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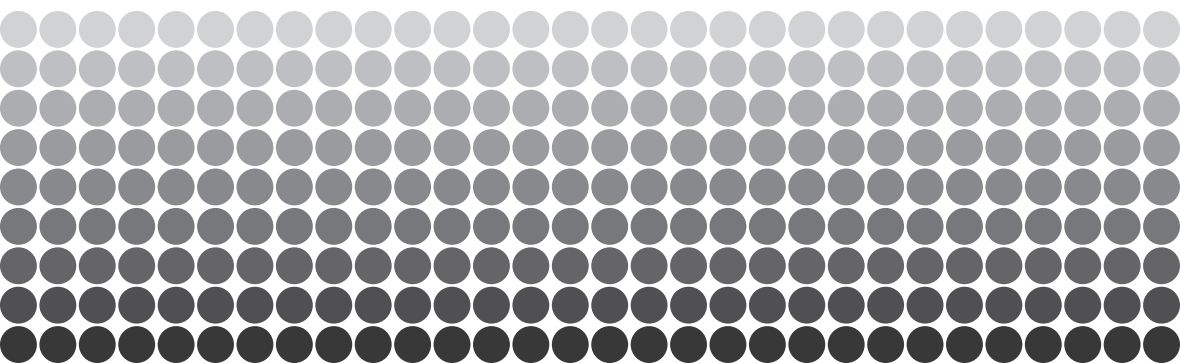
Armaments, Disarmament and International Security

Oversight of dual-purpose research in the life sciences

PETER CLEVESTIG AND JOHN HART



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IV. Oversight of dual-purpose research in the life sciences

PETER CLEVESTIG AND JOHN HART

In 2012 the World Health Organization (WHO) met to consider whether and how to restrict avian influenza research in the midst of a controversy about publishing details on the creation in a laboratory of a strain of influenza that can be transmitted between mammals.[1] Authorities in the United States issued a new policy to mitigate biorisks in life sciences research that attempts to further institutionalize oversight and evaluation procedures in the area of dual-use research of concern in the life sciences. The WHO also confirmed the existence of a novel coronavirus and alerted its members in accordance with the International Health Regulations (IHR).

A novel coronavirus

On 22 September the United Kingdom informed the WHO of the case of a person in London who had presented symptoms of the virus on 3 September and who had previously travelled to Saudi Arabia and Qatar.[2] On 7 September he was admitted to a hospital in Doha, Qatar, and he was transferred to the UK on 11 September.[3]

Professor Maria Zambon's laboratory at the UK's Health Protection Agency (HPA), in consultation with the laboratory at Erasmus Medical Centre in Rotterdam, the Netherlands, and the WHO, evaluated the sample from Qatar. The London strain was '99.5 percent identical with the Dutch team's virus', which had been obtained from a patient travelling from the Arabian peninsula.[4] The HPA then confirmed that the virus matched that obtained from an isolate that was taken from the lung tissue of a 60-year old Saudi national who had died earlier in 2012.[5]

The cases raised concern because of their unknown severity, number and geographic distribution, and the similarity of the virus to another coronavirus which causes severe acute respiratory syndrome (SARS).[6]

[1] World Health Organization, 'Technical consultation on H5N1 research issues: consensus points', 16–17 Feb. 2012, <http://www.who.int/influenza/human_animal_interface/consensus_points/en/>.

[2] World Health Organization, 'Novel coronavirus infection: update', Global Alert and Response (GAR), 25 Sep. 2012, <http://www.who.int/csr/don/2012_09_25/en/index.html>.

[3] World Health Organization (note 2).

[4] Kelland, K., 'Finding a new virus: spit, sequencing and serendipity', Reuters, 28 Sep. 2012, <http://www.reuters.com/article/2012/09/28/us-virus-discovery-idUSBRE88R0U620120928>; and World Health Organization (note 2).

[5] World Health Organization (note 2).

[6] See Raveché, B., 'International public health diplomacy and the global surveillance of avian influenza', *SIPRI Yearbook 2008*, pp. 456–69; and Njuguna, J. T., 'The SARS epidemic: the control of infectious diseases and biological weapon threats', *SIPRI Yearbook 2004*, pp. 697–712.

Biorisks oversight

On 29 March 2012 the US National Institutes of Health (NIH) issued a new policy to mitigate biorisks in life sciences research that defines dual-use research of concern as

> life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.[7]

This definition is based on the US National Science Advisory Board for Biosecurity (NSABB) definition.

