

ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Advice on Experimental working with Influenza Viruses of Pandemic Potential

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Introduction

1. This document replaces the ACDP 2005 publication “Advice on Working with Influenza Viruses”, and provides new guidance on local risk assessment requirements and commensurate laboratory containment for work with influenza viruses of pandemic potential.

Purpose and scope

2. The purpose of this document is to provide guidance on appropriate containment measures to protect both human and animal health and the environment to those working with influenza viruses of pandemic potential in research laboratories or in animal experimentation work or diagnostic work. The recommendations for diagnostic work are provided in a separate section within the document. The guidance recognises the different risks to health presented by influenza strains of pandemic potential.
3. The information in this document is intended to be used as a framework to help those responsible for risk assessment in laboratories to reflect the local risks and to provide a consistent, transparent and unified approach to containment of these influenza viruses.

Current classification and guidance

4. The Approved List of Biological Agents (published in 2004) classifies influenza types A, B and C as Hazard Group 2 agents. ACDP agrees that though most influenza viruses from human sources may be safely handled at containment level 2 (CL2) there are circumstances and activities when a higher containment level is required to protect human and animal health.
5. The Control of Substances Hazardous to Health Regulations 2002 (COSHH) (Schedule 3 para 3) requires that, where an agent with an approved ACDP classification is used, **and** the risk of infection is different to that expected, a local reclassification must be carried out by the employer. Suitable containment and controls must then be selected accordingly, in line with a local risk assessment of the activity being undertaken and in consultation with HSE. That risk assessment must

address, amongst other factors, the immune status of those who will be undertaking the work, taking into account exposure to circulating viruses and any relevant vaccination history, and the availability of vaccines and effective antiviral treatment.

6. Certain influenza virus strains are subject to control under animal health legislation, and specific laboratory containment measures may be required in accordance with a licence issued by DEFRA under the Specified Animal Pathogens Order 2008 (SAPO). This Order may be found at:

http://www.opsi.gov.uk/si/si2008/pdf/uksi_20080944_en.pdf

and more information from Defra is available at:

<http://www.defra.gov.uk/animalh/diseases/pathogens/>

7. Laboratory work involving the genetic modification of influenza viruses is currently subject to the Genetically Modified Organisms (Contained Use) Regulations 2000 as amended. For further information on the requirements of these regulations see <http://www.hse.gov.uk/biosafety/gmo/index.htm>

8. It is also a requirement under the Control of Substances Hazardous to Health regulations that the Health and Safety Executive (HSE) be notified of any:

- o first use of a biological agent (Hazard Group 2, 3 or 4) at a particular premises; and
- o subsequent use of any agent listed in Part V of Schedule 3 of COSHH (as amended)

Further information about the notification process can be found at:

<https://www.hse.gov.uk/forms/notification/cba1notes.htm>

9. The Regulations and arrangements referred to in paragraphs 3–6 above are currently under [legislative reform]. However, similar requirements for notification and for local risk assessment arise under a new single

regulatory framework being prepared, for human and animal pathogens and genetically modified organisms (due to be implemented in 2011).

Recommendations for laboratories deliberately working with influenza viruses

10. These recommendations apply to both laboratory research and animal experimentation, but exclude diagnostic work (see advice in paragraph 11). It is essential that the local risk assessment reflects the inherently unpredictable nature of animal work, especially that involving larger animals.

Though local risk assessment will indicate that most influenza viruses from human sources may be safely handled at CL2, it is recommended that higher containment level measures be applied when working with the following viruses, subject to local risk assessment.

Viruses that should NOT be handled at containment level 2

- a. Viruses potentially highly pathogenic for birds: H5 and H7 isolated from human subjects or from animals should be handled under the appropriate SAPO containment level (i.e. SAPO4) and the hazard they pose to human health should also be evaluated, even if there is no, or limited, evidence of human to human transmission (as for H5N1 strains from human cases). H5 and H7 viruses should thus be handled as though they are highly pathogenic for birds (SAPO4) and for humans (human hazard group 3) until there is evidence to the contrary.
- b. Viruses with pandemic potential should be handled at higher containment (at CL3 or above as determined by risk assessment). These include subtypes H2, H1 and H3 if, in the case of the latter, the viruses being handled are sufficiently different from currently circulating human viruses to warrant an assumption of little or no cross-reactive immunity in the human population (see also below),

and strains of H7 and H9 of low pathogenicity for birds but where transmissions to humans have been documented in the last 10 years.

