When risk outweighs benefit

Dual-use research needs a scientifically sound risk–benefit analysis and legally binding biosecurity measures

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In October 2005, a team of US scientists, headed by Jeffery Taubenberger from the US Armed Forces Institute of Pathology (Rockville, MD, USA), published the full sequence of the highly virulent strain of influenza virus that caused the Spanish influenza pandemic in the winter of 1918–1919 and killed up to 50 million people worldwide (Taubenberger *et al.*, 2005). Further work based on the sequence led to the synthesis of an influenza strain containing all eight gene segments from the 1918 pandemic virus, which showed a high virulence and mortality rate when tested in mice (Tumpey *et al.*, 2005). Both the sequencing and the reconstruction of the Spanish influenza virus are paradigmatic proof that recent developments in genetics, genomics and other areas of the biomedical sciences might create new possibilities for biological warfare. The resurrected 1918 virus has been described as “perhaps the most effective bioweapons agent now known” (von Bubnoff, 2005), and, given the availability of its full genome sequence on the Internet, its reconstruction by rogue scientists is now a real possibility.

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Not surprisingly, the publication of the Spanish influenza research triggered a controversial debate within, but not exclusive to, the scientific community, as arms-control experts questioned whether it was wise to publish a detailed account of its genome and recipe for resurrection. This debate,

although necessary, has some essential shortcomings as it focuses solely on the question of whether to publish such work, and lacks a systematic approach to a general risk–benefit analysis in biomedical research. In addition, the case of the Spanish influenza publications and their relatively superficial assessment by a biosecurity advisory board in the USA exemplifies the fact that we need internationally harmonized and legally binding rules for conducting dual-use research, in order to prevent the misuse of biological knowledge.

Until now, the discussion on dual-use research has focused mainly on whether results should be published. In 2003, a group of scientific journal editors and authors published a joint statement on scientific publication and security; among other things, they suggested that potentially harmful publications should be modified or not published at all (Atlas *et al.*, 2003). Since then, some journals have implemented an additional review tier to assess selected manuscripts for questions of biosecurity. So far, no submitted manuscript is publicly known to have been rejected for security reasons, although the publication of one paper about modelling a terrorist attack on the food supply (Wein & Liu, 2005) was delayed after intervention by the US government (Alberts, 2005).

However, banning the publication of dual-use research results might have dangerous implications, not only for the future of scientific openness and cooperation but also, even more importantly, from an arms-control perspective. As trust and confidence are key elements of international cooperation in the area of arms control and security, only a high level of transparency will allow nations to better determine the intentions of

others, discourage unfounded suspicions and build confidence in the compliance with existing arms-control treaties. Withholding critical information on dual-use research in any one country would therefore undermine arms-control efforts. Once a research project has been conducted and finished—when the ‘genie is out of the bottle’—it should be published to the maximum extent possible.

In fact, the whole debate on dual-use research pays scant attention to the possibility of regulating or stopping experiments of concern before they are started. Indeed, for experiments that touch on matters of security, and where the potential harm is likely to outweigh any potential benefits, the preferred option is not to prevent publication but to stop the research immediately.

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Such an *ex ante* approach—a systematic review of research proposals that could pose threats to national security and/or public health—has been proposed by a variety of national scientific organizations, including The Royal Society (2004) in the UK and the US National Research Council (2004). It is therefore discouraging to see that the recent debate on the Spanish influenza virus has neglected this avenue for preventing the misuse of biological knowledge.

The project to sequence the genome of the 1918 virus started as early as 1995, and the final outcome was clear at that time: to sequence and resurrect an extremely virulent virus that no longer existed. Both the

risks and the benefits of this project could and should have been assessed 10 years ago or at any time since. A last-minute intervention focusing solely on the publication of the results does not seem to be appropriate when its serious security implications have been obvious for a decade.

Arguably, there are cases in which the *ex ante* approach has its limitations. The course of science is not always predictable and experiments might yield completely unforeseen results, including security implications. A quintessential example is the unintended production of a highly lethal mousepox strain by an Australian research group a few years ago (Jackson *et al.*, 2001). In cases like this, it might be justified to contemplate restricting publication of the most sensitive elements of the research results. It should be noted, however, that the overall number of research projects that lead to unpredictable results with significant misuse potential is expected to be relatively small.

Regardless of its timing—*ex ante* or at the point of publication—any intervention in the scientific process should be based on a scientifically sound assessment of risks and benefits. On the ‘risk’ side of the equation, various criteria could be applied to assess the potential for misuse of a specific research project.

First, could the research results be used for military purposes, to construct a weapon with real-world applications from a military or terrorist perspective? Just ‘being deadly’ is not a sufficient prerequisite for a micro-organism to be considered as a weapon. Contagiousness, environmental stability, ease of production and other characteristics can also be important in assessing an organism’s military usefulness.

Second, what is the possible added military value? Would it change the status quo

significantly—that is, would it permit the construction of new types of weapon, or make existing weapons easier to build or handle?

Third, what are the technical prerequisites for performing such military applications, how difficult is it to apply the research results and is it likely that potential proliferators are capable of repeating the work?

