Advisory Committee on Dangerous Pathogens

Working safely with simians: Management of infection risks

Specialist supplement to:
Working safely with research animals:
Management of infection risks

HSE BOOKS

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This guidance was prepared, in consultation with HSE, by the Advisory Committee on Dangerous Pathogens (ACDP). It includes an explanation of the law in simple terms. The ACDP was appointed by the Health and Safety Commission as part of its formal advisory structure and by Health Ministers.

The guidance represents what is considered to be good practice. It has been agreed by the Commission and the Health Minister. Following this guidance is not compulsory and you are free to take other action. But if you do follow it you will normally be doing enough to comply with the law. Health and Safety inspectors seek to secure compliance with the law and may refer to this guidance as illustrating good practice.

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PREFACE

Guidance on infections associated with simians (monkeys and apes) was first issued by the Medical Research Council (MRC) in 1985 and revised in 1990. Following several outbreaks of a novel strain of Ebola virus in primate colonies in the US and Italy (all in macaques imported from the Philippines), the Advisory Committee on Dangerous Pathogens (ACDP), with the full agreement of the MRC, have revised and updated the guidance.

This guidance is aimed at all those working with simians (eg for pharmaceutical research and development, studies on infectious disease, behavioural studies, immunological and cancer research) and only describes those hazards associated with working with simians. It should be seen as a supplement to the ACDP publication *Working safely with research animals: Management of infection risks*[1] which applies to work with **all** infected or potentially infected animals, including simians.

This guidance does not apply to simians kept in zoos and similar premises, but the underlying principles of COSHH will apply. Further guidance may be obtained from HSE.

INTRODUCTION

The hazards associated with simians

1 Simians naturally harbour a range of infectious agents and may pose a significant risk to those exposed to them. Some naturally occurring infections of simians are known to be especially harmful. Simian herpes B virus *(Herpesvirus simiae)*, for example, has been responsible for a number of deaths in laboratory and animal workers. Other agents of concern are the rabies virus and the filoviruses, Marburg and Ebola, which have caused severe outbreaks of haemorrhagic fever with a high mortality rate in both Africa and Europe. The various herpes viruses found in vervets and baboons, whose pathogenicity is uncertain, should be assumed to be potentially harmful to humans.

2 A number of different retroviruses have also been isolated from simians. Simian T-cell lymphotropic virus (STLV) and simian immunodeficiency virus (SIV) are very similar to their human counterparts HTLV and HIV, and SIV has infected laboratory workers (although there is no evidence of any clinical illness to date). More recently, a new parvovirus, closely related to human parvovirus B19, has been recovered from cynomolgus monkeys suffering from anaemia. More familiar pathogens may also be carried by simians including mycobacteria (TB or TB-like infections), *Shigella, Salmonella, Campylobacter* and various protozoa and helminths. Staff should therefore be aware of the possibility of spread of disease in this manner. The guidance contains summary statements on the main infectious agents which may be associated with simians.

3 Simians (monkeys and apes, including New World primates) may be separated into two broad groups, the Old World and New World species. The latter tend to be smaller (eg marmosets) and are not as likely to be infected with serious zoonotic agents as Old World species (eg macaques) which tend to be larger and more difficult to house and handle. A particular pathogen that is only found in one group is not likely to be found in the other unless there are deficiencies in the quarantine or handling arrangements.

Legal duties

4 Employers of staff who work with simians must take account of their general duties under the Health and Safety at Work etc Act 1974, as well as other more specific legislation. In particular, the Control of Substances Hazardous to Health Regulations 1994 (COSHH) provide a framework of actions designed to control the risk from a range of hazardous substances, including biological agents. They require employers to assess the risk of infection both to employees and to others who may be affected by the work, for example, waste-disposal workers, service engineers and members of the public. When a risk has been identified, there is a duty to select and properly apply appropriate prevention or control measures.

5 In addition, employees (and non-employees such as students or visiting researchers) must receive suitable and sufficient information, instruction and training about the risks they may encounter at work, including the handling of simians. An appropriate level of supervision should be maintained. Subject to assessment, there may also be the need to provide health surveillance for employees and offer them vaccinations.

6 This guidance is aimed primarily at the protection of human health and safety but full account should be taken of the requirements of the Animals (Scientific Procedures) Act 1986 (A(SP)A) which is concerned with the protection of animals used for experimental or other scientific purposes. The

advice of the named veterinary surgeon (NVS) should be sought on matters relating to the health and welfare of animals, including simians, housed in facilities designated under the 1986 Act. Guidance on other legislation relevant to work with biological agents and animals can be found in the ACDP publication *Working safely with research animals: Management of infection risks.*[1]

Local codes of practice

7 Having completed a suitable and sufficient assessment of risks, a local code of practice appropriate to all aspects of the work with simians should be drawn up in consultation with the employees concerned or their safety representatives. It should take full account of all relevant health and safety law and the containment requirements in COSHH for work with infected or potentially infected animals.

8 The following points are intended as a guide to the main areas that should be included in any local code of practice. It is not exhaustive and local conditions and considerations will determine the details of a code.

(a) *Introduction* - this could usefully state the reasons for having a local code and its importance, and refer to the existence of other relevant safety documents such as this and other appropriate guidance from the ACDP. Staff must be made aware of the potential risks and receive suitable information, instruction and training.

(b) *Staff health* - should include the requirements for immunisation of staff, for medical examinations and the need for staff to carry a personal record card to alert medical practitioners that they may be exposed to unusual infectious hazards at work. It is also necessary to make employees aware that their illnesses may be transmitted to the animals in their care.

(c) *Protective clothing* - should specify the clothing and other protective equipment to be worn for the various tasks associated with working with simians and should also explain the procedures to be adopted for changing clothing and decontamination procedures. Staff should always wear adequate protective clothing when in contact with simians and used cages, etc. Where assessment shows it to be necessary, specific items of personal protective equipment ([PPE], eg gloves, face-shields, respiratory equipment [RPE], etc) should also be supplied.