Mitigating circumstances

- a. A virus of pandemic potential in humans and/or high pathogenicity in birds as above may be handled at CL2 if it has been manipulated in such a way as to make it less pathogenic in the avian model if:
 1. It has been modified by reverse genetics to eliminate determinants of high pathogenicity such as the polybasic cleavage site found in the haemagglutinin molecules of highly pathogenic H5 or H7 strains;
 2. A virus less likely to cause disease in humans or birds has been derived from it in other ways such as production of high growth reassortants consisting of the core proteins of a laboratory adapted strain such as PR8 with the surface proteins of the strain of concern.

Following manipulation to make them less pathogenic, evidence of the nonpathogenic nature of modified or derived strains should be obtained. This may include tests in animal models such as the ferret or where appropriate the standard chicken test to demonstrate that viruses previously highly pathogenic for avian species are attenuated. In some circumstances demonstration of sequence identity with strains previously shown to be safe may suffice.

- b. Many laboratories will not have access to pathogenicity studies or related data and characteristics of individual strains may be sufficient to determine pathogenicity. So, if the virus is of a subtype that is circulating in humans (currently such as seasonal H1 or H3) and there is a reasonable presumption of complete or partial immunity in the population it may be handled at CL2. Thus

currently circulating H1 or H3 virus strains or strains specifically identified as candidates for seasonal vaccine production may be handled at CL2. However H1N1v would not fall into this category at the start of a pandemic as it is evident that there is little immunity in the population, even though other strains of the H1N1 subtype may be circulating. However as the pandemic H1N1v virus becomes widespread in the community, consideration should be given to reducing containment to level 2 subject to the position of WHO and more specifically , full consideration by ACDP within the UK who will advise HSE accordingly.

Other viral characteristics to consider as part of the risk assessment

- a. Strains resistant to antiviral agents;
- b. Influenza virology is a rapidly developing field and influenza viruses of other subtypes or with other properties will inevitably be identified where CL2 is not suitable and proof of the nonpathogenic nature of modified or derived strains may be required. For strains such as H5N1 where the parental strain is lethal in the standard chicken test and produces clear clinical signs in ferret models, demonstrating pathogenicity is possible. For other strains such as H1N1v proof of attenuation may be more problematic as the parental strain gives a less severe infection in animals and to an extent in humans.

Recommendations for diagnostic work

11. In laboratories that are not intentionally working with viruses of human pandemic potential and/or high pathogenicity to birds, CL2 will usually be appropriate for processing clinical samples, taking into account the need for a microbiological safety cabinet. However, CL3 is more appropriate for certain types of clinical samples, such as respiratory secretions from patients known or suspected of being infected with the agents listed above, or with strains resistant to antiviral agents. This advice applies to all diagnostic work, including that carried out before a human influenza pandemic.

12. SAPO licences are not required for work with human samples submitted to diagnostic laboratories for diagnosis, or for cultures of virus produced from human samples that are intended for forwarding to reference laboratories for identification purposes (for further information see Annex 1). However, a diagnostic laboratory that wishes to hold any stock of live avian influenza virus strain that is a specified animal pathogen, for diagnostic or other purposes, would need to be licensed.

Use of microbiological safety cabinets

13. The risk assessment must take into consideration the potential for any laboratory activities to generate aerosols. COSHH requires that any procedures, either at CL2 or CL3, that are likely to give rise to aerosols of infectious material be carried out in a microbiological safety cabinet, or other suitable containment. When carrying out such activities with biological agents that are infectious by the respiratory route, such as influenza viruses, the assessment must reflect the risk of aerosols and the titre and volume of the virus to be worked with and be carried out in suitable containment.

14. The use of close-fronted microbiological safety cabinets (i.e. Class III cabinets or Class I/III cabinets in Class III mode) should be considered when handling newly recognised viruses with poorly defined pathogenicity.

