

Dual-use research and the H5N1 bird flu: Is restricting publication the solution to biosecurity issues?

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Recent studies altering the host range of the H5N1 bird flu virus have refueled intense debates over the potential misuse of academic life science research. To curtail the bioterrorism threat, it has been suggested that dissemination of the research results and methodology should be restricted. However, doubts have been raised over the suitability and effectiveness of this measure. Using the H5N1 studies as an example, this paper summarizes the main arguments of the debate. Particular attention is paid to the issue of the tacit knowledge required to replicate published life science research results, which has so far received limited attention. Taking into account the importance of tacit knowledge for life science research, it is argued that preventing publication of the methodology does not decrease the threat of bioterrorism.

Keywords: dual-use research of concern; life science research; biosecurity; tacit knowledge; influenza.

1. Introduction

Since the anthrax attacks in 2001, the dual-use potential of life science research has been intensely discussed. Fears of published research findings serving as a blueprint for building biological weapons have especially troubled US policy-makers (Malakoff 2001). Initially, the term dual-use applied to engineering and information technologies and related knowledge that may be used for both peaceful and military purposes with little or no modification (Hall 1965; Panel on Scientific Communication and National Security 1982). The rapid advances of life science research in recent years have pushed its experiments, results, and related technologies into the center of the dual-use debate.

Long before the misuse potential of life science research received so much public attention, the development, production and stockpiling by state actors of bacteriological and toxic weapons had been banned internationally by the 1972 Bioweapons and Toxin Convention (BTWC). However, the apparent ease with which life science knowledge develops and diffuses is perceived to have widened the range of actors with the potential to develop bio-weapons from state actors to non-state actors. The anthrax attacks, and the failure to reinforce the BTWC

to include non-state actors in late 2001, raised doubts over its effectiveness to address the current challenges and initiated this controversial debate (McLeish and Nightingale 2007; Tucker 2002).

The concerns have been publicly discussed after selected scientific papers on pathogenic viruses were published, including a paper on an engineered mousepox virus that overcomes vaccine protection (Jackson et al. 2001), a publication describing the first *de novo* synthesis of a pathogen (the poliovirus) (Cello et al. 2002), a study identifying virulence factors that distinguish the causative agent of smallpox, variola virus, from its close relative, vaccinia virus (Rosengard et al. 2002), a paper characterizing the reconstructed 1918 Spanish influenza pandemic strain (Tumpey et al. 2005), and recent studies on mutated versions of the H5N1 bird flu (Herfst et al. 2012b; Imai et al. 2012). To prevent deliberate misuse of such published knowledge, there have been calls for tighter regulations and restrictions on academic research and the dissemination of research results (Tucker 2002; Wallerstein 2002; Resnik and Shamoo 2004; Gaudioso and Salerno 2004; van Aken 2006). In addition, a variety of international and local policy measures have been implemented. For example, the US government has defined a list of ‘select

agents' with the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products.¹ US government regulations control research with, and transfer of, these 'select agents'.² Further measures include: publication guidelines for journals to pre-screen potentially sensitive publications (Atlas et al. 2003), US government oversight of research projects and possible classification of sensitive research,³ the implementation of screening guidelines for synthetic DNA orders from official providers for sequences encoding select agents and toxins,⁴ and the establishment of codes of conduct for scientists.⁵

In an attempt to address concerns over life science research and to find a formal definition of dual-use research, the US National Academies published the highly influential report 'Biotechnology Research in an Age of Terrorism' (National Research Council 2004). The so-called Fink report⁶ defines dual-use research of concern (DURC) as:

...research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or material.

In addition, the report defined seven categories of 'experiments of concern' to be scrutinized when designing research programs and publishing sensitive results. These include:

- (1) to render a vaccine ineffective
- (2) to create resistance to therapeutically useful antibiotics or antiviral agents
- (3) to enhance the virulence of a pathogen or render a non-pathogen virulent
- (4) to increase the transmissibility of a pathogen
- (5) to alter the host range of a pathogen
- (6) to enable the evasion of diagnostic/detection modalities
- (7) to enable the weaponization of a biological agent or toxin

This paper will outline that categorizing and focusing on 'dangerous technologies and pathogens' reflects a limited perspective on the dual-use dilemma. As McLeish and Nightingale (2007) pointed out, an unambiguous definition of 'dangerous' cannot be agreed upon as this:

...is not a descriptive term that denotes the property of something but an expressive term that refers to how we think about the possible implications of the properties of something.

As a result, different people, even experts, will evaluate the dangerousness of technologies and pathogens differently. This is reflected by the current discourse around two studies on the highly virulent H5N1 bird flu virus. Researchers have mutated the virus so that it can spread amongst mammals via aerosol (Herfst et al. 2012b; Imai et al. 2012). However, as no human studies are desirable,

any attempts to determine the pandemic potential of the virus remain speculative. It is this unknown potential, or in other words, our ignorance about the implications of releasing the virus into the environment, that leads to the disagreement amongst virology experts on whether the mutated H5N1 virus and the related experiments can truly be termed 'dangerous' (Palese and Wang 2012; Bouvier 2012; Inglesby et al. 2011; Morens et al. 2012).

With this in mind, a fixed list of 'dangerous technologies and pathogens' and 'experiments of concern', although helpful, appears to be of limited use to define which type of research may pose a threat to public health and safety. A more flexible perspective on dual-use technology and 'dangerous science' is needed to ensure that policy measures keep up with the rapid developments in life science research and secure the benefits of academic research. This different perspective on the development of life science research and its impact on the dual-use debate has been discussed amongst sociologists (McLeish and Nightingale 2007; Vogel 2008; Tucker 2011). However, it has not yet found its way into the public debate over dual-use research. By using the controversially debated H5N1 studies as a case study, this paper will emphasize the impact of an alternative perspective on the dominant biosecurity discourse and highlight how an alternative view of 'dangerous' life science research may alter the prioritization of policy responses.

Furthermore, in the light of an alternative perspective, this paper will evaluate the effectiveness of one key policy measure: restricting dissemination of the research methodology. It has been argued that the potential dangers and disastrous consequences of academic research demand the implementation of precautionary measures such as restricting publication (Osterholm and Relman 2012; Kuhlau et al. 2011; Resnik 2013). Thus, besides outlining a different perspective on the potential dangers of dual-use life science research, this paper will summarize the main arguments of the dual-use debate around the H5N1 case and make use of the precautionary principle (PCP) to evaluate whether preventing publication of the methodology of DURC is an effective tool to decrease the bioterrorism threat.

2. Research on highly virulent, possibly human transmissible, H5N1 influenza virus strains

Two recent studies on the H5N1 bird flu have intensified the international debate over DURC. They describe a set of mutations necessary for the highly virulent H5N1 bird flu virus to transmit amongst mammals, possibly humans (Herfst et al. 2012b; Imai et al. 2012). The H5N1 case raised concerns for several reasons: the bird flu virus is highly virulent, it is listed on the select agent and toxin list, and the performed experiments can be allocated to

category 5 (to alter the host range of a pathogen) of the Fink report.

When submitted to the journals *Nature* and *Science* for publication, the editors referred the two studies to the National Advisory Board for Biosecurity (NSABB). Established by the US government as a result of the Fink report, the NSABB provides advice, guidance and leadership regarding biosecurity oversight of DURC in the USA.⁷ Its decisions are, however, not legally binding. For the first time, the NSABB had voted against the publication of the methodological details in order to prevent ‘those who would seek to do harm’ from replicating the experiment.⁸ The board had concluded that the harms of fully publishing these results exceeded the benefits of publication (Berns et al. 2012). Two crucial aspect may have influenced the board’s so far unique decision: the official World Health Organization estimate for the case fatality rate of H5N1 avian influenza of around 60% (Beigel et al. 2005)⁹, and misunderstandings of technical details (Morens et al. 2012).¹⁰ Hence, fears of potentially disastrous consequences for public health resulting from an unintended or intended release of the engineered H5N1 strains were particularly strong (Berns et al. 2012).