(d) *General procedures* - the categories of staff authorised to handle the monkeys, the procedures for disposal of waste, general hygiene and transport of animals within the establishment should be described. Staff who handle simians should be trained to an appropriate level of competence and an appropriate level of supervision should be maintained by a person knowledgeable about the dangers of animal diseases transmissible to humans.

(e) *Cleaning of animal rooms* - should specify cleaning procedures, the precautions to be taken by staff and the types of disinfectants that are to be used.

(f) *Handling of animals* - should cover procedures to be used, including transportation of animals and the requirements for the use of anaesthesia.

(g) *Experimental animals* - should include the specific authorisations required prior to the start of experiments and the level of animal containment required.

(h) *Escape of animals, fire and accidents (eg bites)* - this should give clear instructions to be followed, together with the telephone number(s) of relevant personnel and services who should be notified. It should be made clear that medical and veterinary advice is accessible at all times. Sources of such advice should be identified in the written code of practice and contact names and numbers should also be displayed clearly. It is important to ensure that the information is up to date.

(i) *Procedures during isolation* - should include procedures for the authorisation of post-mortem examinations of animals that die when in isolation; disposal of carcasses; arrangements and procedures for tuberculin testing, and for inspection for B virus lesions.

(j) *Contingency plans* - these should give instructions about the handling of newly imported animals that show clinical signs of infection or die, for example, the provision of a designated area to isolate suspect animals.

MANAGEMENT OF NEWLY IMPORTED SIMIANS

9 A key element in preventing or reducing the risk of infection is knowledge of the health status of the animal. Pre-existing or latent infection hazards of simians in closed breeding colonies may not be an issue where their health status has been properly controlled and documented. Animals bred in the UK are to be preferred because they are unlikely to harbour latent infections and the need to import simians that are more likely to be infected should be considered carefully. For imports from third countries, importers must obtain an import licence from the appropriate agricultural department. In addition, imported animals should come from a reputable supplier and should be accompanied by officially authorised documentation stating the health status of the animal and details of any previous clinical history. The supplier should ensure proper separation of consignments during transport to prevent cross-infection.

10 All imported mammals are subject to control under animal health legislation. Establishments wishing to use imported simians either have to:

(a) accept stock that has completed a period of rabies quarantine elsewhere in accommodation approved by the appropriate agriculture department (see Box 1); or

(b) obtain approval to maintain the quarantine on the known premises prior to the animals being imported. Animals under restriction may nevertheless be used for experimental work before the 6 month's quarantine period has elapsed.

11 Primates imported from the EU can only be traded between approved bodies, institutes or centres in accordance with Directive 92/65/EEC. Requests for approval should be made to the divisional veterinary manager (DVM).

12 Non-human primates are included in Schedule 2 of A(SP)A 1986. This means that primates intended for use in regulated procedures must be obtained

from a designated breeding or supplying establishment in the UK unless the Home Office has granted a specific exemption. Where an exemption is made for the acquisition of simians from an overseas breeding or supplying centre, certain conditions apply. The centre must have been accepted by the Home Office and approval must be obtained for each consignment of animals. After arrival in the UK, copies of the veterinary inspection reports, copies or individual animal records and a report on any morbidity or mortality arising within 4 weeks of importation must be submitted to the Home Office.

13 Whether or not the facilities are in quarantine, all animals should, on arrival in an establishment, be segregated from other stock for at least 2 weeks. During this period, they should be handled as little as possible and should, for welfare reasons, preferably be kept in pairs or groups with the same cage partner(s) throughout. Different consignments and different species should be segregated.

Box 1: Approval for rabies quarantine

Before accommodation can be approved as statutory quarantine accommodation, certain standards of isolation, segregation and security must be met; a veterinarian or a medically qualified person has to be approved by the appropriate agriculture department to be responsible for the supervision of the quarantine premises. The supervisor or their authorised deputy must be on call at all times and attend on at least one day a week while the animals are in quarantine.

Full details of the rabies quarantine requirements can be obtained from the local DVM.

14 Records of the health of newly imported simians should be kept and the NVS should be consulted if clinical signs of disease are seen, or if any animal is found dead. The following diseases are the most important to screen for and/or identify in newly imported animals. The summary statements in this guidance should be consulted for clinical descriptions of the diseases.

Simian herpes B virus

15 Simian herpes B virus is a highly hazardous agent that may be present as a latent infection in simians. There are approximately 40 documented deaths arising from occupational infection with B virus. In view of the severity of the disease and the potential difficulties in treatment, ACDP has recently reclassified B virus into Hazard Group 4, the highest hazard group. Regulation 7 of COSHH 1994 and paragraphs 5 and 6 of Schedule 9 of COSHH state that exposure to biological agents should be prevented if this is reasonably practicable, or adequately controlled. For work with simians this may be best achieved by only using animals that are B virus seronegative. Serological tests do not provide complete assurance of freedom from infection. The following measures should be considered to minimise the risk of an animal being infected:

(a) If simians need to be imported, they must come from premises accepted by the Home Office. Wherever practicable, they should be from herpes B virus negative breeding colonies. Such animals do not normally need to be re-tested for herpes B virus on arrival in the UK.

(b) In the case of animals that are not from herpes B virus negative colonies or are wild caught (eg feral baboons) they should be accompanied by officially authorised documentation stating that the animal is B virus seronegative. The animal should be re-tested as soon as appropriate after arrival. If there is reason to suspect that the testing and documentation is inadequate (eg no proven quality control or accreditation of the testing laboratory) then such animals should be handled with extreme caution or assumed to be B virus positive until re-tested and shown to be seronegative.

(c) An animal can be regarded as seronegative if it has had a negative test for B virus antibody on two occasions separated by at least 2 months, during which it has been kept isolated from other animals that may be infected. It is advisable to re-test before beginning a procedure under A(SP)A 1986. Although a seronegative animal has only a low probability of harbouring latent B virus infection, serological tests do not provide absolute assurance of freedom from infection.

