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New approaches to biological risk assessment

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Contents

Summary

On 19 February 2009 the Royal Society and the International Council for the Life Sciences held a joint workshop to explore new approaches to assessing the full spectrum of biological risks. It brought together a group of international experts on infectious disease, international security and risk assessment. This report summarises the themes that emerged during the meeting, with the key points outlined below.

Biological risk spectrum

- The spectrum of biological risks encompasses naturally occurring, unintended, and deliberate risks.
- Naturally occurring diseases present the greatest international risk. Therefore a focus on public health is the most sensible way of addressing the full spectrum.
- A challenge for the scientific community is managing unintended risks associated with dual use research without jeopardising the benefits. This will require openness and transparency, and expanded dialogue amongst the international scientific community to raise awareness and develop a culture of responsibility.
- The risk of deliberate misuse of knowledge, products, or technology in the life sciences applies both to states and non-state groups or individuals.
- It is important to find ways to meet security concerns in a manner that does not hamper scientific research or obstruct international cooperation.

Implications of advances in science and technology

- Advances in the life sciences and the wide accessibility of associated biotechnologies, such as DNA sequencing and synthesis, may result in new dual use and deliberate risks, which will need to be reassessed regularly.
- It is important not to exaggerate the risk of misuse of emerging technologies as these advances will enable more effective responses to the whole spectrum of biological risks.

Common approaches to risk assessment

- Current methodologies for assessing biological risks would benefit from harmonisation, both within nations across sectors and industries, and internationally to enable more effective policy making, resource allocation, international cooperation and sharing of best practices.
- Comprehensive risk assessments should consider the assumptions used to frame them and feedback from risk management approaches. Assessments also need to link epidemiological modelling of disease, economic modelling, and qualitative social science modelling of human behaviour and motivations.
- Given the varying levels of uncertainty, a common approach should incorporate a range of specific risk assessments coupled with an overarching model that builds on the similarities across the spectrum.
- A key issue with deliberate misuse is the need to assess and model intent.
- Any risk assessment should incorporate a net assessment of the consequences of different countermeasures to highlight the most effective countermeasures, establish where countermeasures may have created or exacerbated risks, and illustrate where responses to risks at one part of the spectrum can mitigate risks at another.
- Due to limited data there will be low levels of certainty around assessments of the risk associated with the deliberate misuse of biological agents as weapons. For this reason, countermeasures that can be applied across the full range of the biological risk spectrum are likely to be less risky investments as their effectiveness can be better determined.

1 Biological risk spectrum in context

Methods are needed for undertaking risk assessments across the full spectrum of biological risks, from naturally occurring diseases of humans, animals and plants, through to the deliberate weaponisation of biological agents (Royal Society 2006, 2008a). This spectrum (Figure 1) can be divided into three main areas of risk: naturally occurring, unintended, and deliberate. Unintended risks in the middle part of the spectrum include the unintended consequences of research, known as dual use risks.

Current trends in global security include a number of external factors affecting the nature of risks across the spectrum, such as: the rise of non-state groups; global issues such as climate change and competition for resources; and international inter-dependence (eg finance, energy security). Meanwhile risk assessments are affected by internal factors including: changes in societal attitudes to risk; increased vulnerabilities of modern urban societies; and the impact of advances in science and technology.

In the UK, and other countries, there is a move towards an 'all risks' approach to risk assessment and management that encompasses assessment of both hazards, such as accidents, and threats, such as malign intent (Cabinet Office 2008a). In the context of biosecurity, hazards include new and emerging infectious diseases, unintended consequences of advances in science and technology or dual use research, and laboratory accidents, whilst threats arise from the deliberate use of biological agents as weapons by states, non-state groups, or individuals.