To allow time for evaluating the risks and benefits of the research, the influenza research community proposed a three-month voluntary moratorium¹¹ on research involving highly pathogenic avian influenza H5N1. During that time, the pros and cons of publishing the manuscripts were intensely discussed by scientific and security experts, the NSABB, the WHO and the US government. Finally, a majority vote of 6 to 12¹², strongly opposed by the NSABB member Michael T. Osterholm,¹³ led to the revision of the NSABB’s decision resulting in full publication of the two papers (Herfst et al. 2012b; Imai et al. 2012). The research moratorium proposed by the influenza community was extended beyond the originally proposed three months to provide time for further evaluation of biosafety¹⁴ and biosecurity¹⁵ concerns (Fouchier et al. 2012a). The research finally commenced one year later in January 2013 (Fouchier et al. 2013).

3. To publish or not to publish?

Fouchier and Kawaoka, the two corresponding authors of the studies, defended conducting, publishing and continuing the work on mammalian transmissible H5N1 virus strains by emphasizing the benefits of their work and by stressing the importance of their research for pandemic preparedness. Their proof-of-principle experiments show that few mutations could enable the virus to be transmitted via aerosols amongst mammals, possibly humans, while maintaining virulence (Herfst et al. 2012b; Imai et al. 2012). According to the authors, the study highlighted the need to monitor H5N1 outbreaks in poultry with more urgency, to implement more

aggressive control programs, and to adapt current pandemic preparedness plans (Kawaoka 2012; Fouchier et al. 2012a, 2013).

However, the NSABB experts had initially decided that the benefits of the study would not outweigh the risks of publication (Berns et al. 2012). The main risks in publishing both papers in full were described as twofold. First, the results and methodology of the H5N1 studies, if published, could be directly misapplied by others to pose a threat to public health and safety (biosecurity risk). In particular, the possibility of synthesizing the flu mutant strains based on published sequences and the identified mutations raised concern. The NSABB members Osterholm and Relman argued that:

...reverse engineering and synthesizing a mutant A/H5N1 virus strain will be easier for many scientists if they have access to the complete methods and results of the two research efforts and do not need to surmise the steps of the investigators. (Osterholm and Relman 2012)¹⁶

Second, research with the virus could result in an unintentional release into the environment (biosafety risk).¹⁷ In order to mitigate the biosecurity and biosafety risks associated with publication, the board had suggested redacting the papers and excluding any description of the methodology (Berns et al. 2012). However, the effectiveness of partially restricting or even preventing publication was repeatedly questioned.

The main argument used in favor of publishing the research in full was the necessity to share the research results in the wider scientific community to ensure free and open science. Withholding the methodology has been criticized as unethical, and as an assault on the openness, accessibility and quality of scientific research (Bouvier 2012; Racaniello 2012). It was argued that omitting the methods from the manuscripts presents a barrier for researchers to engage in further research thereby limiting the scientific output essential to combat the natural pandemic threat of influenza viruses (Palese and Wang 2012; Morens et al. 2012; Kawaoka 2012; Perez 2012; Faden and Karron 2012; Casadevall and Shenk 2012). In contrast, it was claimed that, although the results are valuable, publishing the results would not bring about any additional benefit for pandemic preparedness as resources to detect the virus and support programs for a number of the H5N1 endemic countries are often lacking (Osterholm and Relman 2012).

Furthermore, it was argued that publishing the papers in full may result in more laboratories working with the virus, possibly some with insufficient safety standards, thereby increasing the chance of an unintentional release (Inglesby et al. 2011; Osterholm and Henderson 2012). Other opponents of publishing claimed that sharing the results and methodology with a small group of selected experts would be sufficient to secure beneficial outcomes (Osterholm and Relman 2012; Fouchier et al. 2012b).

Table 1. H5N1 debate: Summary of arguments for and against publication of research methodology

Pro publishing	Reference	Contra publishing	Reference
Benefits for pandemic preparedness: public health threat of H5N1 strains (mammalian transmission, maintenance of virulence), enables monitoring of current H5N1 strains for critical mutations, need for enhancement of current preparedness plans 'Nature is more inventive than men'	Fouchier et al. 2012b; Herfst et al. 2012a; Perez 2012; Palese and Wang 2012; Kawaoka 2012; Morens et al. 2012	Knowing the results (mutations) is sufficient (no enhancement of disease surveillance or countermeasure availability expected in the near future)	Osterholm and Relman 2012
Accessibility of the methodology through textbooks and other open sources such as published papers	Herfst et al. 2012a; Perez 2012; Palese and Wang 2012; Morens et al. 2012	Access to the complete methods and results makes it easier for scientists to synthesize a mutant A/H5N1 virus strain (increase in bioterrorism threat through easier access)	Osterholm and Relman 2012
Need for trained experts and high-tech research facilities to replicate results	Palese and Wang 2012; Racaniello 2012; Fouchier 2012	Replication not difficult in technological terms	Zimmer 2012
Sharing the results in the wider scientific is a basic requirement for scientific endeavor (value of free science)	Racaniello 2012; Bouvier 2012	Sufficiency of sharing the results with a small group of selected experts, even benefit of that is questionable	Osterholm and Relman 2012; Fouchier et al. 2012c; Osterholm and Henderson 2012
Prerequisite for ensuring quality of scientific research by enabling post-publication peer-review and replication (value of high quality in science)	Bouvier 2012		
Barrier for researchers to continue the research, need for publication to ensure further research and prospective benefits	Perez 2012; Palese and Wang 2012; Kawaoka 2012; Morens et al. 2012; Bouvier 2012; Faden and Karron 2012; Casadevall and Shenk 2012	Encouragement for more labs to initiate dual-use research on H5N1 (increase of the biosecurity and biosafety threat)	Osterholm and Henderson 2012; Inglesby et al. 2011

This has been rejected for the same reasons as restricting publication (Morens et al. 2012). It was also criticized on the grounds that, while providing a main barrier to research, the measure would be futile in the long term, given that the methodology can be found in virology textbooks (Palese and Wang 2012; Morens et al. 2012; Perez 2012; Herfst et al. 2012a) (for a summary of the arguments see Table 1).

4. DURC and the precautionary principle

Several groups, including the WHO and the NSABB, have proposed adopting risk–benefit analysis when addressing DURC issues.¹⁸ This recommendation has been followed throughout the discourse around the H5N1 studies. However, as pointed out by Andrew Stirling, a risk expert, under conditions of uncertainty and ignorance risk–benefit analysis fails (Klinke et al. 2006; Stirling and Scoones 2009). It is traditionally used for routine risks,

when the possible outcomes and their respective probabilities are known.

With regards to the H5N1 case, especially at the time of publication, the likelihood with which the risks and benefits of the research will come to pass is unknown. For example, to estimate the likelihood of misuse one needs access to information on the degree of training, intentions, financial, and personnel resources of potential bioweaponeers. Such knowledge is, however, not publicly available. It will be held by intelligence and security experts, if anyone has access to it at all (Selgelid 2009). Furthermore, as Rappert (2008) pointed out, risk and benefits will be open to a considerable amount of interpretation. This is reflected in the discourse on the H5N1 case. For example, experts do not agree on how 'dangerous' the mutated virus would be to human health, because data from the ferret model cannot be directly extrapolated to the human context (Bouvier 2012; Racaniello 2012; Fauci and Collins 2012).

In order to address the challenges associated with DURC, the bioethicists Kuhlau et al. (2011) have proposed to make use of the PCP as a 'rule of choice' with regards to DURC:

When and where serious and credible concern exists that legitimately intended biological material, technology or knowledge in the life sciences pose threats of harm to human health and security, the scientific community is obliged to develop, implement and adhere to precautionary measures to meet the concern.