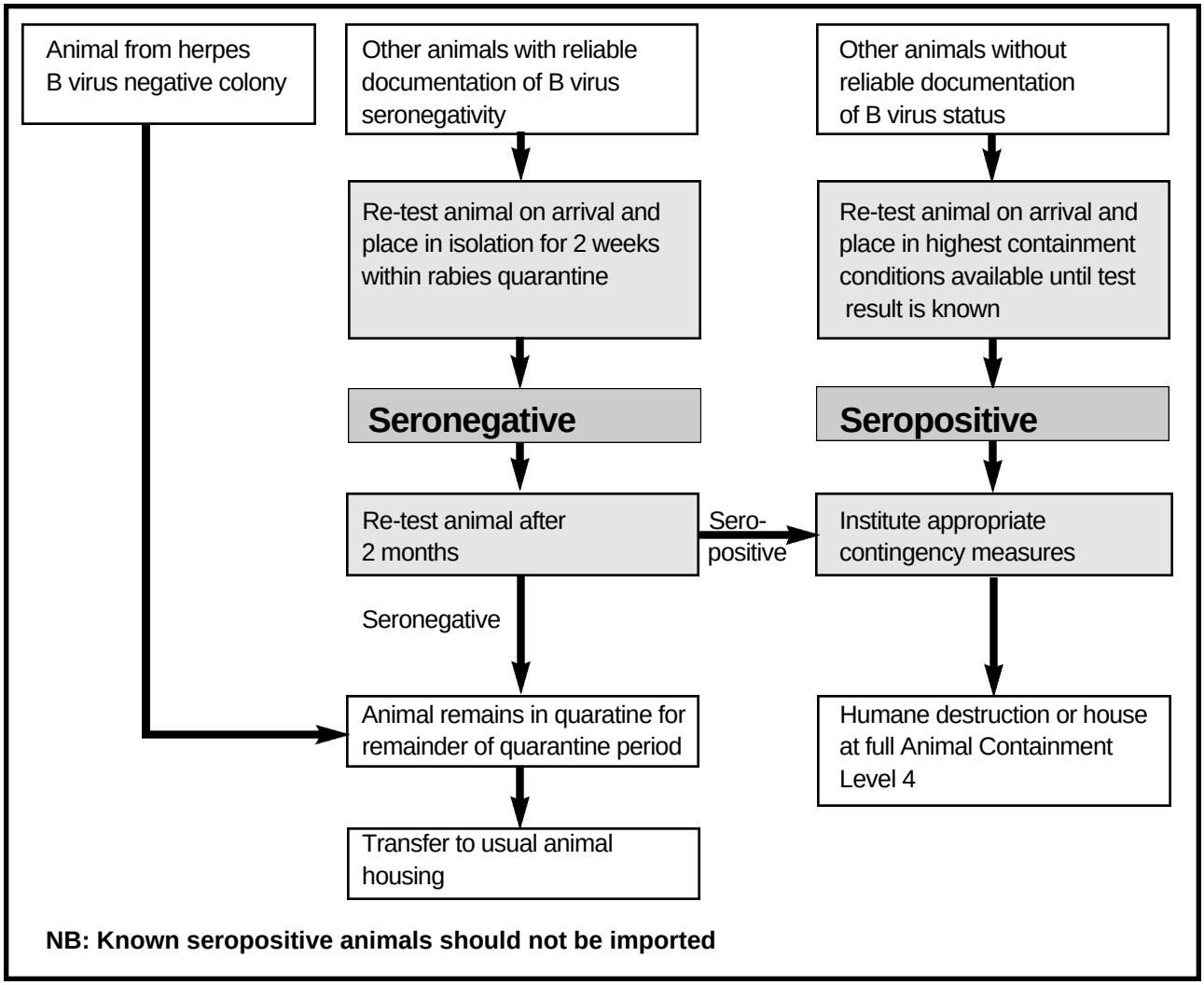
(d) In the event of an animal being diagnosed as B virus seropositive, a decision will need to be made whether or not it is appropriate to keep the animal. **ACDP would strongly advise that such animals are destroyed humanely and incinerated.** In some circumstances this may not be practicable, for example, because of limited availability or practical reasons, in which case HSE should be contacted immediately for advice. Employers have a legal duty to control exposure adequately and therefore, where an animal is known or suspected of being infected with B virus, it must be handled at full Animal Containment Level 4. The animal welfare requirements of the A(SP)A 1986 must also be considered. The Home Office inspector should be advised of a simian identified as herpes B virus seropositive and should be consulted with regard to the fate of the animal.

(e) Since the duration of the presence of maternal antibody has not been established, interpretation of positive results from young (less than 18-months old) or sexually immature monkeys may not be clear-cut. Such seropositive animals should be regarded as genuinely infected until proved otherwise. Negative results from sexually immature macaques should be regarded with caution as latent infection may be present and activated at sexual maturity, by stress or by immunosuppression. Re-testing at 3-monthly intervals until sexual maturity should be considered.

(f) ACDP also recommend that a statistically representative proportion of Old World simians held long term in any facility should be tested annually for B virus antibody and in the event of a seropositive animal being found, the rest of the colony should be tested and the appropriate action taken.

A flow chart showing the control measures and procedures necessary for imported animals during testing for B virus status is given in Figure 1.

