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ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Categorisation of non-circulating strains of influenza virus of known pandemic potential

Issue

1) To seek members advice on whether additional guidance is necessary in relation to the risks associated with work involving the 1918 (H1N1) pandemic Influenza A virus.

Background

2) Influenza pandemics are rare events, but arise when a new strain of influenza A virus emerges that is easily transmissible between people, who have little or no immunity. There have been three worldwide pandemics which occurred in the last century: in 1918/1919 “Spanish Flu” (H1N1); in 1957/1958 “Asian Flu” (H2N2); and in 1968/1969 “Hong Kong Flu” (H3N2), each caused by a different virus subtype, of differing epidemiology and disease severity[1]. In addition, in 1977, a previously circulating subtype H1N1 re-emerged without the anticipated pandemic consequences. It is a widely held opinion that the re-emergence of H1N1 resulted from inadvertent release of the virus from a laboratory[2].

3) Given the shadow of a new pandemic looming on the horizon, basic research is focused on understanding issues such as the determinants of transmission, pathogenicity and virulence; with a view to being able to predict the severity and likelihood of potential pandemics and inform the development of effective anti Influenza viral drugs, therapies and vaccines. In order to achieve this, basic and applied research involving these pandemic Influenza strains is essential. Given the pandemic potential of these strains, applying the appropriate containment, which is proportionate to the risk but will not impede invaluable research, is paramount.

1918 (H1N1) Influenza A virus

4) The 1918 influenza pandemic is considered by many as one of the deadliest human health crises in human history, with estimates that the virus may have infected 50% of the world’s population; approximately 25% suffered clinical illness; and an estimated mortality of 20-50 million people worldwide. In just over one year, the virus infected one-third of the world’s population with death rates approximately 50 times higher than those associated with regular seasonal influenza[1,3-5].

5) Unlike normal seasonal flu outbreaks, where severe complications and death are most common among the elderly and young children, the 1918 virus was unusual because it spread so quickly, was so deadly, and exacted its worst toll among the young and healthy (healthy people aged 20-40). There are reports of people waking up in the morning but dying by nightfall – so rapid was the disease progress[1,3-5]. It's plausible that secondary bacterial infection after severe tissue damage from acute viral infection accounted for many of the excess deaths[5].

6) The premise that the 1918 virus was more virulent than other influenza viruses was only assessed, following its reconstruction and characterisation at the Centers for Disease Control & Prevention (CDC) in the USA as reported in 2005[6]. This research demonstrated that: the 1918 virus possessed a novel trypsin independent proteolytic Haemagglutinin (HA) cleavage mechanism; the 1918 virus genes displayed a high growth phenotype in human bronchial epithelial cells; caused death in mice and embryonated chicken eggs; the 1918 virus HA and polymerase genes are essential for enhanced virulence; and moreover the expression of all eight segments of the 1918 virus generated a virus of exceptional virulence in the model systems examined – no other virus tested showed a similar pathogenicity for mice 3 to 4 days post infection[6]. The comparison influenza strains were human viruses some with differing numbers of 1918 virus segments; highly pathogenic avian H5N1 influenza was not compared as part of these experiments.

7) Subsequent studies have shown that mice and non-human primates infected with the reconstructed 1918 virus, displayed an increased and accelerated activation of the host immune response genes resulting in severe pulmonary pathology (*i.e.* acute focal bronchitis/alveolitis, pulmonary oedema, haemorrhage and destruction of respiratory epithelium)[7,8]. These animals displayed aberrant innate immune responses including activation of pro-inflamatory and cell-death pathways within 24 hours of infection that remained unabated until death or euthanisation. These levels of immune response and pathology were not observed in other influenza viruses tested[7,8]. However similar pathology and subversion of the host immune response is observed in highly pathogenic avian H5N1 influenza infection of humans and experimental models[9].

8) Current anti-viral neuraminidase (*i.e.* zanamivir, oseltamivir) and ion channel inhibitors (*i.e.* amantadine, rimantadine) have been shown to be effective against Influenza virus constructs expressing the 1918 virus HA and neuraminidase (NA) or M segment, in tissue culture and in mice[10]. There is therefore a strong likelihood that they would be effective against the complete 1918 virus if used prophylactically. It's generally thought that both types of antiviral drugs need to administered early for clinical effectiveness, however, recent studies involving treatment with antiviral drugs of severely ill-patients, admitted to intensive care units in Canada, with antiviral drugs active against influenza was associated with a significant reduction in mortality[11]. Similarly use of antiviral drugs late in H5N1

infection, demonstrated continued benefit for patients although higher mortality may be associated with late onset of treatment[12].

Current Classification and Guidance

9) Influenza virus is classified as a Hazard Group 2 pathogen, as detailed in the Approved List of Biological Agents[13]. However, there is a requirement 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 and agreed with HSE[14]. Suitable containment and control can then be selected accordingly and in line with the risk assessment.