These criteria should take into account the fact that a variety of potential suspects might be interested in abusing biological knowledge, including states, terrorist groups, rogue individuals and organized criminals. For each new research result—or ‘new’ agent as in the case of the Spanish influenza—the potential for abuse and the usefulness

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for different people will vary significantly. Some applications, for instance, might require considerable technical expertise not easily available to non-state parties, thus resulting in a limited risk of misuse.

Risk-management tools are another important factor in conducting a thorough risk-assessment procedure. For instance, effective arms-control measures capable of deterring and/or detecting potential abuse might be considered as a risk-management tool that could counter a high risk.

In the case of the reconstructed 1918 influenza virus, this risk assessment is relatively straightforward. Most comments, including those of the authors themselves, agreed that the potential for misuse is comparatively great: a highly virulent influenza virus is an ideal weapon, especially for clandestine operations by states or non-state parties. The 1918 virus provides a high degree of ‘added value’, considering that no virus combining high contagiousness with a comparatively high mortality rate has been readily available so far. Moreover, state-run

biological warfare programmes with some expertise in virology and molecular biology will be able to repeat the work, and there are currently no arms-control measures in place to manage the risk of misuse.

Much more difficult is the assessment of potential benefits. As in many other areas of the life sciences, the debate about dual-use research has so far been characterized by a complete lack of a critical benefit assessment. By default, nearly every biomedical experiment is considered to be beneficial, contributing in some way to an understanding of disease, a cure or improved quality of life in general. Today, promises are the major currency in the life sciences: as soon as hopes for a cure for a life-threatening disease are invoked—however putative, remote or hypothetical—scientific research is deemed to be justified.

The same pattern can be observed in the Spanish influenza debate. It has been claimed, for example, that this work will increase our understanding of virulence and pathogenic factors in influenza viruses, and that it might help to identify the next pandemic strain or to develop appropriate drugs (von Bubnoff, 2005). These general statements are probably true for the majority of biomedical research projects, which contribute in some way to our understanding of a particular disease. Yet such generalities are of little help for a systematic

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risk–benefit analysis, in which concrete risks are weighed against concrete benefits. A more scientific approach to benefit assessment might include the following questions: Does this research address an important health or humanitarian problem? Are there alternative ways to achieve the same scientific or humanitarian goals? How big is the added value—that is, to what extent does a particular experimental approach increase the knowledge and the likelihood of reaching a specific goal?

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If applied to the Spanish influenza work, a mixed picture emerges. Influenza pandemics are, without doubt, an important public-health problem, not least in the light of the recent avian influenza debate. Yet it is less obvious how a reconstructed virus from 1918 is crucial for increasing our understanding of the genesis, prevention and management of influenza pandemics. Hundreds of influenza strains from the past five decades, including some pandemic strains, are available to researchers and are used by initiatives such as the Influenza Genome Sequencing Project (Ghedini *et al.*, 2005) to investigate genetic virulence factors. The added value of one extra strain, even one with an exceptionally high mortality rate, is limited, given that strains with varying degrees of contagiousness and pathogenicity are already available and provide a wealth of research resources for comparative studies.

Thus, the tangible societal benefits of sequencing and reconstructing the 1918 pandemic influenza virus remain poorly defined. Considering the high risk of abuse, the availability of alternative research avenues and the limited added value to public health, this particular research project seems to be one of the few cases in which the risks outweigh the benefits and that therefore should not have proceeded over the course of 10 years.

In a report entitled *Biotechnology Research in an Age of Terrorism*, the US National Research Council (2004) identified several classes of experiment “that will require review and discussion ... before they are undertaken or, if carried out,

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before they are published...” Their criteria included experiments that would demonstrate how to render treatment or detection measures ineffective, increase the pathogenicity, transmissibility or host range of a pathogen, or make it easier to develop a biological agent into a weapon of mass destruction. Future advances in the biomedical sciences might require a few additional criteria to determine, for example, whether an experiment would ease access to dangerous pathogens, which was basically achieved with the reconstruction of the 1918 influenza virus.

At this point, it is important to stress that cases such as the re-creation of the Spanish influenza virus are exceptional. The notion of assessing and—if necessary—limiting certain experiments for security reasons does not imply that every piece of biomedical research should be subjected to a new regulatory burden. In all likelihood, only a small number of research projects in a few areas in the life sciences would be subject to a comprehensive risk–benefit analysis. Even within the fields of microbiology and virology, most experiments would not fall under these criteria and, hence, would not require any review from a biosecurity point of view. A biosecurity assessment would differ from the oversight mechanisms that are already in place, such as those for experiments involving humans, animals or recombinant DNA work, and would affect only a small fraction of researchers worldwide, while at the same time increasing security for all.

So far, this article has touched on the questions of when, how and what to assess. Most important, however, is the question of who should be the assessor—that is, the preferred institutional framework for a biosecurity review. Once again, the case of Spanish influenza provides a perfect example—albeit of the worst type of oversight mechanism.