The application of this policy is based, in part, on a list of 14 agents and toxins of particular concern, and 7 categories of experiment (based on NSABB categories for research of concern). The 7 categories of experiment are: (*a*) 'enhances the harmful consequences of the agent or toxin'; (*b*) 'disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification'; (*c*) 'confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies'; (*d*) 'increases the stability, transmissibility, or the ability to disseminate the agent or toxin'; (*e*) 'alters the host range or tropism of the agent or toxin'; (*f*) 'enhances the susceptibility of a host population to the agent or toxin'; and (*g*) generates or reconstitutes an eradicated or extinct agent or toxin listed in Section (III.1)' (i.e. on the list of 14 agents and toxins).

The new policy would require funders to review ongoing and future research that falls under these criteria and to establish management criteria for such research, including screening by the Institutional Biosafety Committees (IBC) based on eight questions to be answered by the researchers and on a report by the National Research Council.[8] A positive response to any of the eight questions would prompt a two-phase review by a dual-use research review committee (DURRC).

[7] US Department of Health and Human Services, National Institutes of Health (NIH), 'United States Government policy for oversight of life sciences dual use research of concern', [n.d.], <http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf>.

[8] National Institutes of Health, 'Institutional biosafety committees', [n.d.], <http://oba.od.nih.gov/rdna_ibc/ibc.html>; Boston University, 'Dual use research of concern (DURC)', [n.d.], <http://www.bu.edu/orc/durc/>; and National Research Council of the National Academies, *Biotechnology Research in an Age of Terrorism: Confronting the Dual-use Dilemma* (National Academies Press: Washington, DC, 2004).

Avian influenza research controversy[9]

In 2012 important developments in research on highly pathogenic avian influenza A (A/H5N1) occurred following the initial disclosure, at a conference in Malta on 12 September 2011, that influenza capable of airborne transmission between mammals can be derived in the laboratory.[10] The research, funded by the US National Institute of Allergy and Infectious Diseases (NIAID), was performed by two independent groups that were based in the Netherlands and the USA. The two groups submitted their work for publication in *Science* and *Nature* in 2011. However, their publications were delayed and instead initiated international debate on biosecurity versus scientific freedom, especially in regard to the dual-use potential of research on transmissibility of A/H5N1, and led to the further development of research oversight strategies.[11]

Experimental significance

The research originated from a NIAID call for proposals following the 2006 Report of the Blue Ribbon Panel on Influenza Research, which recommended that priority be given to understanding how influenza viruses circulate between animal reservoirs and the evolutionary pressures that lead to new emerging subtypes.[12] In 2009 the WHO also recommended that research on virus-specific factors for transmissibility should be prioritized to allow more rapid identification of emerging influenza strains with pandemic potential.[13]

Both the Dutch and the US research groups set out to evaluate the potential for H5N1 to cause a pandemic, by examining its ability to become transmissible through respiratory droplets, and to identify the required genetic and molecular changes. The researchers genetically modified influenza A strains carrying the H5 hemagglutinine (HA) gene and managed to induce airborne transmissibility through serial passage in ferrets. Serial passage is the process of infecting a series of hosts to either attenuate a

[9] For background see Tucker, J. B. (ed.), *Innovation, Dual-Use and Security: Managing the Risks of Emerging Biological and Chemical Technologies* (MIT Press: Cambridge, MA, 2012).

[10] European Scientific Working Group on Influenza (ESWI), <http://www.eswiconference.org/>.

[11] 'Bridging science and security for biological research: a discussion about dual-use review and oversight at research institutions', Virtual Biosecurity Center, Sep. 2012, <http://virtualbiosecuritycenter.org/library/bridging-science-and-security-for-biological-research-a-discussion-about-dual-use-review-and-oversight-at-research-institutions>.

[12] US National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), 'Report of the Blue Ribbon Panel on Influenza Research', 11–12 Sep. 2006, <http://www.niaid.nih.gov/topics/flu/documents/influenzablueribbonpanel2006.pdf>, pp. 11–12.

[13] World Health Organization (WHO), Global Influenza Programme, 'WHO public health research agenda for influenza, version 1, 2009', 2010, <http://www.who.int/influenza/resources/research/2010_04_29_global_influenza_research_agenda_version_01_en.pdf>; and Shinya, K. et al., 'Avian flu: influenza virus receptors in the human airway', *Nature*, vol. 440, no. 7083 (23 Mar. 2006), pp. 435–36.

virus or enhance its virulence by forcing mutation via exposure to the host immune system. Ferrets are a common model for influenza research as they are susceptible to both human and avian viruses and develop respiratory disease similar to humans.[14] Influenza A/H5N1 does not naturally possess the ability to transmit through respiratory droplets in humans due to its inefficient replication in the upper respiratory tract. Human and avian influenza viruses differ in their receptor recognition by HA. Thus, avian influenza virus has difficulty replicating efficiently in the upper respiratory tract in humans where virus load is essential for droplet (air) transmission.[15] Avian influenza does not readily transmit between mammals due to this difference in co-receptor preference. The research is significant because very small genetic changes can make avian influenza air-borne transmissible between ferrets, which are mammals—as are humans.