Figure 1: Action to be taken for newly imported simians with regard to simian herpes B virus status



Filovirus (Marburg and Ebola virus)

16 If animals are infected with a filovirus, the disease is likely to develop shortly after importation. A contingency plan should be in place providing detailed information on the action to be taken in the event of infection in imported animals. Provision should be made in the contingency plans to allow for segregation of sick, suspect and dead animals from others until the diagnosis is confirmed or refuted. Suspect animals should be housed under the highest containment conditions available and appropriate protective clothing used when obtaining samples of blood for diagnosis. The animals should be anaesthetised during sampling procedures. During the collection of blood, particular care should be taken to avoid inoculation injuries. Samples should be sent under suitable containment to the Enteric and Respiratory Reference Laboratory of the Central Public Health Laboratory (CPHL), Colindale. If the diagnosis is confirmed, infected and in-contact animals should be destroyed humanely and the DVM should be informed. The carcass(es) must be contained securely and destroyed by incineration. The area used to isolate the sick animals should be appropriately cleaned and disinfected.

17 In the case of a sick animal, a blood sample is a suitable specimen for diagnosis, but if the animal has died and blood is not available, the most appropriate tissue for diagnosis is liver. In these circumstances, carcasses should be sent to the Centre for Applied Microbiological Research (CAMR), Porton Down, where the liver will be sampled under Containment Level 4

conditions and used in diagnostic tests. A possible alternative method of establishing the diagnosis is to send a needle biopsy of the liver or skin snips to CPHL. In deciding which approach to take, the risk of taking post-mortem samples needs to be balanced against the risk of transporting the whole carcass. Advice may be obtained from the HSE's specialist inspectorate, CAMR or CPHL at the addresses in Appendix 2.

18 Instructions on transportation of specimens can be found in the ACDP guidance *Management and control of viral haemorrhagic fevers.*[2] In all cases, the senders should contact CAMR or CPHL before despatch to confirm that the laboratory will accept the specimen and to agree packaging and transport arrangements.

Rabies

19 If the possibility of rabies is indicated, the local DVM must be notified. The DVM will take responsibility for further action. Local codes of practice should include suitable contingency measures to protect the health of staff and others.

Tuberculosis

20 Routine tuberculin testing should be carried out in imported animals held long term and similar management principles to those adopted for B virus should apply. It is recommended that tuberculin-positive animals should be destroyed humanely and the carcass incinerated. It is recognised that tuberculin testing can be unreliable. Nevertheless, routine tuberculin testing may be appropriate, particularly for Old World monkeys and those kept for long periods.

Other infection

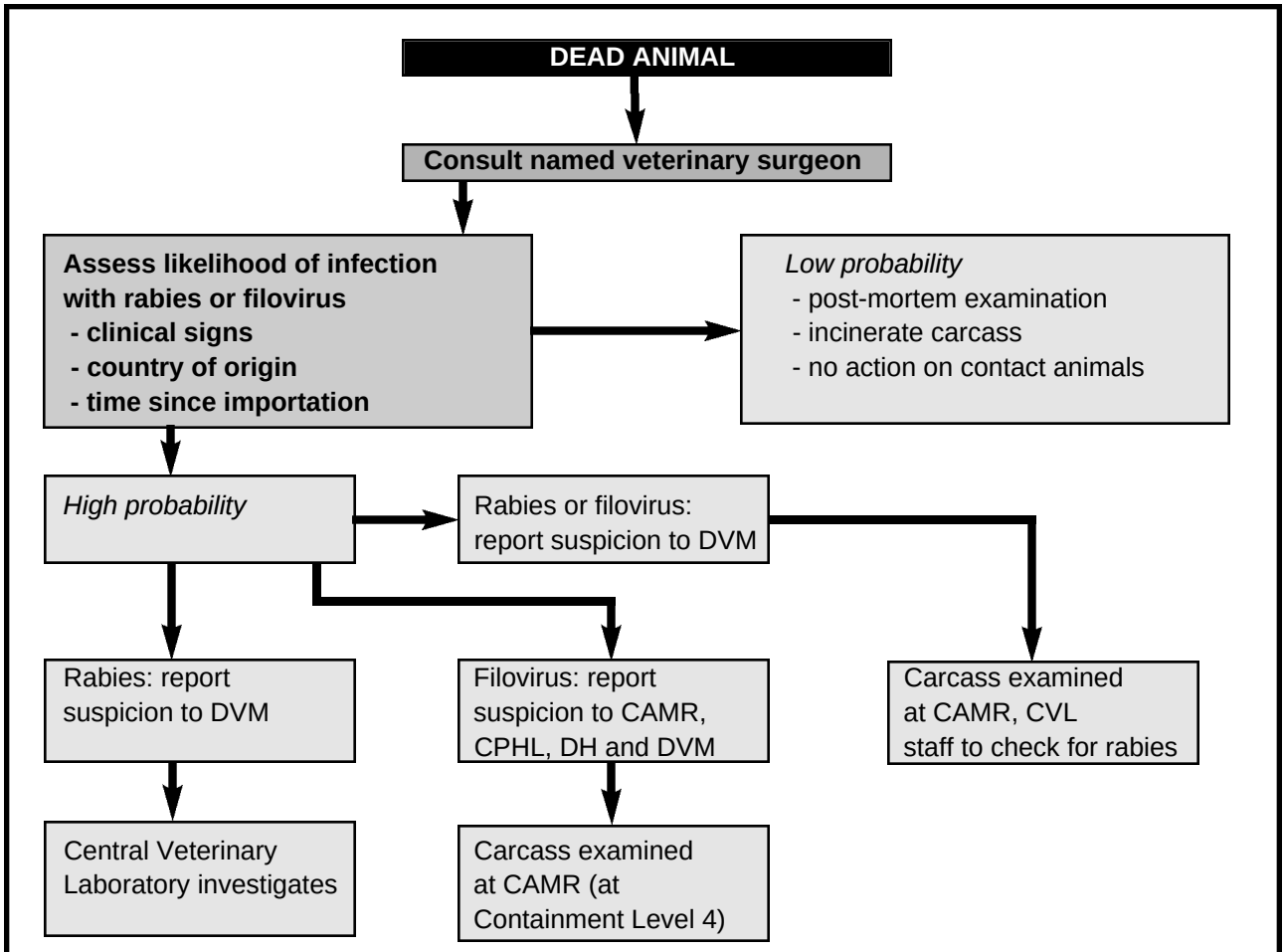
21 The possibility of other infections, such as salmonellosis, melioidosis or giardiasis, particularly in the case of recently imported animals, should always be considered. Animals may also carry *Campylobacter* or *Shigella* and this possibility should be considered. In the event of unexplained illness developing during the isolation period, the veterinary adviser should be contacted immediately. Consideration should be given to routine screening of individual animals or a statistically representative sample of the animals in containment.