In an editorial in *Science*, Editor-in-Chief Donald Kennedy provided some sobering insights into the last-minute interventions by a US biosecurity review body shortly before the publication of the Spanish influenza paper (Kennedy, 2005). In 2003, the US government established the National Science Advisory Board for Biosecurity

(NSABB), which had its first meeting in June 2005 after two years of preparations. Just one day before *Science* went to press with the Spanish influenza paper, the US Department of Homeland Security ordered a review of the publication by the NSABB. Members were polled and approved the paper within a day. Obviously, it was not possible to conduct a thorough review of risks and benefits in such a short time, so the scientific basis for the NSABB’s approval remains obscure. The only concrete step the NSABB took was to suggest the addition—in a ‘note added in proof’ to the *Science* paper—of information on public-health benefits of the reconstructed Spanish influenza virus. Instead of critically assessing the benefits, the NSABB provided an *ex post* justification of the project.

It should be noted that, in this case, the NSABB had little choice but to give blanket approval. As Kennedy rightly pointed out, the NSABB is not in a position to prevent the publication of a paper. The NSABB is an advisory body with no legal power, which was established solely to provide advice on biosecurity issues to the US government. It is charged, *inter alia*, with awareness-building activities, and the development of a non-binding system of institutional research review and similar guidelines for the identification of experiments of concern.

Although it is laudable that the USA is far ahead of most other countries in devising such a biosecurity review system, the current approach does not meet even the minimal requirements for a scheme that would be both effective and sufficiently focused in order to avoid placing an unnecessary administrative burden on the scientific community. Such a review system should meet three key requirements, in order to ensure that experiments in which potential harm outweighs potential benefits are identified and stopped before they start.

First and foremost, any such system must be able to cast legally binding verdicts, even if scientists favour non-binding systems based on their own individual or collective responsibility. Anthony Fauci, Head of the US National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA), put it bluntly when he said “The goal is not to regulate” (Couzin, 2004). Yet it is doubtful that any system based solely on responsibility and self-regulation will be sufficiently comprehensive and effective to address grave security concerns.

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Every effort should be made to involve scientists and increase their awareness of any potential security implications of their work. Codes of conducts for scientists, as recently discussed in the framework of the Biological and Toxin Weapons Convention, are an important tool for educating, and raising awareness among, the scientific community. Yet an effective oversight body must have the legal authority to halt a specific research project if it concludes that the risks outweigh the benefits. The non-binding framework of an advisory body does not have this authority.

Institutional Biosafety Committees (IBCs) are an important element of the current US biosecurity regulations. Currently, they mainly review experiments involving recombinant DNA, although there are efforts to add biosecurity reviews to their portfolio. However, a recent survey of nearly 400 IBCs in the USA by an international arms-control organization, The Sunshine Project (2004), indicated that the non-binding IBC system is not functioning properly. Even at major research institutions, committee meetings are rare, critical experiments have been approved without full committee review, and committees have often failed to meet the basic composition and disclosure requirements of the non-binding guidelines under which they were set up.

The IBC experience exemplifies an inherent problem of any self-regulatory approach: scientists hesitate to place any restrictions on each other's work and regard oversight mechanisms largely as a bureaucratic burden. A regulatory body based on voluntary guidelines with no legal authority and consisting solely of scientists is unlikely to stop even the most critical experiments of concern.

Second, any review system should adhere to internationally harmonized rules. The research community is global. Failure to harmonize biosecurity measures on an international scale will create gaps in security and might hamper legitimate scientific

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research in other countries. For example, a survey we conducted in 2004 in Germany revealed that new US biosecurity regulations are having an adverse impact on German microbiological research (van Aken *et al.*, 2004). Microbiologists reported negative effects, such as delays in some research projects or even the need to stop certain experiments. In order to avoid similar problems in the future, and to prevent research tourism to countries with limited oversight, an international standard-setting body, such as the proposed International Pathogens Research Agency (Steinbruner & Harris, 2003), should be responsible for defining experiments of concern and for reviewing those that are most critical.

Third and last, security gaps will arise if some research institutions, including private laboratories and military research facilities, are excluded from biosecurity review. An exemption for classified research, as it is envisaged in the USA, seems to be particularly ill-conceived, because this is likely to be the area in which most dual-use experiments are performed. Proposals to restrict biosecurity reviews to governmentally funded projects are also problematic, as this would exempt companies and other privately financed research from the process. It might be a good idea, however, to make the discussion of potential biosecurity implications of proposed experiments a mandatory prerequisite for grant applications. Although this might have only limited practical impact, it would greatly contribute to building awareness in the scientific community.

A recent article in *EMBO reports* described *Atlantic Storm*, a simulated bioterrorism exercise based on the deliberate release of smallpox viruses in various European and North American cities (Hamilton & Smith, 2006). The exercise demonstrated the serious political and public-health challenges, while making proposals as to how to strengthen international regimes and policies in order to counter such a bioterrorist attack effectively. Although this is certainly needed and helpful, it would be more effective if the knowledge about deadly pathogens and how to use them for nefarious purposes did not exist in the first place. "The age of engineered biological weapons is neither science fiction nor suspense thriller—it is here today," the authors wrote. In view of this threat, identifying dual-use research with a high risk potential and closely regulating it seems to be a sensible measure.

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