Further Information

15. Queries about licensing under SAPO, containment requirements for avian influenza viruses and the application of SAPO to genetic material derived from such viruses can be obtained from:

The Pathogens Licensing Team
Defra
Area 5A, Nobel House
17 Smith Square

London SW1P 3JR

Tel: 020 7238 6212

Fax: 020 7238 6105

Email: pathogens@defra.gsi.gov.uk

Website: <http://www.defra.gov.uk/animalh/diseases/pathogens/>

16. For specific virological information e.g. about cultivating the virus, contact:

HPA Virus Reference Department

61 Colindale Avenue

London NW9 5EQ

Tel: 020 8200 6868

17. For enquiries relating to specific legal/technical issues, such as risk assessment, containment measures or detailed interpretation of H&S legislation or guidance, advice on the new single regulatory framework, or advice on general government policy on safety issues relating to micro-organisms and GMOs, you should contact:

Biological Agents Unit

Health and Safety Executive

1.2 Redgrave Court

Bootle

Merseyside L20 7HS

Tel: 0151 951 4718

Email: germs.gmos@hse.gsi.gov.uk

Annex 1 -

Guidance on the application of the Specified Animal Pathogens Order 2008 (SAPO) to work with avian influenza viruses

The Specified Animal Pathogens Order 2008

Animal pathogens that can cause serious diseases in farmed livestock and poultry are controlled under the Specified Animal Pathogens Order 2008 (SAPO). The purpose of the Order is to prevent the introduction and spread into Great Britain of specified animal pathogens which, if introduced, could cause serious disease and economic loss to the British livestock and poultry industries.

Avian influenza viruses that are:

- (a) novel viruses yet to be characterised; or
- (b) type A viruses which have an intravenous pathogenicity index in six week old chickens of greater than 1.2; or
- (c) type A viruses H5 or H7 subtype for which nucleotide sequencing has demonstrated multiple basic amino acids at the cleavage site of haemagglutinin

are specified animal pathogens and are controlled under SAPO.

SAPO prohibits people from having avian influenza viruses that are specified animal pathogens in their possession, or carriers (living creatures except man or materials derived from them known to contain a specified animal pathogen), unless they have a licence authorising them to do so. It also prohibits the introduction into any animal or bird of any avian influenza virus that is a specified animal pathogen, except under licence.

To be considered for licensing to hold and work with avian influenza viruses that are specified animal pathogens, laboratories must meet DEFRA's containment and operating requirements for DEFRA Group 4 specified animal pathogens. See:

www.defra.gov.uk/animalh/diseases/pathogens/category4.htm

DEFRA administers SAPO in England, but the Scottish Government Directorate of Rural Affairs and the Environment and the Office of the Chief Veterinary Officer at the Welsh Assembly Government are responsible for administering the Order in Scotland and Wales respectively. Similar but separate legislation is administered in Northern Ireland by the Department of Agriculture and Rural Development Northern Ireland (DARDNI).

HSE carry out inspections and enforcement under SAPO on behalf of these departments in Great Britain.

Additional guidance notes

SAPO is concerned only with the control of specified animal pathogens once they are within the geographical boundaries of Great Britain.

- Human diagnostic samples are not carriers under SAPO
- Diagnostic or clinical laboratories do not need SAPO licences if they hold inactivated avian influenza viruses that are specified animal pathogens for use as control materials
- Clinical /diagnostic laboratories do not require SAPO licences if they culture suspected avian influenza virus from human diagnostic samples for forwarding to reference laboratories for identification or confirmation of identification
- The requirements of both COSHH and SAPO apply to the handling of avian influenza viruses that are specified animal pathogens. Neither takes precedence. COSHH requirements relate to the risk the pathogens pose to humans, while SAPO requirements relate to preventing the spread of specified animal pathogens from the laboratory to the environment, causing disease in farmed livestock and poultry
- In the event of an outbreak of avian influenza in birds in this country, samples taken from humans for diagnosis should be submitted to HPA or other human diagnostic laboratories for testing, not to veterinary laboratories. Samples taken from birds (and any other animals) should be submitted to a veterinary laboratory.