Correspondingly, the NSABB members Osterholm and Relman have, in the light of the potentially disastrous consequences associated with the release of a human transmissible H5N1 virus, suggested to err in favor of 'do no harm'. They proposed to make:

...use of the precautionary principle when approaching the issue of DURC. (Osterholm and Relman 2012)

The PCP is designed for making practical decisions under uncertainty when no reliable quantitative data is available. It was originally created as a way to respond to environmental risks (Goklany 2001). For example, the PCP has been used to address issues such as: global warming, intensive dichlorodiphenyltrichloroethane (DDT)¹⁹ use, and the commercialization of genetically modified food. The principle has often been criticized for being too vague, overly risk-averse and an unscientific approach to decision-making due to a lack of a scientific basis (Brombacher 1999; Gray and Bewers 1996). Contrasting this critique, risk experts argue that under conditions of uncertainty,²⁰ ignorance²¹ and ambiguity²² sound scientific methods of risk assessment have in any case little justification (Stirling 2007; Hoffman-Riem and Wynne 2002). It is under these conditions that the PCP can be viewed as a general normative guide for policy-makers to acknowledge the benefit of doubt (Stirling 2007).

The critique of the PCP may also be related to the fact that the principle does not define which types of hazards it applies to, what level of (scientific) evidence is required, which preventive measures should be taken and with what force they are recommended (Sandin et al. 2002). However, Sandin, a bioethicist, argues that the PCP does not contradict science and has recommended establishing the following criteria when deciding whether to use the PCP (Sandin et al. 2002; Sandin 2009):

An action A is precautionary with respect to something undesirable U, if and only if 1) A is performed with the intention of preventing U, 2) the agent does not believe it to be very likely that U will occur if A is performed, and 3) the agent has externally good epistemic reasons a) for believing that U might occur, b) for believing that A will in fact at least contribute to the prevention of U, and c) for not believing that it to be certain or very likely that U will occur if A is performed.

Along these lines, Resnik (2003) argues that:

... the principle can be scientific provided that (1) the threats addressed by the principle are plausible threats, and (2) the precautionary measures adopted are reasonable.

He proposes to use epistemic criteria to determine whether a threat is plausible and to use practical considerations to determine whether a response to a threat is reasonable.

Considering the ignorance of risks and benefits associated with DURC studies such as the H5N1 research, the PCP could be a useful tool to analyze the reasonableness of preventing or banning the publication of results and methods as a precautionary measure. When applying the PCP using Resnik's and Sandin's framework, there are two main questions to answer. First, how plausible are the threats associated with publishing the H5N1 studies? Second, is censorship a reasonable mean to address the threat and prevent possible negative consequences?

In order to determine whether publishing the H5N1 papers in full presents a reasonable threat, one needs to discuss whether the engineered H5N1 strain could, in principle, cause a disastrous pandemic and whether the H5N1 publications could easily be misused by those who seek to do harm. In this context, the PCP does not specify the degree of scientific evidence required to determine what a reasonable threat might be. To solve this issue, Sandin et al. (2002) proposed to use a degree of evidence in qualitative terms such as 'scientifically supported strong suspicions' to evaluate the threat.

Thus, what is the scientific evidence supporting the suspicion that engineered H5N1 strains could pose a reasonable threat to human health? To begin with, it is true that the H5N1 virus infects humans, although transmission between humans remains limited (Yang et al. 2007). Another source of concern is the official mortality rate of about 60% (Beigel et al. 2005).²³ Virology experts, such as Palese, Bouvier, and Taubenberger believe the rate to be overestimated (Bouvier 2012; Palese and Wang 2012).²⁴ The true case fatality rate of the unmodified H5N1 virus is estimated to be between 1% and 33% (Li et al. 2008; Morens et al. 2012). In comparison, the fatality rate of the 1918 pandemic virus was estimated to be 2.5% (Li et al. 2008). The worst human influenza pandemic in history so far, raged from 1918 to 1919 and claimed an estimated 50 million lives (Taubenberger and Morens 2006). However, even if the true mortality rate of the mutant virus strains was much below the rate of the 1918 virus, pandemic spread of a deadly H5N1 variant would be a cause for significant public health concern.

Further data comes from the animal model in which human influenza viruses cause influenza-like illness (Maher and DeStefano 2004). Ferrets are susceptible to infection with the mutated H5N1 virus. According to the two studies, the virus can be transmitted amongst ferrets via aerosol while maintaining virulence (Herfst et al.

2012b; Imai et al. 2012). Hence, the mutant virus has the potential to infect and spread amongst humans. However, it should be noted that the results of these infection studies cannot be used directly to predict the transmissibility and pathogenicity of the virus in humans (Bouvier 2012; Morens et al. 2012; Racaniello 2012; Fauci and Collins 2012).

In conclusion, the threat is plausible: it is possible that the virus could cause a pandemic that would be devastating to the world's population, although there is no (and there will not be) concrete scientific evidence available. Next, the second question needs to be answered: is preventing or restricting publication a reasonable response to the threat of misuse? Would it significantly contribute to the prevention of the feared consequences?

5. The role of tacit knowledge

Many scientists have argued that preventing publication of the results and methodology does not prevent misuse. They argued that even if the methodology was omitted from the paper, an individual with the relevant training would be able to repeat the experiments. For example, Fouchier and colleagues, stated that their methodology can be found in many virology textbooks (Herfst et al. 2012a):

Individuals with bad intentions do not need to read the details in our manuscript because the methods for creating similar viruses have already been published widely.

A similar argument was used by Wimmer (2006):

... all methods used for the synthesis of poliovirus were published long before the experiment was conceived. Thus, we neither described new technologies to synthesize DNA nor invented novel methods to convert cDNA into infectious viral RNA.

This argument contrasts the current discourse about DURC, which assumes a direct correlation between technological advances in the life sciences and an increased threat of bioterrorism. By focusing on the ease of diffusion of knowledge and technologies, socio-technical aspects of biotechnology such as tacit knowledge, complexity and contingency are overlooked and possible challenges are disregarded, thus leading to the perception of an increased threat (Vogel 2008). Moreover, relying on this linear model of technical change may lead to a false prioritization of policy measures and an inappropriate focus on high-tech research (McLeish and Nightingale 2007; Vogel 2008; Leitenberg 1999).

Chyba (2006) has compared the rapid development of life science technologies to the evolution of computer power. He argued that the pace of development will make DNA synthesis and other biotechnologies increasingly available to individuals with only basic scientific skills. This view was repeatedly presented in media

reports covering the H5N1 case, for example by the *New York Times* (Zimmer 2012).

Indeed, as has been pointed out, life science research has evolved rapidly over the past decades. The emergence of gene technology, the development of high-throughput DNA synthesis and DNA sequencing machines, the completion of the human and other genome projects have significantly enhanced research efficiency and opened new possibilities. However, by taking this view, two important aspects are overlooked. First, it ignores the significant financial means and trained specialists required to operate these new technologies. For example, to ensure constant access to this vital scientific and technological expertise and to help to rationalize institutional resources, more and more so-called 'core service facilities' are being established at major universities with a life science focus (Sa 2008).²⁵ Those facilities are operated by staff scientists with various backgrounds and expert training ranging from bioinformatics to molecular biology, chemistry and engineering.

Second, the non-technological component of research is overlooked. In addition to sophisticated machines and technologies, there are many more steps involved when performing life science research. These often require very specific expertise and technical skills of the individual researcher that can only be learned through constant practice and observation of peers. Hence, even if 'laboratory processes have become more automated' as Chyba (2006) pointed out, it does not follow that 'less and less tacit knowledge is needed' to conduct life science research. Tacit knowledge was, and still is, an important factor not only for the success of life science research, but for science and technology in general.

