wild virus reference strains or working stocks are required; and 6) Appropriate sterilization and/or incineration is used for disposing of wild polioviruses, infectious materials, and potentially infectious materials. All laboratories wishing to retain wild poliovirus infectious or potentially infectious materials must begin implementing *BSL-3/polio* containment procedures one year after detection of the last wild poliovirus and provide documentation of implementation by the second year. Laboratories wishing to qualify as a BSL-3/polio facility and retain wild poliovirus infectious materials must then be listed on Agency/Institutional and National Inventories. Laboratories not wishing to convert to BSL-3/polio containment must destroy all wild poliovirus and potentially infectious materials by autoclaving or incineration. Alternatively, laboratories may contact a WHO-designated BSL-3/polio repository to arrange for transfer and storage of selected materials. When OPV immunization stops, all work with wild poliovirus will be restricted to maximum containment (BSL-4) laboratories. These may be suit or cabinet laboratories (Section III).

Transfer of Agent: For a permit to import this agent, contact CDC.

Agent: Poxviruses

Sporadic cases of laboratory-associated infections with pox viruses (smallpox, vaccinia, yaba, tanapox) have been reported.⁽⁶¹⁾ Epidemiological evidence suggests that transmission of monkeypox virus to humans from nonhuman primates or rodents to humans may have occurred in nature, but not in the laboratory setting. Naturally or experimentally infected laboratory animals are a potential source of infection to exposed unvaccinated laboratory personnel. Genetically engineered recombinant vaccinia viruses pose an additional potential risk to laboratory personnel, through direct contact or contact with clinical materials from infected volunteers or animals.

Laboratory Hazards: The agents may be present in lesion fluids or crusts, respiratory secretions, or tissues of infected hosts. Ingestion, parenteral inoculation, and droplet or aerosol exposure of mucous membranes or broken skin with infectious fluids or tissues, are the primary hazards to laboratory and animal care personnel. Some poxviruses are stable at ambient temperature when dried and may be transmitted by fomites.

Recommended Precautions: The possession and use of variola viruses is restricted to the World Health Organization Collaborating Center for Smallpox and Other Poxvirus Infections, located at the Centers for Disease Control and Prevention, Atlanta, Georgia. Biosafety Level 2 practices and facilities are recommended for all activities involving the use or manipulation of poxviruses, other than variola, that pose an infection hazard to humans. All persons working in or entering laboratory or animal care areas where activities with vaccinia, monkey pox, or cow pox viruses are being conducted should have documented evidence of satisfactory vaccination within the preceding ten years.⁽⁶²⁾⁽⁶³⁾ Activities with vaccinia, cow pox, or monkey pox viruses, in quantities or concentrations greater than those present in diagnostic cultures, may also be conducted at Biosafety Level 2 by immunized personnel, provided that all manipulations of viable materials are conducted in Class I or II biological safety cabinets. Immunosuppressed individuals are at greater risk of severe disease if infected with a poxvirus.⁽⁶⁴⁾

Transfer of Agent: For a permit to import these agents, contact CDC. Contact the Department of Commerce for a permit to export these agents. Laboratory registration with CDC is required before sending or receiving these select agents.

Agent: Rabies Virus

Laboratory-associated infections are extremely rare. Two have been documented. Both resulted from presumed exposure to high titered infectious aerosols, one generated in a vaccine production facility⁽⁶⁵⁾ and the other in a research facility.⁽⁶⁶⁾ Naturally or experimentally infected animals, their tissues, and their excretions are a potential source of exposure for laboratory and animal care personnel.

Laboratory Hazards: The agent may be present in all tissues of infected animals. Highest titers are present in CNS tissue, salivary glands, and saliva. Accidental parenteral

inoculation, cuts, or sticks with contaminated laboratory equipment, bites by infected animals, and exposure of mucous membranes or broken skin to infectious tissue or fluids, are the most likely sources for exposure of laboratory and animal care personnel. Infectious aerosols have not been a demonstrated hazard to personnel working with clinical materials and conducting diagnostic examinations. Fixed and attenuated strains of virus are presumed to be less hazardous, but the only two recorded cases of laboratory associated rabies resulted from exposure to a fixed Challenge Virus Standard (CVS) and an attenuated strain derived from SAD (Street Alabama Dufferin) strain, respectively. ⁽⁶⁷⁾⁽⁶⁸⁾

Recommended Precautions: Biosafety Level 2 practices and facilities are recommended for all activities utilizing known or potentially infectious materials. Immunization is recommended for all individuals prior to working with rabies virus or infected animals, or engaging in diagnostic, production, or research activities with rabies virus. Immunization is also recommended for all individuals entering or working in the same room where rabies virus or infected animals are used. While it is not always feasible to open the skull or remove the brain of an infected animal within a biological safety cabinet, it is pertinent to wear heavy protective gloves to avoid cuts or sticks from cutting instruments or bone fragments, and to wear a face shield to protect the mucous membranes of the eyes, nose, and mouth from exposure to infectious droplets or tissue fragments. If a Stryker saw is used to open the skull, avoid contacting the brain with the blade of the saw. Additional primary containment and personnel precautions, such as those described for Biosafety Level 3, may be indicated for activities with a high potential for droplet or aerosol production, and for activities involving production quantities or concentrations of infectious materials.