The US research group, headed by Dr Yoshihiro Kawaoka at the University of Wisconsin–Madison, used a reassortant influenza strain with seven gene segments from the 2009 pandemic influenza A/H1N1 (swine flu) and a H5N1-derived H5 subtype HA gene.[16] Ferrets were infected with the virus, which was allowed to reassort between the animals. The air transmissibility of one reassortant virus carrying four mutations in H5 HA was tested by placing the infected animal adjacent to healthy ferrets. Two-thirds of the healthy animals became infected and all of those that were exposed developed antibodies (in a process known as seroconversion).[17]

The Dutch research group, headed by Dr Ron Fouchier, used a wild-type influenza A/H5N1 strain (i.e. the state in nature of the pathogen) sourced from Indonesia to explore potential mutation towards air transmissibility. The Influenza virus A/Indonesia/5/2005, derived from a human patient, was chosen due to its incidence of human infections and high mortality rate. Similar to the US group, the Dutch researchers used site-directed mutagenesis to induce four amino acid substitutions (mutations) in the receptor binding site (RBS) of the H5 subtype HA gene, which has been identified in a human case of H5N1 infection.[18] The researchers aimed at

[14] Smith, W. et al., 'A virus obtained from influenza patients', *The Lancet* (1933), pp. 66–68.

[15] Sorrell, E. M. et al., 'Predicting "airborne" influenza viruses: (trans-) mission impossible?', *Current Opinion in Virology*, vol. 1, no. 6 (Dec. 2011), pp. 635–42.

[16] On reassortment see Neumann, G. et al., 'Generation of influenza A viruses entirely from cloned cDNAs', *Proceedings of the National Academies of Science*, vol. 96, no. 16 (3 Aug. 1999), pp. 9345–50.

[17] Imai, M. et al., 'Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets', *Nature*, vol. 486 (21 June 2012), pp. 420–28.

[18] On site-directed mutagenesis (also known as site-specific mutagenesis) see Flavell, R. A. et al., 'Site-directed mutagenesis: effect of an extracistronic mutation on the in vitro propagation of bacteriophage Qbeta RNA', *Proceedings of the National Academy of Sciences*, vol. 72 no. 1 (Jan. 1975), pp. 67–71. On the RBS of H5 subtype HA gene see also Chutinimitkul S. et al., '*In vitro* assessment of attachment pattern and replication efficiency of H5N1 influenza A viruses with altered receptor specificity', *Journal of Virology*, vol. 84, no. 13 (July 2010), pp. 6825–33; and Russell, C. A. et al., 'The potential for respiratory droplet transmissible A/H5N1 influenza virus to evolve in a mammalian

attaining mutant H5N1 viruses with a specificity towards a receptor that predominates on mammalian upper respiratory tract cells, including in ferrets. The viruses were then 'passaged' 10 times and mutants selected for testing of airborne-transmissibility using the same technique as that used by the US group. The researchers concluded that highly pathogenic avian influenza A virus (HPAI) has the potential to evolve directly into an air-transmissible variant without an intermediate host, as previously assumed, highlighting the risk of such a variant emerging and posing a pandemic threat to humans.[19]

The security implications

All experiments with live viruses were conducted under enhanced biosafety level 3 (BSL-3+) containment conditions following current standards and guidelines for work.[20] The research was presented before peers prior to submission for publication and concerns about its potential malicious use were not raised at the time. However, both experiments came under much criticism from security specialists following submission to journals, despite the scientists' claiming to have carefully planned the experiments in regard to biosafety and biosecurity and in consultation with experts.[21] In December 2011 the US NSABB, which is tasked with providing advice and guidance on biosecurity oversight of dual-use research, reviewed the potential security implications of the research papers. It concluded that both papers carried potentially sensitive methodological information and recommended to *Nature* and *Science* that, before publishing, the papers be redacted by having key methodological parts removed, that the potential public health benefits be better explained, and that the biosafety and biosecurity measures taken during experimentation be detailed. Specifically, the NSABB recommended that 'the manuscripts not include the methodological and other details that could enable replication of the experiments by those who would seek to do harm'.[22]

host', *Science*, vol. 336, no. 6088 (22 June 2012), pp. 1541–47. On the human case of H5N1 infection see Yamada, S. et al., 'Letter, haemagglutinin mutation responsible for the binding of H5N1 influenza A viruses to human-type receptors', *Nature*, 16 Nov. 2006, pp. 378–82.

[19] Herfst, S. et al., 'Airborne transmission of influenza A/H5N1 virus between ferrets', *Science*, vol. 336, no. 6088 (22 June 2012), pp. 1534–41.