The term tacit knowledge was first coined by Polanyi who defined it as:

... things that we know but cannot tell. (Polanyi 1962)

Since the 1960s much research has been done on the concept of tacit knowledge. Different forms have been defined including somatic-limit and collective tacit knowledge,²⁶ which are widely accepted, for example in the field of economics, psychology, and education.

Scholars have attempted to describe and measure the impact of tacit knowledge on the success of academic endeavors and the translation of academic knowledge into industrial applications (Leonard and Insh 2005; Somech and Bogler 1999; Zucker et al. 2002). For example, Harry M. Collins, a social scientist, has presented an insightful analysis of the importance of tacit knowledge for scientific research in physics (Collins 2001). He described the attempt of Western researchers to repeat experimental results published by Russian scientists during the Cold War. Only in the 1990s, after closely observing how the experiments were performed, did the Western researchers succeed in replicating the results. Collins drew the following

conclusions from his field observations: In order to successfully replicate an experimental result, researchers first have to understand and acknowledge the importance of tacit knowledge. Second, they have to trust the validity of the results, and third they need to know how difficult a procedure is, meaning how much patience with trial and error is required (Collins 2001).

The concept of tacit knowledge has not yet gained much attention in the biosecurity debate within life science research. Tucker (2011) and Vogel (2008) are among the few who have highlighted the importance of tacit knowledge used by life scientists during experimentation. In the context of life science research, Tucker (2011) defines 'tacit knowledge' as knowledge:

... that cannot be transmitted in writing but must be gained through years of hands-on experience in the laboratory.

Tacit knowledge plays, as Tucker (2011) recognizes, a central role when aiming to determine the biosecurity risks associated with life science research.

One of the few studies on tacit knowledge in the life sciences has been conducted by Kathleen Vogel. It involved members of the Wimmer group who published the first *de novo* synthesis of a virus (Cello et al. 2002; Vogel 2008). The group revealed that the most difficult part of the poliovirus synthesis was not the partially automated DNA synthesis. Instead, it was the construction of the virus: the production of the virus components, the assembly of those components into virus particles, and finally the incorporation of the virus' synthetic genetic material. According to the group, these steps, although around for more than 20 years '... require specialized laboratory know-how and practices only obtained by training, care, and attention to detail [and are difficult even for experienced researchers] (Vogel 2008). That the reconstruction or recovery of a pathogen would currently require someone 'skilled in the art' has been supported by other experts including the NSABB Working Group on Synthetic Genomics.²⁷ In the context of the H5N1 studies, Palese and Wang argue that the generation of engineered H5N1 based on the published raw sequence would require:

... (i) access to a sophisticated laboratory setting, (ii) proficiency in relevant concepts of molecular biology, and (iii) experience with laboratory methods related to viruses. (Palese and Wang 2012)

The author of one of the criticized H5N1 studies has used a similar argument:

It takes a lot of knowledge, together with perhaps ten years of training and a well-equipped high containment lab, even to reproduce our work. (Fouchier 2012)

In his simplistic portrait of biotechnology research, Chyba (2006) nevertheless raised an important question: Why is it that modern bioterrorist attacks²⁸ have been so

rare? Could the lack of capabilities be a main reason? Previous studies on failed and successful attempts to develop bioweapons provide possible answers. Two studies illustrating the impact of socio-technical aspects on bioweapons have been presented by Ouagrham-Gormley and Vogel (2010) and by Leitenberg (1999). Ouagrham-Gormley and Vogel (2010) show that a substantial part of the Soviet smallpox bioweapon development program was unable to create a workable biological weapon even though they had substantial expertise, resources, time, infrastructure and even detailed protocols at their disposal. They highlight:

... the local and personal character of bioweapons knowledge, specialized skills, and scientific know-how, which cannot be transferred easily from one person to another and from one location to another. (Ouagrham-Gormley and Vogel 2010)

They also concluded that depending on the social context, tacit knowledge plays an important role not only on the individual, but also on the communal level (collective tacit knowledge). As the most effective policy recommendation to prevent former Soviet weaponeers working in the USA from selling their knowledge, they suggested separating them from one another in order 'to allow the BW-related skills to decay over time'.

Leitenberg, a security expert, reached a similar conclusion on the importance of tacit knowledge for biological weapons construction. Despite extraordinary financial resources, access to modern equipment, despite sufficient time and the fact that there were individuals with graduate and postgraduate training amongst their members, the religious Japanese Aum Shinrikyo group failed to produce and disperse botulinum toxin or *Bacillus anthracis* (Leitenberg 1999; Ballard et al. 2001). Leitenberg concluded that:

... the experience of the Aum is therefore in marked contrast to the legion of statements by senior US government officials and other spokesmen claiming that the preparation of biological agents and weapons could be carried out in 'kitchens', 'bathrooms', 'garages', 'home breweries', and is a matter of relative ease and simplicity.

In a related study from 1995, the sociologists McKenzie and Spinardi (1995) highlighted the importance of socio-technological aspects with regards to nuclear weapons development. In their analysis based on interviews with nuclear weapons designers and computing experts, they emphasized that:

... tacit knowledge is also crucial to nuclear weapons development.

Thus, the work of Ouagrham-Gormley and Vogel, Leitenberg, and McKenzie and Spinardi indicates that:

... Because tacit knowledge is transmitted person to person, there are greater barriers to the spread of competence than

the traditional view might lead us to expect. (McKenzie and Spinardi 1995)

Another aspect to be considered in this context is the accessibility of bioweapons material. Rather than buying state-of-the-art laboratory equipment and investing great financial resources and time to synthesize a virus from scratch, pathogens more suited for a bioweapon could, for example, be stolen or isolated from the wild and subsequently modified to turn it into a category A bioterrorism agent as defined by the US Center for Disease Control²⁹ (Herfst et al. 2012a; Tucker 2003). Moreover, a study by Suk et al. (2011) suggests that instead of 'high-tech' activities, 'low tech' activities may be especially attractive to bioterrorists:

Contamination of food and water, and direct injection/application of a pathogen, all have much lower technical hurdles and might be expected to be rather more successfully deployed.

Indeed, in 1984, followers of Bhagwan Shree Rajneeshee, an Indian guru, deliberately contaminated salad bars at ten restaurants in the USA with salmonella resulting in 754 individuals with food poisoning (Wheelis et al. 2006).

Furthermore, many scientists have pointed out that although ferrets are a good model for human influenza infection, the results may not be directly applicable to humans as the potential for the transmission and lethality of engineered H5N1 in humans is unknown (Bouvier 2012; Morens et al. 2012; Racaniello 2012; Fauci and Collins 2012). Consequently, bioterrorists run the risk of discovering that the mortality and transmission rates of the engineered strains are comparable to a seasonal influenza after having invested much time and resources in replicating the H5N1 experiments.

Thus, it seems that attempting to replicate published dual-use results may pose more challenges than the common discourse reflects. Considering the importance of tacit knowledge, an individual with only minimal training should not be able to repeat the experiments even if the methodology was published. The more pressing question is how easily could a professional virologist replicate the results and produce sufficient amounts of the virus? First, withholding the methodology would likely result in a need for more time for 'trial and error'. Another factor that comes into play is the form and length of the methodology sections in papers. The explanations in such sections are usually short and of limited depth due to space limitations, besides only providing information on explicit knowledge. Commonly, researchers exchange more detailed protocols or even visit each other in their laboratories to be able to replicate published results. Furthermore, tacit knowledge may be essential for translating or adapting technologies to a new environment, not only on an individual level, but also on a communal level (Ouagrham-Gormley and Vogel 2010). In summary, depending on the degree of training and the tacit

knowledge needed to reproduce the experimental results, the task may pose significant hurdles even for specially trained individuals.