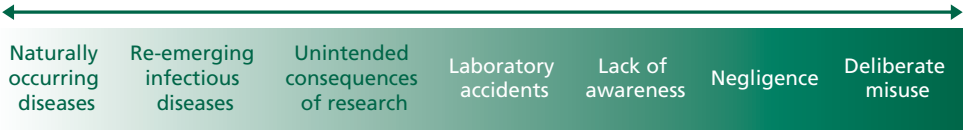
The UK Government has published a National Risk Register, which provides an assessment of the likelihood and potential impact of a range of risks (Cabinet Office 2008b). These two dimensions, combined with an assessment of vulnerabilities, inform anticipatory policies and contingency planning to build 'resilience'. The focus of preparedness and response efforts is driven by risks assessed to be both high impact and high likelihood. A major difficulty, however, is the assessment of emerging risks, both hazards and threats, particularly those without significant historical precedent such as newly emerging diseases or malign criminal or terrorist use of biological agents. It is also important not to over emphasise one particular risk, such as terrorism, which can undermine public confidence in risk assessments of the range of hazards and threats.

2 Naturally occurring risks

Naturally occurring biological risks affecting human populations encompass common infectious diseases, emerging and re-emerging infectious diseases, and chronic diseases with infectious causes. They present the greatest international biological risk, particularly re-emerging diseases with global reach such as pandemic influenza, due to the potentially catastrophic levels of mortality that might arise (Royal Society & Academy of Medical Sciences 2006). Therefore a focus on public health is the most sensible way of addressing the full spectrum of biological risks.

Common infectious diseases are responsible for approximately 14 million deaths each year (World Health Organisation 2000, 2008) with the major killers being diarrhoeal disease, HIV/AIDS, malaria, measles, pneumonia, and tuberculosis. The most

Figure 1: Spectrum of biological risks (Taylor 2006)



devastating incidence of acute infectious disease in the 20th Century was the influenza pandemic of 1918, which killed an estimated 40-50 million people worldwide. This pandemic demonstrated the great risk posed by biological agents that combine virulence, high transmissibility and persistence in the environment.

While much attention is rightly paid to acute infectious diseases, chronic diseases kill more people. In 2002, 17 million people were killed by cardiovascular disease, 7 million by cancer, 4 million by chronic lung disease, and almost 1 million by diabetes mellitus (Yach et al 2004).

Good data are available on the patterns of common infectious diseases, which illustrate the importance of human behaviour in determining the level of risk and mitigating the incidence and spread of disease. Therefore, education to influence behaviours is part of an effective response. However, a crucial factor for vulnerability is the geographical location in which you live, both in terms of incidence of endemic disease and the strength of the public health system.

Historical responses to the risks posed by naturally occurring infectious diseases illustrate where progress has been made. A global programme succeeded in eradicating smallpox as a naturally occurring disease by 1977. A similar programme to eradicate polio has reduced the number of polio-endemic countries to four as of 2006, and less than 2,000 cases per year (Global Polio Eradication Initiative 2009). There has been less success with HIV/AIDS since the emergence of the virus in the early 1980s. In 2007 there were an estimated 33 million people infected with HIV worldwide (UNAIDS 2008). However, with greater understanding of the disease and the application of very large funding there has been some progress in mitigating its impact, for instance in the development of many anti-viral drugs that target HIV.

In recent years several new and re-emerging diseases have tested public health responses. The severe acute respiratory syndrome (SARS) epidemic in 2002-3 infected over 8,000 people in 26 countries, causing 774 deaths (World Health Organisation 2004). Avian influenza (H5N1) infected 433 humans between 2003 and 2009, causing 262 deaths (World Health Organisation 2009a). An outbreak of swine influenza A (H1N1) originating in Mexico led the World Health Organisation to declare a global pandemic in June 2009, which had resulted in 94,512 infections in over 100 countries including 429 deaths as of 6 July 2009 (World Health Organisation 2009b).

We tend to be fearful of new and re-emerging diseases even when mortality rates are low, until we have greater understanding of the epidemiology and efficacy of our response capabilities. Public perception of risk increases with this perceived lack of control and increased uncertainty on the part of experts.