Transfer of Agent: For a permit to import this agent, contact CDC.

Agent: Retroviruses, including Human and Simian Immunodeficiency Viruses (HIV and SIV)

Data on occupational HIV transmission in laboratory workers are collected through two CDC-supported national surveillance systems: surveillance for 1) AIDS and 2) HIV-infected persons who may have acquired their infection through occupational exposures. For surveillance purposes, laboratory workers are defined as those persons, including students and trainees, who have worked in a clinical or HIV laboratory setting anytime since 1978. Cases reported in these two systems are classified as either documented or possible occupational transmission. Those classified as documented occupational transmission had evidence of HIV seroconversion (a negative HIV-antibody test at the time of the exposure which converted to positive) following a discrete percutaneous or mucocutaneous occupational exposure to blood, body fluids, or other clinical or laboratory specimens. As of June 1998, CDC had reports of 16 laboratory workers (all clinical) in the United States with documented occupational transmission. ⁽⁶⁹⁾

In 1992, two workers in different laboratories were reported to have developed antibodies to simian immunodeficiency virus (SIV) following exposures. One was associated with a

needle stick which occurred while the worker was manipulating a blood-contaminated needle after bleeding an SIV-infected macaque monkey.⁽⁷⁰⁾ The other involved a laboratory worker who handled macaque SIV-infected blood specimens without gloves. Though no specific incident was recalled, this worker had dermatitis on the forearms and hands while working with the infected blood specimens.⁽⁷¹⁾ The first worker seroconverted and has no evidence of persistent SIV infection. The second worker has been seropositive for at least nine years with no evidence of illness or immunological incompetence.

Recent publications⁽⁷²⁾⁽⁷³⁾ have identified the prevalence (4/231, 1.8%) of infection with simian foamy viruses (SFV) among humans occupationally exposed to nonhuman primates. Evidence of SFV infections included seropositivity, proviral DNA detection, and isolation of foamy virus. The infecting SFV originated from an African green monkey (one person) and baboons (three people). These infections have not as yet resulted in either disease or sexual transmission, and may represent benign endpoint infections.

Laboratory Hazards: HIV has been isolated from blood, semen, saliva, tears, urine, cerebrospinal fluid, amniotic fluid, breast milk, cervical secretion, and tissue of infected persons and experimentally infected nonhuman primates.⁽⁷⁴⁾ CDC has recommended that blood and body fluid precautions be used consistently when handling any blood-contaminated specimens.⁽⁷⁵⁾⁽⁷⁶⁾ This approach, referred to as "universal precautions," precludes the need to identify clinical specimens obtained from HIV-positive patients or to speculate as to the HIV status of a specimen.

Although the risk of occupationally acquired HIV is primarily through exposure to infected blood, it is also prudent to wear gloves when manipulating other body fluids such as feces, saliva, urine, tears, sweat, vomitus, and human breast milk. This also reduces the potential for exposure to other microorganisms that may cause other types of infections.

In the laboratory, virus should be presumed to be present in all blood or clinical specimens contaminated with blood, in any unfixed tissue or organ (other than intact skin) from a human (living or dead), in HIV cultures, in all materials derived from HIV cultures, and in/on all equipment and devices coming into direct contact with any of these materials.

SIV has been isolated from blood, cerebrospinal fluid, and a variety of tissues of infected nonhuman primates. Limited data exist on the concentration of virus in semen, saliva, cervical secretions, urine, breast milk, and amniotic fluid. In the laboratory, virus should be presumed to be present in all SIV cultures, in animals experimentally infected or inoculated with SIV, in all materials derived from HIV or SIV cultures, and in/on all equipment and devices coming into direct contact with any of these materials.⁽⁷⁷⁾

In the laboratory, the skin (especially when scratches, cuts, abrasions, dermatitis, or other lesions are present) and mucous membranes of the eye, nose, and mouth should be considered as potential pathways for entry of these retroviruses. Whether infection can occur via the respiratory tract is unknown. The need for using sharps in the laboratory should be evaluated. Needles, sharp instruments, broken glass, and other sharp objects must be carefully handled and properly discarded. Care must be taken to avoid spilling and

splashing infected cell-culture liquid and other virus-containing or potentially infected materials.⁽⁷⁸⁾

Recommended Precautions:

In addition to the following recommended precautions, persons working with HIV, SIV, or other bloodborne pathogens should consult the OSHA Bloodborne Pathogen Standard.⁽⁷⁹⁾ Questions related to interpretation of this Standard should be directed to Federal, regional or state OSHA offices.