Two possible conclusions can be drawn from this analysis. Unskilled individuals or groups do not possess the explicit and tacit knowledge currently needed to make use of the published methodology of the H5N1 studies and reproduce the results. On the other hand, omitting the methodology would significantly delay, but not prevent, a skilled team of specifically trained scientists with the will, enough time, the right equipment and sufficient financial resources from replicating the H5N1 study results. With this in mind, prohibiting dissemination of the methodology could be regarded as ineffective in reducing the bioterrorism threat and as a result may be considered an unreasonable response to the biosecurity threat of DURC.

6. Discussion

This paper outlines that prohibiting publication of the methodology and results is not a reasonable response to the uncertain biosecurity threat. It contrast a recent analysis published by Resnik (2013) who argues that:

...re-dacted publication would have been a reasonable response to the threats posed by the controversial H5N1 papers if not for practical and legal problems.

Resnik seems to support the common assumption that the papers:

... provide terrorists with a recipe for making a bioweapon.

However, I would question that assumption and argue that replicating the H5N1 experiments is not very easy for individuals or groups with minimal training, or even for trained specialists. Neither is replicating the H5N1 studies the most suitable and easiest way to obtain a bioweapon. However, for individuals with specialty knowledge in influenza virology, this will not provide a real barrier. With enough time and resources at hand, they do not need to rely on the short methods section in the H5N1 papers, but will be able to combine their expert knowledge with textbook methodology in order to replicate the experiments.

Although replicating the results of the H5N1 studies is doable for trained individuals even without access to the methodology, omitting this information will provide a barrier for well-intentioned scientists. As the current system of academic research is built on openness and the exchange of study results, classification of results and potential funding cuts may divert scientists to other research fields. Prohibiting publication may even impose new risks. As Sandin et al. (2002) point out, the PCP should also:

...be applied to precautionary measures prescribed by the principle itself.

Less scientific research may mean a lack of crucial knowledge for pandemic preparedness necessary to address threats imposed by future natural human H5N1 pandemics. For example, the development of counter-measures (e.g. vaccination) may be prevented, thereby precluding society from obtaining the benefit of the research. This is especially worrisome as the prospective of benefits for public health are the motivation of such research and justification for public funding. In their analysis of the case, the bioethicists Faden and Karron (2012) refer to a:

... moral obligation to ensure that the results of that research are used to help reduce risks to global health.

There are further risks from limiting scientific openness. For example, sharing the results is a prerequisite for responsible conduct in science as peer review significantly contributes to ensuring the quality of the research and the research teams. Preventing this mechanism might have a negative impact on the quality of the research and thus may increase the likelihood of viral escape from the laboratory.

Regarding the biosafety concerns associated with a higher number of researchers working with the engineered strains—this issue may better be solved through enhanced biosafety regulations than through censoring the research, given the potential negative implication of censorship. Although it was discussed that enhanced Biosafety Level 3 (BSL 3) conditions are sufficient (Casadevall and Shenk 2012; Herfst et al. 2012a), Imperiale and Hanna (2012) proposed using BSL4 conditions until more evidence is available on the danger of the virus. A further biosafety measure would be to plan ahead and use a less virulent strain of the H5N1 virus. In fact, one of the two labs, in which the controversial H5N1 studies have been performed, did decide to use less virulent strains for their experiments (Imai et al. 2012).

In contrast to censorship, education and personnel screening to identify individuals with malicious intentions may be more reasonable and effective measures to mitigate biosecurity risks. For example in the USA, the Public Health Security and Bioterrorism Preparedness and Response Act (PL107-188) from 2002 requires that persons seeking to possess, use, or transfer agents and toxins listed on the 'select agents and toxins' list must undergo registration and must have a legitimate need to handle or use such agents and toxins.³⁰ Finally, secrecy is an ineffective tool of prevention. Before publication, the information on the H5N1 experiments had been available to many scientists and the editors of the two journals. Even if the US-based journal, *Science*, had been forced to follow the original NSABB recommendation to not publish the methodology, the UK-based *Nature* could have (and did) proceed with publication. There are many other journals and editors who do not fall under US legislation and may be willing to publish such manuscripts. Redaction of the papers would thus not be effective in reducing the threat as it would not prevent dissemination of the sensitive knowledge.

This analysis does not conclude that we should ignore the DURC problem, as it would not be a reasonable response to the threat. Preventing terrorists and states from using bioweapons is important. The DURC problem calls for a more detailed investigation of the biosafety and biosecurity risks associated with DURC that includes a fact- and case-based assessment of the potential for misuse. In this respect, the H5N1 papers could be regarded as a wake-up call for the scientific community. Although the dual-use issues associated with life science research have been discussed for the last decade, the H5N1 example illustrates how the restriction of research funding and publication could become a reality in the near future. In response to the H5N1 case, the US government has issued a new policy that allows research funding proposals sent to government agencies to be screened for DURC. It also allows for the classification of research results and the restriction of funding of research that raises concerns.³¹ However, how research proposals will be evaluated, that is how risks and benefits will be assessed and who will evaluate the proposals, remains unclear.³² Major differences in assessment of the term 'dangerous' in association with DURC might either result in the underestimation of risks and threats or may lead to the restriction of legitimate academic research. Thus, it has become more important than ever for the scientific community to address public concerns over DURC by establishing a transparent governance system (see Miller and Selgelid (2008) for an overview of possible options).

Governance options that restrict and control access to research results, as for example proposed by experts from the Center for International and Security Studies at Maryland (Steinbruner et al. 2007), may not be useful in the light of the analysis presented above. For ensuring oversight, the WHO has been suggested as an ideal governance body (Fouchier et al. 2012b). However, based on decades of experience with regulating smallpox research, the WHO may not be the ideal choice to prevent deliberate misuse of DURC due to financial and political dependencies and a strong influence of the pro-research fraction (Tucker 2006).

Nevertheless, the scientific community has a duty to consider the negative implications of their research and thus must find a way to address and possibly regulate DURC issues (Kuhlau et al. 2008). As has been repeatedly suggested, scientists should receive education in bioethics and familiarize themselves with 'experiments of concern' as defined by the Fink report and the BTWC (Dando et al. 2008; Pearson and Mahaffy 2006; Rappert et al. 2006). If possible, plans to mitigate potential risks, for example intensified security measures and personnel training and screening, must be prepared before the results of DURC are communicated to the public.

However, scientists will not be able to ensure that their research will never be misused. Thus, it is important that

the research is conducted with the intention of benefitting the public. The peer review system of science, which can only function if access to research result remains unrestricted, needs to ensure that only such research is supported. Furthermore, the potential benefits of the research need to be explained to the public as best as possible. Media sensationalism should be contrasted by facts. Scientists will need to explain in their papers, and possibly with accompanying media campaigns, the relevance and potential benefits of their DURC to ensure public understanding and support.

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Notes

1. The list includes a selection of viral, bacterial and fungal species as well as toxins. An updated list of select agents is accessible at <http://www.selectagents.gov/select%20agents%20and%20toxins%20list.html> accessed 11 September 2013.
2. Uniting and Strengthening America by providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA Patriot) Act, 2001 Public Law 107–56, and the Public Health Security and Bioterrorism Preparedness and Response Act, 2002.
3. National Institute of Health (2012) United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf accessed 11 September 2013.
4. US Government, Screening Framework Guidance for Synthetic Double-Stranded DNA Providers, Department of Health and Human Services, Office of the Secretary Federal Register Vol. 74, p. 224 <http://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf> accessed 11 September 2013
5. The Interacademy Panel on International Issues, IAP Statement on biosecurity, Trieste, Italy <http://www.interacademies.net/File.aspx?id=5401> accessed 11 September 2013.
6. The report committee was headed by Professor Gerald R. Fink, Professor of Genetics, Whitehead Institute, MIT, Boston, MA.

