



ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Advice on Experimental working with Influenza Viruses of Pandemic Potential

Issue

Latest draft of revised guidance on working with Influenza viruses of Pandemic potential, reflecting comments by members on an earlier draft.

Background

The committee previously agreed that there was a need for supplementary guidance on local risk assessment requirements and commensurate laboratory containment levels for work with influenza viruses of pandemic potential.

At the October meeting of ACDP, members discussed and commented on an earlier draft document. The issue of importance was the need for identification of those viruses presenting increased hazard potential or concern for which a higher level of containment may be required.

Higher Classification

A subgroup of the Committee's virologists including Philip Minor, Richard Tedder and Will Irving drafted a classification which now forms paragraph 10 of the new document. Amongst others, the draft has been seen or commented upon by John Wood, Maria Zambon, Othmar Engelhardt, Colin Howard and Keith Howard (SACGM). The document has also been amended to include previous comments by members. Further comments have since been received by Professor Ian Brown at VLA and these are included in the draft for further consideration by members.

Action

Members views are required on;

- The comments provided by Professor Brown (VLA)
- The lengths to which it is considered reasonably practicable or feasible for duty holders to go to, to demonstrate reduced pathogenicity or apathogenicity of viral strains.
- Members are specifically asked if the sentence (at paragraph 10(1)c) for testing in chicken or ferret models. Should be retained or to suggest alternative wording.
- Members are asked if the guidance should be circulated to the wider scientific community before publication

Secretariat

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**Advice on Experimental working with Influenza
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Pandemic Potential**

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Introduction

1. Against the background of recent pandemic influenza activity across the globe, the Advisory Committee on Dangerous Pathogens (ACDP) at its meeting on 9 February 2010, discussed and agreed the need for additional guidance on laboratory containment to that first given by the Committee in the document “Advice on Working with Influenza Viruses”, published in 2005.

Purpose and Scope

2. This document replaces the 2005 publication and incorporates supplementary new guidance on local risk assessment requirements and commensurate laboratory containment levels for work with influenza viruses of pandemic potential. It contains firstly, advice and recommendations relevant to laboratory research and animal experimentation work and secondly, a separate section with recommendations for diagnostic work.

Current classification and guidance

3. The Approved List of Biological Agents (published in 2004) classifies influenza types A, B and C as Hazard Group 2 agents. However, there is a requirement in the Control of Substances Hazardous to Health Regulations 2002 (COSHH) (Schedule 3 para 3(1)) that, where an agent with an approved ACDP classification is used, and the risk of infection is different to that expected, then a local reclassification must be carried out by the employer. Suitable containment and controls can then be selected accordingly, in line with a local risk assessment of the activity. That risk

assessment needs to address, amongst other things, the age of those who will be undertaking the work, and the availability of prophylactic treatment.

4. Some types of influenza virus are also subject to control under animal health legislation, and different laboratory containment measures may be required in accordance with a licence issued by DEFRA under the Specified Animal Pathogens Order 2008 (SI 2008/944) (SPO). The Order is 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/>

5. 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>

6. 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:

- first use of a biological agent (Hazard Group 2, 3 or 4) at a particular premises; and
- 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>

7. 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 2010)

8. Although in both current and proposed Regulations, duties arise for local assessment, the information in this document can be used as a framework to help complete the assessment and help to provide a consistent, transparent and unified approach to containment of these viruses.

Recommendations for laboratories deliberately working with influenza viruses

9. These recommendations apply to both laboratory research and animal experimentation, but exclude diagnostic work (see advice in paragraph 11). Note that animal work, especially that involving larger animals is inherently more unpredictable. This should be reflected in the local risk assessment.

10. ACDP recommend that most influenza viruses from human sources may be safely handled at containment level 2. In a number of circumstances however higher containment is required.

Viruses that should not be handled at containment level 2

1. Highly pathogenic ses: H5 and H7 isolated from human subjects or from animals should be handled under the appropriate SAPO containment level (ie SAPO4) but should also be evaluated from the point of view of hazard for humans, even where there is evidence of human infection but not human to human transmission (as for H5N1 strains from human cases). Uncharacterised H5 and H7 viruses should be handled as if they are highly pathogenic (that is, containment conditions that meet the requirements of both human hazard group 3 and SAPO 4).

2. Viruses with pandemic potential should be handled at higher containment:  H2, H3, as all have caused pandemics in the past; low pathogenicity H7 and  because they have transmitted to humans in the recent past.

Mitigating circumstances

1. A virus of a category listed above that would normally merit containment higher than category 2 may be handled at category 2 if it has been manipulated in such a way as to make it less hogenic: if
 - a. It has been modified by reverse genetics to eliminate determinants of high pathogenicity such as the basic cleavage site nd in the haemagglutinin molecules of highly pathogenic H5 or 7 strains.

- b. A less pathogenic virus 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.
 - c. Following manipulation to make them less pathogenic, proof of the apathogenic nature of modified or derived strains should be obtained in the standard chicken test and in ferret models.
2. 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 containment level 2 subject to the position of WHO and more specifically, full consideration by ACDP within the UK. For example H1N1swine would not fall into this category at the start of a pandemic as it is evident that there is little immunity in the population, although other strains of the H1N1 subtype are circulating. However as the pandemic H1N1 virus becomes widespread in the community, consideration should be given to reducing containment to level 2.

Circumstances causing concern

1. Strains resistant to antiviral agents may cause concern.
2. Influenza virology is a continuously evolving field and viruses of other subtypes or other properties will be identified where containment level 2 is not suitable. Proof of the apathogenic nature of modified or derived strains may be required. For strains such as H5N1 the parental strain is lethal in the standard chicken test and produces clear clinical signs in ferret models. For other strains such as H1N1swine proof of attenuation is problematic as the parental strain gives only a mild infection in animals and to an extent in humans.

Recommendations for diagnostic work

11. In laboratories that are not intentionally working with such novel viruses, Containment Level 2 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.

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12 DEFRA advice is that 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. 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 safety cabinet, or other suitable containment. Although many laboratory activities (e.g. centrifugation) are known to generate aerosols, other routine tasks (e.g. slide agglutination and even opening ampoules) may also have the potential for aerosol production. When carrying out such activities with biological agents that are infectious by the respiratory route such as influenza viruses, the assessment should reflect this risk and therefore 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 the more virulent strains of virus e.g. H5N1, potential pandemic
 ins.

Contacts

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
Redgrave Court
Bootle
Merseyside L20 7HS
Tel: 0151 951 4718
Email: germs.gmos@hse.gsi.gov.uk

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) uncharacterised; 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 Executive Environment and Rural Affairs Department (SEERAD) 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 in 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