DEATH OF NEWLY IMPORTED SIMIANS

22 The actions that should be taken in the event of a primate dying in quarantine will depend on the circumstances (Figure 2). In general, **all** simians that die in captivity (including stillbirths and aborted foetuses) should be examined post-mortem by a veterinary pathologist. A veterinary surgeon should be consulted to help assess the likelihood of infection with rabies or filovirus. Accidental trauma may be indicated as the cause of death, in which case the risk may be assessed as low.

23 Infection with simian haemorrhagic fever virus or filovirus should be considered in newly imported animals with haemorrhage from orifices, hypovolaemic shock or melena. All deaths of animals which have shown clinical signs of nervous disease or altered behaviour should be considered as a suspect rabies case and the DVM notified. In cases where the cause of death has not been ascertained, it would be prudent to assume that filovirus infection could be involved.

24 In all cases, the local codes of practice should consider the procedures for the safe handling and transport of carcasses. Advice can be obtained from the local DVM or other contact points shown in Figure 2 (see Appendix 2).



The telephone number of the DVM should be immediately available for use in emergencies. Advice and diagnostic testing is available for filoviruses from CAMR or the CPHL

CAMR = Centre for Applied Microbiological Research, Porton Down
CPHL = Central Public Health Laboratory, PHLS, Colindale
CVL = Central Veterinary Laboratory, Weybridge
DH = Department of Health
DVM = MAFF Divisional Veterinary Manager.

WORKING WITH SIMIANS

25 In addition to the requirements and recommendations in the ACDP guidance, *Working safely with research animals: Management of infection risks,*[1] there are a number of recommendations specific for work with simians. In particular, the *Code of practice for the housing and care of animals used in scientific procedures* [3] should be consulted.

26 Simians should be moved within an establishment as little as possible to reduce the risk of transmitting infection from, eg scattered cage debris and urine. However, every attempt should be made to offer the simians as much exercise and opportunity to pursue normal behaviour as possible.

27 Before handling animals, particularly larger animals (eg over 1 kg) careful consideration should always be given to the need to do so and to the procedures to be used. Anaesthetised animals should only be moved in a transit container, appropriately constructed to contain the animal if it were to revive. The local code should cover the availability of extra anaesthetic and syringes. The use of boards with a restraining harness is not to be recommended for transporting animals from one location to another.

28 The careful choice and design of cages will minimise the risk of infection to handlers. Cages should be appropriate to the species to be housed, being strong enough to contain animals securely and providing adequate space for their comfort; they should be fixed securely. Cage design should minimise the risk of skin penetration, whether from sharp metal, rough surfaces, a fingernail or a bite. They should be made without sharp edges internally or externally. The cage door should be designed so that conscious animals can safely be transferred from the delivery crate without risk of escape.

29 Cages should be designed so that the animal cannot reach out to scratch the unwary, eg through gaps around doors or feeding hoppers, or where a false back mechanism operates. Gangways between cages should be of sufficient width. The local risk assessment should consider the degree of containment that is required. For example, cages with bars may allow animals to reach out and an operator may be scratched unexpectedly. If cages are positioned carefully, however, unexpected contact between animal and operator can be avoided and the animal's environment and welfare will be enriched by the ability to reach between the bars. If the animal is able to reach through the grid floor, litter containing food may be placed in the tray below the floor and the animal can forage for seeds and nuts, further enriching its environment. However, this arrangement allows access to faeces that may be scattered outside the cages. Monitoring for the presence of zoonotic agents will assist the risk assessment.

30 Maintenance of cages is particularly important when working with simians. Larger Old World simians are capable of undoing nuts and bolts, bending wire mesh and tearing sheet steel if they can work at flexing an edge. Cages and their fixing should be checked routinely to ensure that faults have not arisen, particularly after autoclaving and cage washing.

31 It should be possible to change food hoppers and water bottles without breaching containment. Plastic rather than glass bottles will avoid scattering glass splinters in the room if bottles break.

32 The design of the cage should permit the animal to be injected safely with anaesthetic or a tranquilliser while still securely held inside the cage. The most convenient arrangement is the false back wall which can be used to bring the animal forward and locked close against the front mesh, where it can be injected. A written procedure for this is essential.

STAFF HEALTH

33 Staff who handle simians, or other animals or tissues known to be infected with simian pathogens, should carry a personal record card which states that they may be at risk of unusual infection. The card should show the telephone number(s) of staff such as the medical officer or other responsible person who could be contacted at any time, together with the full address of the place of work.

34 It is recommended that staff involved with animals in quarantine (or their tissues) should be vaccinated against rabies. Making effective vaccines available, where appropriate, for those who are or are liable to be exposed to biological agents is just one of the control measures specified in COSHH. Vaccination should not, however, be seen as a substitute for other control measures or prevention of exposure.

35 If encephalitis or any unusual illness occurs in people who have been in contact with simians, simian tissues or simian viruses, the possibility of occupationally acquired infection should be considered seriously. Should such an infection occur or any incident be noted that may have resulted in the release of a biological agent that could cause serious disease, COSHH requires that employees or their representatives are informed. The causes of the accident or incident and the measures taken must also be relayed. In these circumstances, such infections and releases are reportable under the Reporting of Incidents, Diseases and Dangerous Occurrences Regulations 1995 (RIDDOR).

36 It should be remembered that simians are susceptible to a number of human infections, such as tuberculosis, and staff should therefore be aware of the possibility of spread of disease in this manner.