7. National Science Advisory Board for Biosecurity (2007), About NSABB http://oba.od.nih.gov/biosecurity/about_nsabb.html accessed 11 September 2013.
8. National Institute of Health. Press statement on the NSABB review of H5N1 research, 2011 <http://www.nih.gov/news/health/dec2011/od-20.htm> accessed 11 September 2013.
9. World Health Organization. FAQs: H5N1 influenza, Q1: What is H5N1? www.who.int/influenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/ accessed 11 September 2013.
10. The Fouchier lab reported fatal infections of ferrets following ‘intratracheal inoculation’ with the mutated H5N1 virus (Herfst et al. 2012b). However, intratracheal inoculation is a method that:

... is not directly relevant to viral transmissibility or natural pathogenesis. [...] Influenza viruses that are otherwise considered to be of low pathogenicity often induce severe and even fatal disease in animals when administered by this route. (Morens et al. 2012: 336)

11. A moratorium can be defined as a period of time during which a certain activity is not allowed.
12. 14 April 2012, statement on NSABB’s recommendations to the National Institute of Health on H5N1 research, dated 30 March 2012 http://www.nih.gov/about/director/04142012_NSABB.htm accessed 11 September 2013.
13. See <http://news.sciencemag.org/2012/04/flawed-flu-papers-process> accessed 11 September 2013.
14. Biosafety includes:
 - ... containment principles, facility design, practices and procedures to prevent occupational infections in the biomedical environment or release of the organisms to the environment. (Nordmann 2010)
15. Biosecurity can be defined as:
 - ... the sum of risk management practices in defense against biological threats’, which includes aversion of biological terrorism and other disease breakouts. (Meyerson and Reaser 2002)
16. The press has also discussed how easily the results could be replicated even by non-scientists (Zimmer 2012).
17. See <http://news.sciencemag.org/2012/04/flawed-flu-papers-process> accessed 11 September 2013.
18. The World Health Organization (2010) stated that:

Just as scientists should weigh benefits against the risks when deciding which projects to pursue, governments should be encouraged to do the same when deciding which projects to fund.

The NSABB (2007) stated that:

The NSABB will [...] develop guidelines for the oversight of dual use research, including guidelines for the risk-benefit analysis of dual use biological research and research results.

19. DDT was extensively used as an insecticide in agriculture and for malaria control in the middle of the 20th century. Today, due to concerns over its potential toxic side effects, intensive use of DDT is banned worldwide.
20. Under the condition of uncertainty, possible outcomes can be characterized, but the available information or analytical models do not present a definitive basis for assigning probabilities (Stirling 2007).
21. Under ignorance neither probabilities nor outcomes can be fully characterized (Stirling 2007; Collinridge 1980).
22. Under the condition of ambiguity, outcomes are prone to different interpretation and evaluation (Stirling 2007).
23. World Health Organization. FAQs: H5N1 influenza, Q1: What is H5N1? (2012) <www.who.int/influenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/> accessed 11 September 2013.
24. The mortality rate is based on diagnostically confirmed cases of human H5N1 infections in hospitalized patients in Southeast Asia. Due to a lack of epidemiologic and virologic studies and limited access to health care in rural areas, mild forms of infection may likely have passed undetected. Increased diagnostic efforts have retrospectively identified previously undetected asymptomatic infections (Beigel et al. 2005).
25. For example, the Functional Genomics Center Zurich, a joint state-of-the-art research and training facility of the ETH Zurich and the University of Zurich, Switzerland, provides the latest technologies and expert support in genomics, transcriptomics, proteomics, metabolomics, and bioinformatics <<http://www.fgc.zh.ch/>> accessed 11 September 2013.
26. According to the social scientist Harry M. Collins, somatic limit and collective tacit knowledge are experienced and acquired by humans through immersion in society and guided practice: Somatic-limit tacit knowledge is defined by the limited capacities and particular nature of the human brain and body, and collective tacit knowledge

has to be known tacitly, because it is located in human collectivities and, therefore, can never be the property of the any one individual. (Collins 2007)
27. NSABB. Addressing biosecurity concerns related to the synthesis of select agents (2006) <http://oba.od.nih.gov/biosecurity/pdf/Final_NSABB_Report_on_Synthetic_Genomics.pdf> accessed 11 September 2013.
28. According to the US Center for Disease Control:

... a bioterrorism attack is the deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals, or plants. (<<http://emergency.cdc.gov/bioterrorism/overview.asp>> accessed 11 September 2013)
29. The US Center for Disease Control separates bioterrorism agents into three categories, depending on how easily they can be spread and the severity of illness or death they cause. Category A agents are considered the highest risk, because they can be easily spread or transmitted from person to person, they result in high death rates and have the potential for major public health impact, they might cause public panic and social disruption, and they require special action for public health preparedness <<http://emergency.cdc.gov/bioterrorism/overview.asp>> accessed 11 September 2013. With a few exceptions, there are more steps required beyond the synthesis and replication or isolation of a particular pathogen in order to use it as a bioweapon of category A, including stabilization and dispersal of the pathogenic material (Tucker 2003). For example, the pathogen *Bacillus anthracis* could be isolated from the wild as it is still endemic amongst cattle, e.g. in Equatorial Africa. Infections are also sporadically detected in the USA (see <http://www.vetmed.lsu.edu/whocc/mp_world.htm> accessed 11 September 2013). However, virulence varies amongst naturally occurring *Bacillus anthracis* strains, and environmental conditions determine the stability and hence the infectiousness of anthrax spores. Bioweaponeers would need to isolate many strains to find a suitable one, and would need to stabilize the spores (Dragon and Rennie 1995). The same would be true for naturally occurring H5N1 avian influenza strains, which would need to be modified to adapt to humans as a host.
30. According to the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107–188, June 12, 2002, Sec. 351A, pp. 637ff.

... the Secretary [...] shall include provisions to ensure that persons seeking to register under such regulations have a lawful purpose to possess, use, or transfer such agents and toxins. [...] The Secretary shall maintain a national database that includes the names and locations of registered persons, the listed agents and toxins such persons are possessing, using, or transferring, and information regarding the characterization of such agents and toxins. [...] Requirements under paragraph (1) shall include provisions to ensure that registered

persons [...] deny access to such agents and toxins by individuals whom the Attorney General has identified as 'restricted persons.' Restricted persons are defined as individuals reasonably suspected of 'committing a crime [...]', individuals with 'knowing involvement with an organization that engages in domestic or international terrorism' [...] or 'being an agent of a foreign power.'

31. The National Institute of Health (2012) US Government Policy for Oversight of Life Sciences Dual Use Research of Concern (<http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf> accessed 11 September 2013). States that:

If the risks posed by the research cannot be adequately mitigated with the measures above, Federal departments and agencies will determine whether it is appropriate to: [...] Classify the research [...] Not provide or terminate research funding.

32. The policy demands the following action for research that involves certain agents and toxins as listed in the document or/and if the research includes experiments of concerns as defined by the Fink report. In case of such research it demands federal departments and agencies to:

Assess the risks and benefits of such projects, including how research methodologies may generate risks and/or whether open access to the knowledge, information, products, or technologies generates risk. (National Institute of Health (2012) United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern <http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf> accessed 11 September 2013)

However, no further details are given.