1. BSL-2 standard and special practices, containment equipment and facilities are recommended for activities involving **all** blood-contaminated clinical specimens, body fluids and tissues from **all** humans, or from HIV- or SIV-infected or inoculated laboratory animals.
2. Activities such as producing research-laboratory-scale quantities of HIV or SIV, manipulating concentrated virus preparations, and conducting procedures that may produce droplets or aerosols, are performed in a BSL-2 facility, but using the additional practices and containment equipment recommended for BSL-3.
3. Activities involving industrial-scale volumes or preparation of concentrated HIV or SIV are conducted in a BSL-3 facility, using BSL-3 practices and containment equipment.
4. Nonhuman primates or other animals infected with HIV or SIV are housed in ABSL-2 facilities using ABSL-2 special practices and containment equipment.

Additional Comments:

1. There is no evidence that laboratory clothing poses a risk for retrovirus transmission; however, clothing that becomes contaminated with HIV or SIV should be decontaminated before being laundered or discarded. Laboratory personnel must remove laboratory clothing before going to non-laboratory areas.
2. Work surfaces are decontaminated with an appropriate chemical germicide after procedures are completed, when surfaces are overtly contaminated, and at the end of each work day. Many commercially available chemical disinfectants ⁽⁸⁰⁾⁽⁸¹⁾⁽⁸²⁾⁽⁸³⁾⁽⁸⁴⁾ can be used for decontaminating laboratory work surfaces and some laboratory instruments, for spot cleaning of contaminated laboratory clothing, and for spills of infectious materials. Prompt decontamination of spills should be standard practice.
3. Human serum from any source that is used as a control or reagent in a test procedure should be handled at BSL-2.
4. It is recommended that all institutions establish written policies regarding the management of laboratory exposure to HIV and SIV in conjunction with applicable

federal, state and local laws. Such policies should consider confidentiality, consent for testing, administration of appropriate prophylactic drug therapy,⁽⁸⁵⁾ counseling, and other related issues. If a laboratory worker has a parenteral or mucous-membrane exposure to blood, body fluid, or viral-culture material, the source material should be identified and, if possible, tested for the presence of virus. If the source material is positive for HIV antibody, virus, or antigen, or is not available for examination, the worker should be counseled regarding the risk of infection and should be evaluated clinically and serologically for evidence of HIV infection. Post-exposure prophylaxis should be offered according to the latest guidelines. The worker should be advised to report and seek medical evaluation of any acute febrile illness that occurs within 12 weeks after the exposure.⁽⁸⁶⁾ Such an illness - particularly one characterized by fever, rash, or lymphadenopathy - may indicate recent HIV infection. If the initial (at time of exposure) test is negative, the worker should be retested 6 weeks after the exposure and periodically thereafter (i.e., at 12 weeks and 6, 9 and 12 months after exposure). During this follow-up period exposed workers should be counseled to follow Public Health Service recommendations for preventing transmission of HIV.⁽⁸⁷⁾⁽⁸⁸⁾⁽⁸⁹⁾⁽⁹⁰⁾⁽⁹¹⁾

5. Other primary and opportunistic pathogenic agents may be present in the body fluids and tissues of persons infected with HIV. Laboratory workers should follow accepted biosafety practices to ensure maximum protection against inadvertent laboratory exposure to agents that may also be present in clinical specimens or in specimens obtained from nonhuman primates.⁽⁹²⁾⁽⁹³⁾⁽⁹⁴⁾

Research involving other human (i.e., human T-lymphotrophic virus types I and II) and simian retroviruses occurs in many laboratories. Recently, surveillance for such infections revealed occupational exposure and infection by simian foamy virus among animal caretakers at laboratory research facilities.⁽⁹⁵⁾⁽⁹⁶⁾ The precautions outlined above are sufficient while working with these agents.

Laboratory work with retroviral vectors, especially those containing full-length infectious molecular genomes (HIV-1), should be handled in BSL-2 facilities under BSL-2/3 practice. This includes infectious clones derived from nonhuman viruses, but possessing xenotropic (especially for human cells) host ranges.

Transfer of Agent: For a permit to import these agents, contact CDC.

Agent: Transmissible Spongiform Encephalopathies (Creutzfeldt-Jakob, kuru and related agents)

Laboratory-associated infections with the transmissible spongiform encephalopathies (prion diseases) have not been documented. However, there is evidence that Creutzfeldt-Jakob disease (CJD) has been transmitted iatrogenically to patients by corneal transplants, dura mater grafts and growth hormone extracted from human pituitary glands, and by exposure to contaminated electroencephalographic electrodes.⁽⁹⁷⁾ Infection is always fatal. There is no known nonhuman reservoir for CJD or kuru. Nonhuman primates and other

laboratory animals have been infected by inoculation, but there is no evidence of secondary transmission. Scrapie of sheep and goats, bovine spongiform encephalopathy and mink encephalopathy are transmissible spongiform encephalopathies of animals that are similar to the human transmissible diseases. However, there is no evidence that the animal diseases can be transmitted to man. (See also Section VII-D, Prions.)