Action in the event of a bite or other incident

37 The need for prompt action cannot be over-stated and particular emphasis should be placed on quickly applying first-aid measures for cleaning the wound.

38 If this guidance has been followed the B virus status of the animal should be known. However, an animal should not be assumed to be uninfected (unless it came from a B-virus-free colony) as infection has been reported following exposure to an apparently healthy monkey; the animal may have been excreting virus asymptomatically. The recommended action to be taken in the event of exposure to B virus is given in Appendix 1. The information is included so that it can be made readily available to the occupational health doctor should exposure occur.

SUMMARY STATEMENTS ON PARTICULAR PATHOGENS OF SIMIANS

SIMIAN HERPES B VIRUS *(HERPESVIRUS SIMIAE)*

Hazard Group	4
Reservoir	Old World simians, mainly the rhesus monkey, but other macaques, including cynomolgus monkeys, may also carry the virus.
Disease in animals	Disease generally subclinical or benign with mild vesicular lesions on the tongue, mouth and lips similar to primary herpetic stomatitis in man. Animals which have seroconverted probably remain latently infected with B virus for life. Infection in monkeys rarely reactivates spontaneously but, like humans, might be expected to do so if the animal is immunosuppressed, severely stressed or is pregnant. This reactivation may be clinically inapparent.
Disease in humans	Human B virus infection most frequently presents as an ascending encephalomyelitis, which if untreated has a mortality rate of 80% and survivors may have permanent brain damage. A few cases have presented early with vesicular lesions and/or pain and itching at the bite site. CNS disease presents with headache, fever, limb stiffness, nausea and vomiting. There is some evidence for secondary transmission.
Transmission to humans	By bites, from handling monkey tissues or secretions, possibly from aerosols of secretions or from penetrating injuries sustained while handling cages.
Likelihood	The risk is linked to stress and newly imported simians may present the greatest risk. Excretion has also been linked to oestrus.
Control measures	Seronegative animals should be used wherever possible. Seropositive animals should be destroyed, or must be handled at Animal Containment Level 4. Animals expressing the virus should be isolated. Monkeys should only be handled by suitably qualified and trained staff at all times. If human exposure occurs, the actions recommended in Appendix 1 should be followed. Laboratory work involving propagation of the agent must be done under full Containment Level 4 conditions. Diagnostic work which does not involve propagation may be done at a lower containment level by specialised laboratories such as the CPHL, Colindale.

MONKEYPOX

Hazard Group	3
Reservoir	The virus has been isolated from ground squirrels (*Funishiurus* spp., *Heliosciurus* spp.) in Africa and it is generally accepted that these represent the reservoir. Outbreaks have occurred in captive Asiatic monkeys; cross-infection is the most likely cause. There is no evidence that the virus exists in Asia.
Disease in animals	Skin lesions, few in number and benign.
Disease in humans	Illness of 2-4 weeks usually begins with fever, severe headache and backache. May give rise to an extensive rash similar to that of smallpox. There is a mortality rate of about 10% (in unvaccinated subjects), this increases to 16% in unvaccinated children.
Transmission to humans	Could occur by inhalation or direct contact with the excreted virus, either from live animals or carcasses. Secondary transmission can occur but less frequently than smallpox.
Likelihood	There has been no evidence of human infection in those handling animals in the laboratory but there have been at least 10 outbreaks amongst captive simians.
Control measures	Smallpox vaccine provides protection against monkeypox infection as the two viruses are closely related. The risk of complications from using smallpox vaccine may outweigh the possible benefits although when working with monkeypox virus in the laboratory or with infected animals, vaccination is strongly recommended and the guidance from the ACDP and ACGM[4] should be followed. In other circumstances a case-by-case assessment is indicated. Animals imported from different places should be segregated to avoid cross infection. It should be noted that work with (including provision of diagnostic services) and consignment of this agent requires prior notification to HSE as the virus is listed in Part V of Schedule 9 of COSHH 1994.

FILOVIRUS INFECTIONS (EBOLA AND MARBURG)

Hazard Group	4
Reservoir	Unknown, but primates may serve as intermediate hosts and are susceptible to infection.
Disease in animals	If animals are infected, disease is likely to develop shortly after importation. The incubation periods for Marburg and Ebola virus infections are between 3-16 days. Clinical signs include fever, anorexia, lethargy, vomiting, hypovolaemic shock, melena and haemorrhage. The animal usually deteriorates rapidly and death occurs in the second week. *Note: a similar clinical presentation is seen with simian haemorrhagic fever which is caused by an unrelated virus that is not known to infect humans; infection with this virus should be considered during differential diagnosis.*
Disease in humans	***Marburg -*** is an acute febrile illness with severe haemorrhage and diarrhoea with an incubation period of 6-9 days. Secondary transmission has been reported. ***Ebola -*** the incubation period is usually from 5 to 9 days (range 2-15 days) but can be shorter with parenteral transmission. Disease onset is abrupt with severe malaise, headache, high fever, myalgia, joint pains and sore throat. The disease runs a rapid course and death occurs mainly as a result of the decrease in the volume of circulating blood (hypovolaemic shock). There is no specific treatment for either disease and therefore, intensive supportive measures are given. Person-to-person transmission can occur.
Transmission to humans	By direct contact with infected blood, organs and other secretions. Possible transmission by aerosols (Ebola Reston).
Likelihood	Can be high. In one outbreak in people exposed to monkeys or their tissues, 25 laboratory-acquired cases of Marburg, with seven deaths, occurred. Five secondary cases involved persons with direct contact with a primary case. One case of laboratory-acquired Ebola has been reported.
Control measures	Importers of monkeys need to remain alert to the possibility of infection with filoviruses. The recommendations set out in this guidance, particularly those relating to the isolation and examination of simians, should provide adequate safeguards against infection for staff caring for animals during the quarantine period.