References

- Atlas, R., Campbell, P., Cozzarelli, N. R., Curfman, G. *et al.* (2003) 'Statement on scientific publication and security', *Science*, 299/5610: 1149.
- Ballard, T., Pate, J., Ackerman, G., McCauley, D. *et al.* (2001) 'Chronology of Aum Shinrikyo's CBW activities', pp. 1–17. Monterey, CA: James Martin Center for Nonproliferation Studies.
- Beigel, J. H., Farrar, J., Han, A. M., Hayden, F. G. *et al.* (2005) 'Avian influenza A (H5N1) infection in humans', *New England Journal of Medicine*, 353/13: 1374–85.
- Berns, K. I., Casadevall, A., Cohen, M. L., Ehrlich, S. A. *et al.* (2012) 'Policy: Adaptations of avian flu virus are a cause for concern', *Nature*, 482/7384: 153–4.
- Bouvier, N. M. (2012) 'The science of security versus the security of science', *Journal of Infectious Diseases*, 205/11: 1632–5.
- Brombacher, M. (1999) 'The precautionary principle threatens to replace science', *Pollution Engineering*, Summer: 32–4.
- Casadevall, A. and Shenk, T. (2012) 'Mammalian-transmissible H5N1 virus: Containment level and case fatality ratio', *MBio*, 3/2: e00054–00012.
- Cello, J., Paul, A. V. and Wimmer, E. (2002) 'Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template', *Science*, 297/5583: 1016–8.
- Chyba, C. F. (2006) 'Biotechnology and the challenge to arms control', *Arms Control Today*, 36/8: 11–7.
- Collinridge, D. (1980) *The Social Control of Technology*. Buckingham, UK: Open University Press.
- Collins, H. (2007) 'Bicycling on the moon: Collective tacit knowledge and somatic-limit tacit knowledge', *Organization Studies*, 28: 257–62.
- Collins, H. M. (2001) 'Tacit knowledge, trust and the Q of sapphire', *Social Studies of Science*, 31: 71–85.
- Dragon, D. C. and Rennie, R. P. (1995) 'The ecology of anthrax spores: Tough but not invincible', *Canadian Veterinary Journal*, 36: 295–301.
- Faden, R. R. and Karron, R. A. (2012) 'Public health and biosecurity. The obligation to prevent the next dual-use controversy', *Science*, 335/6070: 802–4.
- Fauci, A. S. and Collins, F. S. (2012) 'Benefits and risks of influenza research: Lessons learned', *Science*, 336/6088: 1522–3.
- Fouchier, R. A. (2012) 'Interview with virologist Dr. Ron Fouchier', *BIF Futura*, 27/3: 12.
- , Garcia-Sastre, A., Kawaoka, Y., Barclay, W. S. *et al.* (2012a) 'Pause on avian flu transmission research', *Science*, 335/6067: 400–1.
- , —, —, — *et al.* (2013) 'Transmission studies resume for avian flu', *Science*, 339/6119: 520–1.
- , Herfst, S. and Osterhaus, A. D. (2012b) 'Public health and biosecurity. Restricted data on influenza H5N1 virus transmission', *Science*, 335/6069: 662–3.
- , Osterhaus, A. B., Steinbruner, J., Yuen, K. Y. *et al.* (2012c) 'Preventing pandemics: The fight over flu', *Nature*, 481/7381: 257–9.
- Gaudioso, J. and Salerno, R. M. (2004) 'Science and government. Biosecurity and research: Minimizing adverse impacts', *Science*, 304/5671: 687.
- Goklany, I. (2001) *The Precautionary Principle: A Critical Appraisal of Environmental Risk Assessment*. Washington, DC: Cato Institute.
- Gray, J. S. and Bewers, J. M. (1996) 'Towards a scientific definition of the precautionary principle', *Marine Pollution Bulletin*, 32: 768–71.
- Hall, J. A. (1965) 'Atoms for peace, or war', *Foreign Affairs*, 43: 602–15.
- Herfst, S., Osterhaus, A. D. and Fouchier, R. A. (2012a) 'The future of research and publication on altered H5N1 viruses', *Journal of Infectious Diseases*, 205/11: 1628–31.
- , Schrauwen, E. J., Linster, M., Chutinimitkul, S. *et al.* (2012b) 'Airborne transmission of influenza A/H5N1 virus between ferrets', *Science*, 336/6088: 1534–41.
- Hoffmann-Riem, H. and Wynne, B. (2002) 'In risk assessment, one has to admit ignorance: Explaining there are things we can't know could improve public confidence in science', *Nature*, 416/6877: 123.
- Imai, M., Watanabe, T., Hatta, M., Das, S. C. *et al.* (2012) 'Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets', *Nature*, 486/7403: 420–8.

- Imperiale, M. J. and Hanna, M. G., III (2012) 'Biosafety considerations of mammalian-transmissible H5N1 influenza', *MBio*, 3/2: e00043–00012.
- Inglesby, T. V., Cicero, A. and Henderson, D. A. (2011) 'The risk of engineering a highly transmissible H5N1 virus', *Biosecurity and Bioterrorism-Biodefense Strategy Practice and Science*, 10/1: 151–2.
- Jackson, R. J., Ramsay, A. J., Christensen, C. D., Beaton, S. et al. (2001) 'Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox', *Journal of Virology*, 75: 1205–10.
- Kawaoka, Y. (2012) 'H5N1: Flu transmission work is urgent', *Nature*, 482/7384: 155.
- Klinke, A., Dreyer, M., Renn, O., Stirling, A. and Van Zwanenberg, P. (2006) 'Precautionary risk regulation in European governance', *Journal of Risk Research*, 9: 373–92.
- Kuhlau, F., Eriksson, S., Evers, K. and Hoglund, A. T. (2008) 'Taking due care: Moral obligations in dual use research', *Bioethics*, 22: 477–87.
- , Hoglund, A. T., — and Eriksson, S. (2011) 'A precautionary principle for dual use research in the life sciences', *Bioethics*, 25: 1–8.
- Leitenberg, M. (1999) 'Aum Shinrikyo's efforts to produce biological weapons: A case study in the serial propagation of misinformation', *Terrorism and Political Violence*, 11: 149–58.
- Leonard, N. and Insch, G. S. (2005) 'Tacit knowledge in academia: A proposed model and measurement scale', *Journal of Psychology*, 139: 495–512.
- Li, F. C., Choi, B. C., Sly, T. and Pak, A. W. (2008) 'Finding the real case-fatality rate of H5N1 avian influenza', *Journal of Epidemiology and Community Health*, 62: 555–9.
- Mackenzie, D. and Spinardi, G. (1995) 'Tacit knowledge, weapons design, and the uninvention of nuclear-weapons', *American Journal of Sociology*, 101: 44–99.
- Maher, J. A. and DeStefano, J. (2004) 'The ferret: An animal model to study influenza', *Laboratory Animals*, 33/9: 50–3.
- Malakoff, D. (2001) 'Breakthrough of the year. The year of living dangerously', *Science*, 294/5551: 2443.
- Mancini, G. and Revill, J. (2008) 'Fostering the biosecurity norms: Biosecurity education for the next generation of scientists', Working Paper, pp. 1–28. Bradford, UK: Landau Network-Centro Volta & Disarmament Research Center, University of Bradford. <http://www.brad.ac.uk/bioethics/media/SSIS/Bioethics/docs/European_Case_study.pdf> accessed 11 September 2013.
- McLeish, C. and Nightingale, P. (2007) 'Biosecurity, bioterrorism and the governance of science: The increasing convergence of science and security policy', *Research Policy*, 36: 1635–54.
- Meyerson, L. A. and Reaser, J. K. (2002) 'Biosecurity: Moving toward a comprehensive approach', *Bioscience*, 52: 593–600.
- Miller, S. and Selgelid, M. J. (2008) 'Ethical and Philosophical Consideration of the Dual-Use Dilemma in the Biological Sciences', *Science and Engineering Ethics*, 13/4: 523–80.
- Morens, D. M., Subbarao, K. and Taubenberger, J. K. (2012) 'Engineering H5N1 avian influenza viruses to study human adaptation', *Nature*, 486/7403: 335–40.
- National Research Council. (2004) *Biotechnology Research in an Age of Terrorism*. New York: National Academies Press.
- National Science Advisory Board for Biosecurity. (2007) 'Proposed framework for the oversight of dual use life sciences research: Strategies for minimizing the potential misuse of research information', pp. 1–62. Washington, DC: National Research Council. <http://oba.od.nih.gov/biosecurity/pdf/Framework%20for%20transmittal%200807_Sept07.pdf> accessed 11 September 2013.
- Nordmann, B. D. (2010) 'Issues in biosecurity and biosafety', *International Journal of Antimicrobial Agents*, 36(Suppl 1), S66–9.
- Osterholm, M. T. and Henderson, D. A. (2012) 'Public health and biosecurity. Life sciences at a crossroads: respiratory transmissible H5N1', *Science*, 335/6070: 801–2.
- and Relman, D. A. (2012) 'Creating a mammalian-transmissible A/H5N1 influenza virus: Social contracts, prudence, and alternative perspectives', *Journal of Infectious Diseases*, 205/11: 1636–8.
- Ouagrham-Gormley, S. B. and Vogel, K. M. (2010) 'The social context shaping bioweapons (non)proliferation', *Biosecurity and Bioterrorism-Biodefense Strategy Practice and Science*, 8: 9–24.
- Palese, P. and Wang, T. T. (2012) 'H5N1 influenza viruses: Facts, not fear', *Proceedings of the National Academy of Sciences*, 109/7: 2211–3.
- Panel on Scientific Communication and National Security, Committee on Science, Engineering, and Public Policy, National Academy of Sciences et al. (1982) 'Scientific communication and national security', pp. 1–204. Washington, DC: National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. <http://www.nap.edu/catalog.php?record_id=253> accessed 11 September 2013.
- Pearson, G. S. and Mahaffy, P. (2006) 'Education, outreach, and codes of conduct to further the norms and obligations of the Chemical Weapons Convention (IUPAC technical report)', *Pure and Applied Chemistry*, 78: 2169–92.
- Perez, D. R. (2012) 'Public health and biosecurity. H5N1 debates: Hung up on the wrong questions', *Science*, 335/6070: 799–801.
- Polanyi, M. (1962) 'Tacit knowing: Its bearing on some problems of philosophy', *Reviews of Modern Physics*, 34: 601–16.
- Racaniello, V. R. (2012) 'Science should be in the public domain', *MBio*, 3/1: e00004–12.
- Rappert, B. (2008) 'The benefits, risks, and threats of biotechnology', *Science and Public Policy*, 35: 37–43.
- , Chevrier, M. and Dando, M. (2006) 'In-depth implementation of the BTWC: education and outreach', Bradford Disarmament Research Centre, Department of Peace Studies, University of Bradford, pp. 1–39. *Bradford Biological and Toxic Weapons Convention Review*, Conference Papers, No. 18. <http://www.brad.ac.uk/acad/sbtwc/briefing/RCP_18.pdf> accessed 11 September 2013.
- Renn, O. (2012) 'Risk governance in a complex world'. In: Chadwick, R. (ed.) *Encyclopedia of Applied Ethics*, pp. 846–54. San Diego, CA: Academic Press.
- Resnik, D. (2013) 'H5N1 avian flu research and the ethics of knowledge', *Hastings Center Report*, March–April: 22–33.
- Resnik, D. B. (2003) 'Is the precautionary principle unscientific?', *Studies in History and Philosophy of Biological and Biomedical Sciences*, 34: 329–44.
- and Shamoo, A. E. (2004) 'Bioterrorism and the responsible conduct of biomedical research', *Drug Development Research*, 63: 121–33.
- Rosengard, A. M., Liu, Y., Nie, Z. and Jimenez, R. (2002) 'Variola virus immune evasion design: Expression of a highly efficient inhibitor of human complement', *Proceedings of the National Academy of Sciences*, 99: 8808–13.
- Sa, C. M. (2008) '"Interdisciplinary strategies" in US research universities', *Higher Education*, 55: 537–52.
- Sandin, P. (2009) 'A new virtue-based understanding of the precautionary principle'. In: Bedau, M. and Parke, E. (eds) *Ethics of Protocells: Moral and Social Implications of Creating Life in the Laboratory*, pp. 88–104. Cambridge, MA: MIT Press.