[20] BSL-3+ denotes laboratories with appropriate enhancements above the defined containment criteria of BSL-3 containment laboratories. US Department of Health and Human Services (HHS), *Biosafety in Microbiological and Biomedical Laboratories*, 5th edn, HHS publication no. (CDC) 21-1112 (HHS: Washington, DC, Dec.2009), pp. 236–38.

[21] Roos, R., 'Research on contagious H5N1 viruses: space suites needed?', University of Minnesota, Center for Infectious Disease Research & Policy (CIDRAP), 6 Mar. 2012, <http://www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/mar0612biosafety.html>.

[22] US Department of Health and Human Services, National Institutes of Health (NIH), 'Press statement on the NSABB review of H5N1 research', NIH News, 20 Dec. 2011, <http://www.nih.gov/news/health/dec2011/od-20.htm>.

In January 2012 a group of leading influenza researchers reported, through a letter in *Science*, that they had agreed to a 60-day moratorium on sensitive H5N1 research in order to allow international discussion of the future safe and secure communication of such research.[23] The following month the WHO hosted a meeting of 22 influenza experts, public health officials and journal editors from 11 countries to discuss the reports. In contrast to the NSABB, the WHO recommended that they be published in full, after a delay.[24] The meeting concluded, although not unanimously, that the public health benefits and scientific value of improving influenza pandemic preparedness and response—in conjunction with the complexity of attempting to share the full methodology—overshadowed the bioterrorism concerns expressed by the NSABB. Nonetheless, the participants supported delaying publication in accordance with the voluntary 60-day moratorium that expired on 20 March. At the meeting the lead researchers distributed original unredacted versions of the papers and versions redacted in accordance with the NSABB's recommendations; all distributed copies were subsequently destroyed in front of the group.[25]

The export control laws of both the Netherlands and the USA include limits on the export of sensitive information, with exemptions for material that is shared openly and fully in scientific publications. The guidelines of the Australia Group, an informal, non-legally binding, multilateral trade control arrangement, do not restrict research that is basic, although 'applied' research may be subject to transfer controls.[26] Since the NSABB recommended redactions to which the authors also subsequently acceded, export control regulations were in principle applicable to both papers and their immediate publication could have been in violation of the law, carrying criminal penalties.[27]

Ultimately, the NSABB voted unanimously that the Kawaoka group's research be published in full, but it voted 12 to 6 for endorsing publication of the Fouchier group's research. Michael Osterholm, a US virologist, complained that the parameters of the NSABB meeting were 'designed to produce the outcome that occurred'.[28]

[23] Fouchier, R. et al., 'Letters: pause on avian flu transmission research', *Science*, vol. 335 (27 Jan. 2012), pp. 400–401.

[24] World Health Organization (WHO), 'Public health, influenza experts agree H5N1 research critical, but extend delay', News release, 17 Feb. 2012, <http://www.who.int/mediacentre/news/releases/2012/h5n1_research_20120217/en/index.html>.

[25] Cohen, J., 'WHO group: H5N1 papers should be published in full', *Science*, vol. 35 , no. 6071 (24 Feb. 2012), pp. 899–900.

[26] For a brief description of the Australia Group see annex B in this volume; and on developments in 2012 see chapter 10, section IV, in this volume.

[27] Greenfieldboyce, N., 'Bird flu studies mired in export control law limbo', National Public Radio, 10 Apr. 2012, <http://www.npr.org/blogs/health/2012/04/10/150311034/bird-flu-studies-mired-in-export-control-law-limbo>; and Ohio State University, Office of Research Compliance, 'Export control', <http://orc.osu.edu/regulations-policies/exportcontrol/>.

[28] 'Jail-bird flu', *The Economist*, vol. 403, no. 8782 (27 Apr.–4 May 2012), p. 69.

On 2 May 2012 *Nature* published the paper by the Kawaoka group, following revision and another review by the NSABB, which reversed its recommendations on redaction, thus removing the export control restriction.[29] The Dutch paper, in principle, remained under Dutch export restrictions until 23 April, when the group received an export licence; *Science* published the paper on 22 June.[30]

[29] Roos, R., 'Export controls still blocking publication of Fouchier's H5N1 study', University of Minnesota, Center for Infectious Disease Research & Policy (CIDRAP), 10 Apr. 2012, <http://www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/apr1012h5n1.html>.

[30] See also explanatory letter submitted by the Dutch Ministry of Societal Health, Well-being and Sport to the Chairman of the Second Chamber of the Dutch Parliament, available at 'Kamerbrief met de stand van zaken onderzoek Erasmus Medisch Centrum naar H5N1' [Letter on the state of H5N1 research at the Erasmus Medical Centre], 7 Mar. 2012, <http://www.rijksoverheid.nl>.