In assessing naturally occurring risks, it is important to consider the effectiveness of existing countermeasures, such as disease surveillance, diagnostics, vaccines, and drugs. Disease detection and surveillance systems are crucial in countering naturally occurring diseases and detecting new ones. There is also a need to develop more broad-spectrum treatments including antibiotics, anti viral drugs, and immune modulators. In the case of bacterial diseases, antimicrobial resistance is a growing problem, requiring new antibiotics and possibly radically new approaches to drug treatment (Royal Society 2008b).

There is international recognition of the importance of disease detection and surveillance in countering the range of biological risks. Article X of the Biological Weapons Convention (BWC) encourages international cooperation between countries on the prevention of disease. At the BWC Meeting of Experts in August 2009 States Parties will *'…discuss, and promote common understanding and effective action on promoting capacity building in the fields of disease surveillance, detection, diagnosis, and containment of infectious diseases'* (United Nations 2009).

3 Unintended risks

3.1 Dual use research

Unintended consequences of scientific research are commonly described as dual use risks. The US National Science Advisory Board for Biosecurity (NSABB) defines dual use research as 'research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health, agriculture, plants, animals, the environment, or materiel' (NSABB 2007).

In 2004 the National Research Council (NRC) of the US National Academy of Sciences highlighted seven general 'experiments of concern' that require the particular attention of the scientific community. These are experiments that: demonstrate how to render a vaccine ineffective; confer resistance to therapeutically useful antibiotics or antiviral agents; enhance the virulence of a pathogen or render a non-pathogen virulent; increase transmissibility of a pathogen; alter the host range of a pathogen; enable the evasion of diagnostic/detection modalities; or enable the weaponisation of a biological agent or toxin (NRC 2004).

The challenge facing the scientific community is to identify measures to manage dual use risks without jeopardising the benefits of research advances. Some consider that researchers are best placed to assess the risks from their own research, however scientists may come to different conclusions about a piece of research, as illustrated by the differences in expert opinion on risks and benefits posed by the reconstruction of the 1918 flu genome. This is further complicated by differing perceptions of risks between scientists and others, including the wider public, and varied assessments between those in developed and developing countries. A problem with divergent opinions on such high profile cases is the difficultly in conveying a clear message to policy makers. The benefits of being able to present clear messages to policy makers are discussed further in section 6.2.

Central to managing dual use risks will be the need to maintain openness and transparency in scientific information whilst raising awareness and developing a culture of responsibility among life scientists worldwide (NRC 2006).Sharing information encourages scientific progress and ensures the benefits of scientific advances are realised so that all countries are better prepared to deal with the spectrum of biological risks, which highlights the danger of censorship. Very few scientific papers reviewed in recent years have raised sufficient concern to warrant consideration of preventing publication. Consensus might be reached on the dangers of publication in some areas, such as research on the aerosolisation of particular biological agents. However, for the most part, it would be very difficult to prevent publication of a given piece of research elsewhere, whether in another journal or in another format, such as a newspaper or website.

Raising awareness about the potential consequences of research can contribute to managing dual use risks and limiting negligence. This can be a challenge as many scientists in the wider life sciences community do not associate their research with dual use risks and may not be aware of the BWC, despite the efforts of scientific academies and other organisations to raise awareness (eg InterAcademy Panel 2005). However, in developing constructive dialogue it will be important to weigh the likely benefits of scientific research against any potential risks of misuse.

Discussions amongst the international community at the 2008 meetings of the BWC highlighted the importance of continuing efforts in awareness raising and education at the international level to mitigate dual use risks (United Nations 2008). A recent survey of the attitudes of a sample of US scientists found that there is a need to expand dialogue amongst the wider life science community and increase awareness raising efforts. However, it also identified a critical need to better define the scope of what is considered dual use research of concern (NRC 2009).