- , Peterson, M., Hansson, S. O., Rudén, C. and Juthe, A. (2002) 'Five charges against the precautionary principle', *Journal of Risk Research*, 5: 287–99.
- Selgelid, M. J. (2009) 'Governance of dual-use research: An ethical dilemma', *Bulletin of the World Health Organization*, 87: 720–3.
- Somech, A. and Bogler, R. (1999) 'Tacit knowledge in academia: Its effects on student learning and achievement', *Journal of Psychology*, 133: 605–16.
- Steinbruner, J., Harris, E. D., Gallagher, N. and Okutani, S. M. (2007) 'Controlling dangerous pathogens: A prototype protective oversight system'. College Park, MD: Center for International and Security Studies at Maryland.
- Stirling, A. (2007) 'Risk, precaution and science: Towards a more constructive policy debate', *EMBO Reports*, 8: 309–15.
- Stirling, A. C. and Scoones, I. (2009) 'From risk assessment to knowledge mapping: Science, precaution, and participation in disease ecology', *Ecology and Society*, 14/2: 14.
- Suk, J. E., Zmorzynska, A., Hunger, I., Biederbick, W. *et al.* (2011) 'Dual-use research and technological diffusion: Reconsidering the bioterrorism threat spectrum', *PLoS Pathog*, 7/1: e1001253.
- Taubenberger, J. K. and Morens, D. M. (2006) '1918 Influenza: The mother of all pandemics', *Emerging Infectious Diseases*, 12: 15–22.
- Tucker, J. B. (2002) 'Putting teeth in the Biological Weapons Convention', *Issues in Science and Technology*, 18/3: 71–7.
- (2003) 'Biosecurity: Limiting terrorist access to deadly pathogens', *Peaceworks* No. 52, pp. 1–52. Washington, DC: US Institute of Peace. <<http://www.usip.org/sites/default/files/pwks52.pdf>> accessed 11 September 2013.
- (2006) 'Preventing the misuse of biology: Lessons from the oversight of smallpox virus research', *International Security*, 31: 116–50.
- (2011) 'Could terrorists use synthetic biology?', *New Atlantis*, 31/Spring: 69–81.
- Tumpey, T. M., Basler, C. F., Aguilar, P. V., Zeng, H. *et al.* (2005) 'Characterization of the reconstructed 1918 Spanish influenza pandemic virus', *Science*, 310/5745: 77–80.
- van Aken, J. (2006) 'When risk outweighs benefit. Dual-use research needs a scientifically sound risk-benefit analysis and legally binding biosecurity measures', *EMBO Reports*, 7/Spec No: S10–13.
- Vogel, K. M. (2008) 'Framing biosecurity: An alternative to the biotech revolution model?', *Science and Public Policy*, 35: 45–54.
- Wallerstein, M. B. (2002) 'Science in an age of terrorism', *Science*, 297/5590: 2169.
- Wheelis, M., Lajos, R. and Dando, M. (2006) *Deadly Cultures: Biological Weapons Since 1945*. Boston, MA: Harvard University Press.
- World Health Organization. (2010) 'Responsible life sciences research for global health security: A guidance document', pp. 1–69. Geneva: World Health Organization. <http://whqlibdoc.who.int/hq/2010/WHO_HSE_GAR_BDP_2010.2_eng.pdf> accessed 11 September 2013.
- Wimmer, E. (2006) 'The test-tube synthesis of a chemical called poliovirus. The simple synthesis of a virus has far-reaching societal implications', *EMBO Reports*, 7/Spec No: S3–9.
- Yang, Y., Halloran, M. E., Sugimoto, J. D. and Longini, I. M., Jr (2007) 'Detecting human-to-human transmission of avian influenza A (H5N1)', *Emerging Infectious Diseases*, 13: 1348–53.
- Zimmer, C. (2012) 'Amateurs are new fear in creating mutant virus', *N Y Times*, March 6: D1.
- Zucker, L. G., Darby, M. R. and Armstrong, J. S. (2002) 'Commercializing knowledge: University science, knowledge capture, and firm performance in biotechnology', *Management Science*, 48: 138–53.