Laboratory Hazards: High titers of a transmissible agent have been demonstrated in the brain and spinal cord of persons with kuru. In persons with Creutzfeldt-Jakob disease and its Gerstmann-Sträussler-Schenker Syndrome variants, a similar transmissible agent has been demonstrated in the brain, spleen, liver, lymph nodes, lungs, spinal cord, kidneys, cornea and lens, and in spinal fluid and blood. Accidental parenteral inoculation, especially of nerve tissues, including formalin-fixed specimens, is extremely hazardous. Although non-nerve tissues are less often infectious, all tissues of humans and animals infected with these agents should be considered potentially hazardous. The risk of infection from aerosols, droplets, and exposure to intact skin, gastric and mucous membranes is not known; however, there is no evidence of contact or aerosol transmission. These agents are characterized by extreme resistance to conventional inactivation procedures including irradiation, boiling, dry heat and chemicals (formalin, betapropiolactone, alcohols); however, they are inactivated by 1 N NaOH, sodium hypochlorite (2% free chlorine concentration) and steam autoclaving at 132°C for 4.5 hours.

Recommended Precautions: Biosafety Level 2 practices and facilities are recommended for all activities utilizing known or potentially infectious tissues and fluids from naturally infected humans and from experimentally infected animals. Extreme care must be taken to avoid accidental autoinoculation or other traumatic parenteral inoculations of infectious tissues and fluids.⁽⁹⁸⁾ Although there is no evidence to suggest that aerosol transmission occurs in the natural disease, it is prudent to avoid the generation of aerosols or droplets during the manipulation of tissues or fluids, and during the necropsy of experimental animals. It is further strongly recommended that gloves be worn for activities that provide the opportunity for skin contact with infectious tissues and fluids. Formaldehyde-fixed and paraffin-embedded tissues, especially of the brain, remain infectious. It is recommended that formalin-fixed tissues from suspected cases of transmissible encephalopathy be immersed in 96% formic acid for 30 minutes before histopathologic processing.⁽⁹⁹⁾ Vaccines are not available for use in humans.⁽¹⁰⁰⁾

Transfer of Agent: For a permit to import these agents, contact CDC. An importation or domestic transfer permit for Bovine spongiform encephalopathy can be obtained from USDA/APHIS/VS.

Agent: Vesicular Stomatitis Virus

A number of laboratory-associated infections with indigenous strains of VSV have been reported.⁽¹⁰¹⁾ Laboratory activities with such strains present two different levels of risk to laboratory personnel and are related, at least in part, to the passage history of the strains utilized. Activities utilizing infected livestock, their infected tissues, and virulent isolates

from these sources are a demonstrated hazard to laboratory and animal care personnel.⁽¹⁰²⁾⁽¹⁰³⁾ Rates of seroconversion and clinical illness in personnel working with these materials are high.⁽¹⁰⁴⁾ Similar risks may be associated with exotic strains such as Piry.⁽¹⁰⁵⁾

In contrast, anecdotal information indicates that activities with less virulent laboratory-adapted strains (e.g., Indiana, San Juan and Glasgow) are rarely associated with seroconversion or illness. Such strains are commonly used by molecular biologists, often in large volumes and high concentrations, under conditions of minimal or no primary containment. Some strains of VSV are considered restricted organisms by USDA regulations (9CFR 122.2). Experimentally infected mice have not been a documented source of human infection.

Laboratory Hazards: The agent may be present in vesicular fluid, tissues, and blood of infected animals and in blood and throat secretions of infected humans. Exposure to infectious aerosols, infected droplets, direct skin and mucous membrane contact with infectious tissues and fluids, and accidental autoinoculation, are the primary laboratory hazards associated with virulent isolates. Accidental parenteral inoculation and exposure to infectious aerosols represent potential risks to personnel working with less virulent laboratory-adapted strains.

Recommended Precautions: Biosafety Level 3 practices and facilities are recommended for activities involving the use or manipulation of infected tissues and virulent isolates from naturally or experimentally infected livestock. Gloves and respiratory protection are recommended for the necropsy and handling of infected animals. Biosafety Level 2 practices and facilities are recommended for activities utilizing laboratory-adapted strains of demonstrated low virulence. Vaccines are not available for use in humans.

Transfer of Agent: Contact the Department of Commerce for a permit to export this agent. An importation or domestic transfer permit for this agent can be obtained from USDA/APHIS/VS.

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