10) The criteria for classification of biological agents are set out in Schedule 3 of COSHH[14]:

- Group 1 – a biological agent that is unlikely to cause human disease
- Group 2 – a biological agent that can cause human disease and may be a hazard to employees; it is unlikely to spread to the community and there is usually effective prophylaxis or treatment available;
- Group 3 – a biological agent that can cause severe human disease and may be a serious hazard to employees; it may spread to the community, but there is usually effective prophylaxis or treatment available;
- Group 4 – a biological agent that causes severe human disease and is a serious hazard to employees; it is likely to spread to the community and there is usually no effective prophylaxis or treatment

11) In 2005, following an incident in which the H2N2 influenza virus was distributed internationally as part of a panel of proficiency testing samples, the World Health Organisation recommended that the biosafety procedures for work with non-contemporary strains of pandemic Influenza (*e.g.* H2N2) be reviewed. ACDP considered the issue of Influenza classification and provided a generic assessment of the risks of different types of Influenza viruses, to facilitate a consistent, transparent and unified approach to containment of these viruses across the UK. HSE issued the ACDP advice in the form of guidance entitled '*Advice on working with Influenza viruses*'[15] (Annex 1).

12) Although the 1918 virus falls into the category of non-contemporary strains of pandemic Influenza, the guidance did not specifically mention or consider the 1918 virus as at the time, this virus was not held in any laboratory worldwide and the potential for its re-emergence from a natural source was considered remote. Since publication of the guidance, as mentioned above, the 1918 virus has been re-constructed at the CDC. Research on 1918 virus has also been undertaken at the Public Health Laboratories in Canada hence the potential for its distribution or its reconstruction in UK laboratories therefore exists. In advance of this eventuality, the categorisation of the 1918 virus needs to be considered.

Containment

13) In the USA, based on the availability of prophylaxis, the reconstruction of the virus was undertaken at BSL3 with specific enhanced containment measures, including change of clothing, showering, use of powered air-purifying respirators (half-suits) and occupational health requirements (e.g. baseline serum levels, prophylactic use of antivirals). Further work on the 1918 virus requires 'BSL3-enhanced' containment, with the caveat that such work should only be undertaken with '*extreme caution*'[16]. In Canada, the studies in non-human primates were undertaken at BSL-4 including the use of fully enclosed body suits.

14) In the UK, the guidance on working with Influenza viruses (Annex 1) indicates that for non-contemporary pandemic strains (*e.g.* H2N2), CL3 is required including the use of closed fronted (Class III) MSCs for more virulent strains. However, the guidance does not specifically mention the 1918 virus or any enhanced containment measures for work of this nature.

Proposed Classification

15) Whilst work in the UK, with 1918 virus may be some way off, studies to create viruses with pandemic potential or viruses containing virulence determinants derived from the 1918 virus are more imminent. There is therefore a need to determine the benchmark risk assessment for the 1918 virus, to which these proposed studies can be compared. Similarly comparison of the 1918 virus to other virulent Influenza viruses (*e.g.* H5N1) with equally high case fatality rates would be useful to inform the assessment.

16) Given the inherent virulent properties of the virus; severity of infection; rapid onset of disease; and person to person transmission; there is a case to advise work involving the 1918 virus should only be undertaken at CL4 as for the non-human primate work in Canada. However, given the availability of prophylaxis, the criteria set out in COSHH indicates that it may be sufficient to advise on CL3 with specific additional containment measures dependent on the nature of the work. This is the approach adopted in the USA i.e. '*BSL3-enhanced*'.

17) The local risk assessment would need to consider amongst other things, the starting material (*e.g.* volumes, titres), routes of exposure (*e.g.* aerosols, splashes, spillages, use of sharps, infected animal bites), activities affecting the risk of exposure (*e.g.* diagnostic assays or transmission studies in animal models), when determining the most appropriate containment. Wider consultation (particularly amongst the Influenza community) on the inherent properties of the 1918 virus, the effectiveness of prophylaxis and the potential type and range of activities envisaged may be beneficial in assessing the most appropriate containment for work with this virus.

Action

17) Advice is being sought in relation the risks to workers and others from work involving the 1918 influenza A virus. In particular, members' views are sought on the following:

- Does the HSE guidance '*Advice on Working with Influenza virus*' (attached) need to be amended to reflect the need for specific advice on containment for the 1918 virus?
- Consultation with the wider scientific community, in particular those working in the influenza field on the inherent properties of the 1918 virus; the effectiveness of prophylaxis; and the potential type and range of activities envisaged.

References

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4) Taubenberger & Morens (2006), '*1918 Influenza: the Mother of all pandemics*', Emerging Infectious Diseases; 12; 15-22;
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9) Zambon (2007), '*Lessons learned from the 1918 Influenza*', Nature Biotechnology, 25(4); 433-434
10) Tumpey *et al* (2002), '*Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus*', Proceedings of the National Academy of Science; 99; 13849-13854;
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12) *Update on Avian Influenza A (H5N1) Virus Infection in Humans: Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus',* New England Journal of Medicine; 358; 261-273
13) Approved List of Biological Agents, HSE Books, HSE website
14) Approved Code of Practice & Guidance (L5)

15) HSE guidance entitled '*Advice on working with Influenza viruses*', HSE website
16) Biosafety in Microbiological & Biomedical Laboratories (BMBL), 2007, 5th Edition, USDHHS, NIH, CDC – '*Agent Summary Statement for Influenza*', pg 209-213.