Guidance on the clinical care of patients with viral haemorrhagic fevers can be found in the ACDP publication *Management and control of viral haemorrhagic fevers*.[2] Some of the procedures in the guidance, eg the transport of specimens, may also apply to animals known or suspected of being infected with the Marburg or Ebola virus.

Ebola Reston/Siena virus infection

Infections caused by a filovirus closely related to Ebola virus have been reported in cynomolgus monkeys imported from the Philippines. No unusual illnesses were reported in any persons who came into contact with the infected animals or with blood or tissues from them anywhere in transit or at the point of destination. However, studies undertaken at the four major holding facilities and at other centres in the Philippines showed serological evidence of sub-clinical infection in staff handling these animals.

SIMIAN IMMUNODEFICIENCY VIRUS (SIV) AND SIMIAN T-CELL LYMPHOTROPIC VIRUS (STLV)

Hazard Group	3
Reservoir	SIV infections are common in wild African green monkeys. SIV (closely related to HIV-2) was isolated from captive rhesus macaques *(Macaca mulatta).* It is not detected in wild caught macaques and transfer is thought to have occurred in captivity. It is closely related to SIV in wild caught sooty mangabeys. STLV, isolated from African green monkeys and chimpanzees, is very similar to HTLV-1.
Disease in animals	AIDS-like disease. STLV has been associated with lymphoid cancer in captive macaques.
Disease in humans	SIV infection has been reported in laboratory workers but no disease has yet been associated with these infections.
Transmission to humans	By direct contact with blood and other body fluids, via contaminated needles and other sharps.
Likelihood	Low. An anonymous serostudy of 472 laboratory workers and animal technicians involved in SIV research revealed three SIV antibody positive samples.
Control measures	SIV is a Hazard Group 3 biological agent and animals infected (naturally or deliberately) should be handled at Animal Containment Level 3. Although there is no evidence of infection, ACDP has recommended that similar containment should be used for STLV and other simian retroviruses. It is recommended that experimental establishments consider the need to test simians for SIV in cases where close contact with them is an inevitable requirement for the type of work being undertaken. Such testing is now available commercially.
D-type retrovirus	There is a report of B cell lymphoma associated with D-type infection in an immunosuppressed individual. This is a virus which infects a significant proportion of macaques bred in the UK, commonly causing an AIDS-like condition.

RABIES

Hazard Group	3
Reservoir	Many wild and domestic carnivores. Disease exists in two epidemiological forms - urban rabies which is spread mainly by feral and domestic dogs and is prevalent mainly in developing countries; and sylvatic rabies which occurs in a wide range of species including bats.
Disease in animals	Clinical signs are variable but are similar to those of encephalitis. Signs include irritability, loss of appetite, paralysis, self mutilation (constant licking and biting at the site of virus inoculation) and atypical aggressive or friendly behaviour. Dumb and paralytic rabies have been described and also cases where clinical signs were absent. Invariably, death is extremely rapid.
Disease in humans	Symptoms include fever, change in behaviour, anxiety, insomnia, headaches, restlessness and spasms of swallowing muscles leading to hydrophobia. Without medical intervention, duration is usually 2-6 days. Death is often due to respiratory paralysis.
Transmission to humans	Most human infections are from bites of domestic carnivores. Person-to-person transmission has occurred via infected corneal grafts.
Likelihood	Very low in the UK. There have only been 28 cases in animals in quarantine, none involving primates and two cases of rabies in animals outside quarantine since 1922.
Control measures	Rabies is a Hazard Group 3 biological agent and animals infected (naturally or deliberately) should be handled at Animal Containment Level 3. Anyone deliberately importing or working with rabies virus must apply to the appropriate agriculture department for a licence. Vaccination is effective and is essential for any person intending to work with the virus. It is recommended for those who work with animals in quarantine. Post-exposure vaccination in conjunction with specific immunoglobulin is also effective.

APPENDIX 1 THE MANAGEMENT OF EXPOSURE TO B VIRUS

1 The following advice on action in the event of exposure to B virus is based on advice first published in 1988[5,6] and since updated by the MRC and ACDP. Further information is also available in the guidelines from the B-virus Working Group of the US Centers for Disease Control, Atlanta.[7]

2 Determining, and if possible excluding, the risk of B virus infection is of value in the management of cases of exposure since the incubation period in humans is unknown. It is advisable to collect a specimen of blood from the injured person so that serum can be stored for future reference. Staff who develop clinical signs of infection with B virus, or who have been in contact with a monkey with suspected herpetic lesions, should be referred immediately to a consultant in a specialised infectious disease unit. It is therefore preferable to make arrangements in advance with a named unit and/or physician so that appropriate medical examination and treatment can be applied without delay.

3 Although the use of acyclovir is the treatment of choice in B virus infections, reports of two surviving cases in the US suggest that the drug was only suppressing viral replication as virus was re-isolated from one patient immediately after therapy was stopped.

4 The following actions should be used if the injury occurred while handling possibly infected unfixed monkey tissue, blood, animal carcasses, or dirty instruments used in the preparation of specimens and where there has been an incident involving direct contact with an animal, eg bite or scratch. Blood specimens from the animal should be taken for testing wherever possible.

(a) The wound should be washed immediately with plenty of water and, if possible, allowed to bleed. The wound should not be scrubbed.

(b) The wound should be cleaned by appropriately trained staff, eg a member of the occupational health service and should be treated with 10% iodine in alcohol. In the case of a deep puncture wound, where the risk is high, a swab should be taken for virus culture before cleansing and the application of antiseptic.

(c) Unless the monkey colony is known to be B virus antibody negative, the injured person should be treated, starting as soon as possible after the exposure. The current recommendation is 800 mg oral acyclovir five-times a day for 3 weeks. Instructions should be given to report any symptoms of ill health, particularly skin lesions or itching, pain or numbness near the site of the wound. Finally, an incident card should be issued to warn other medical practitioners of the potential problem and giving a contact telephone number so that information and help may be obtained at any time. The occupational health department, with advice from the Central Public Health Laboratory (CPHL) should consider the need for counselling.

(d) The animal should be observed while conscious, and then examined under anaesthesia or deep sedation by a veterinary surgeon for signs of infection, especially vesicles in or near the mouth. Blood should be taken for B virus antibody testing. If the colony is not known to be B virus negative, it is strongly recommended that specimens are taken from the mouth, conjunctivae and other appropriate sites for virus culture. If the monkey is well, it should be kept under observation for the next 2 weeks

and any signs of ill health immediately notified to the occupational health service and/or medical officer in charge of the case. A follow-up examination of the animal should be carried out on the 14th day .

(e) The occupational health service should check on the health of the exposed person at weekly intervals for the following 7 weeks. After that the incident card is withdrawn.

(f) If during follow-up, B virus is cultured from any specimens or if any signs are found in the monkey or symptoms of ill health or signs develop in the injured person, they should be referred to a consultant in an infectious diseases unit who may decide to take further samples for virus culture (including a biopsy of the wound). If symptoms of ill health are present, the recommended treatment is acyclovir (10 mg per kg) given 8-hourly by intravenous transfusion over 1 hour for 14 days. During treatment it is important to monitor renal function and maintain a high flow of urine. Subsequent treatment with oral acyclovir 800 mg five-times daily indefinitely is currently recommended to prevent reactivation of virus.

APPENDIX 2 SOURCES OF INFORMATION AND ADVICE

The following sources of advice or specialist diagnostic facilities are referred to in the text.

Centre for Applied Microbiology Research (CAMR)
Diagnostic Reference Laboratory,
CAMR,
Porton Down, Tel: 01980 612224
Salisbury, Fax: 01980 612731
Wiltshire SP4 OJG e-mail: diagnosis.ref@camr.org.uk

Central Public Health Laboratory
Enteric and Respiratory Virus Laboratory,
PHLS Central Public Health Laboratory,
61 Colindale Avenue, Tel: 0181 200 4400 ext 3016
London NW9 5HT Fax: 0181 200 1569

Central Veterinary Laboratory (CVL)
Virology Department, CVL,
New Haw, Addlestone, Tel: 01932 341111
Surrey KT15 3NB Fax: 01932 347046

Department of Health
Department of Health,
Skipton House,
80, London Road, Tel: 0171 972 5348
London SE1 6LW Fax: 0171 972 5155

Health and Safety Executive
Microbiology/Dangerous Pathogens
Directorate of Science and Technology,
Magdalen House, Tel: 0151 951 3622
Bootle, Liverpool L20 3QZ Fax: 0151 951 3474

Home Office
Animals (Scientific Procedures) Inspectorate,
50 Queen Anne's Gate, Tel: 0171 273 2382
London SW1H 9AT Fax: 0171 273 2423

MAFF Divisional Veterinary Manager
Addresses and telephone numbers of specific DVMs can be obtained from:
Veterinary Adviser (Rabies),
Block B, Government Buildings, Tel: 0181 330 4411
Hook Rise South, Tolworth, Surrey KT6 7NF Fax: 0181 337 3640

In Scotland
Veterinary Adviser (Rabies),
Pentland House,
43 Robbs Loan, Tel: 0131 244 6280
Edinburgh EH14 1TY Fax: 0131 244 6475

Scottish Office Department of Health
St. Andrews House, Tel: 0131 556 8400
Edinburgh EH1 3DG

Scottish Centre for Infection and Environmental Health
Clifton House,
Clifton Place, Tel: 0141 300 1100
Glasgow G3 7LN Fax: 0141 300 1170

REFERENCES

1 Health and Safety Commission's Advisory Committee on Dangerous Pathogens *Working safely with research animals: Management of infection risks* HSE Books 1997 ISBN 0 7176 1377 1

2 Health and Safety Commission's Advisory Committee on Dangerous Pathogens *Management and control of viral haemorrhagic fever* HMSO 1996 ISBN 0 11 321860 5

3 Home Office *Animals (Scientific Procedures) Act 1986*
Code of practice for the housing and care of animals used in scientific procedures HMSO 1989 ISBN 0 1021 0789 0

4 Health and Safety Commission's Advisory Committee on Dangerous Pathogens and Advisory Committee on Genetic Modification *Vaccination of laboratory workers handling vaccinia and related poxviruses infectious for humans* HMSO 1990 ISBN 0 11 885450 X

5 Wansbrough-Jones M H et al 'Prophylaxis against B virus infection' *BMJ* 1988 **297**: 909

6 Brown D et al 'Prophylaxis against B virus infection' *BMJ* 1988 **297**: 1332

7 Holmes G P et al 'Guidance for the prevention and treatment of B virus infections in exposed persons' *Clinical infectious diseases* 1995 **20**: 421

FURTHER READING

Health and Safety Commission *Control of Substances Hazardous to Health Regulations 1994 - General COSHH ACOP, Carcinogens ACOP and Biological Agents ACOP* L5 HSE Books 1997 ISBN 0 7176 1308 9

Health and Safety Commission's Advisory Committee on Dangerous Pathogens *Categorisation of biological agents according to hazard and categories of containment* HSE Books 1995 ISBN 0 7176 1038 1

Health and Safety Commission's Education Services Advisory Committee *Health and safety in animal facilities* HSE Books 1992 ISBN 0 11 886353 3

Laboratory Animal Handbooks 4 *Hazards of handling simians* Laboratory Animals Ltd 1996 ISBN 901334 02 2

Home Office *Animals (Scientific Procedures) Act 1986*
Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 HMSO 1990 ISBN 0 10 218290 6

Home Office *Animals (Scientific Procedures) Act 1986*
Code of practice for the housing and care of animals in designated breeding and supplying establishments HMSO 1995 ISBN 0 10 212595 3

Home Office *Animals (Scientific Procedures) Act 1986*
Code of practice for the housing and care of animals used in scientific procedures HMSO 1989 ISBN 0 10 210789 0

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