3.2 Laboratory accidents

The risk posed to the public by laboratory accidents can be mitigated with good training, proper laboratory design and management, and appropriate maintenance of high-containment facilities. Good laboratory practice also limits the risk to laboratory workers.

Where good laboratory practice and proper maintenance is not adhered to, risks from laboratory accidents will necessarily be greater. Following a laboratory infection there is the risk of further transmission from the infected worker to those outside the laboratory, as illustrated by the spread of SARS from a Chinese laboratory in 2004 (Brown 2004). Although there are concerns over the implementation of biosafety practices in the developing world, the potential for accidents in countries with advanced biotechnology infrastructure and safety regulations has been illustrated by a number of incidents. These include the UK foot and mouth disease virus (FMDV) outbreak in 2007, which was found to originate from errors in effluent control at laboratories in Pirbright (Health and Safety Executive 2007).

The expansion of high-containment laboratories worldwide offers the potential to reduce laboratory risks if good practice and maintenance is upheld, as more work can be carried out at higher containment levels, with lower risks of laboratory infections and pathogen escape. Conversely, if biosafety is not strictly enforced this expansion could exacerbate laboratory risks.

4 Deliberate risks

4.1 States

Some participants disagreed over the relative risks posed by state biological weapons programmes as opposed to criminal or terrorist use of biological weapons. However, there was agreement that the risk of misuse of knowledge, products, or technology in the life sciences applies both to states and non-state groups or individuals. The risk of bioterrorism should not obscure concerns that states may remain interested in or consider revisiting biological weapons, given the history of numerous military programmes that developed biological agents as weapons against humans, animals, and plants (Wheelis et al 2006). This is exacerbated by existing weaknesses in the BWC, which does not have an institutional base or a mechanism to verify compliance with the treaty's prohibitions.

Potential drivers that could lead states to breach their commitments under the BWC may be strategic and/or operational, as illustrated by past biological weapons programmes. As regards operational drivers, one particular concern is the persistent state interest in the development of 'mid-spectrum' agents as incapacitating weapons for use in law enforcement and counter-terrorism. The focus has been on chemical agents, such as potent anaesthetic and sedative drugs, but consideration has also been given to biological agents, including bioregulatory neuropeptides (Lakoski et al 2000, Davison 2009).

Another dimension of state-related biological risks is the potential for countermeasures to increase, unintentionally, the risk of deliberate use of biological weapons. The history of biological weapons development illustrates that intelligence difficulties led to misperceptions of capabilities and intent, which resulted in arms racing and 'mirror imaging' (Wheelis et al 2006). Transparency is vital in avoiding misperceptions of current biodefence research, especially as some of this military and security dual use research carried out in response to the perceived risk of bioterrorism is of the type that would be defined as 'experiments of concern' (Leitenberg et al 2004) At the international level, a way of improving transparency would be for States Parties to the BWC to improve their Confidence Building Measure (CBM) submissions and make them publicly available. The expansion of biodefence research poses other unintended risks through the increase in the number of individuals with expertise that could be misused for development of biological weapons.

4.2 Non-state groups or individuals

The use of biological weapons is not necessarily compatible with non-state groups having particular political aims, especially highly transmissible agents whose spread cannot be confined to a particular geographical area. The risk posed by criminal or terrorist use may be greater from the use of highly virulent or toxic biological agents, with less emphasis on persistence and transmissibility. However the overall risk becomes more acute in the context of individual extremists with apocalyptic ideology or sociopathic tendency, where there may not be reluctance to use of highly transmissible agents. Overall approaches to countering the risk of terrorism, including bioterrorism, should seek to address the root causes of this risk, such as poor governance, poverty and inequality, rather than overemphasising its symptoms (Abbott et al 2007).

Despite widespread attention to the risk of bioterrorism during the 2000s, there have been very few incidents of the use of biological agents for criminal or terrorism purposes by non-state groups or individuals. Notable exceptions include: the contamination of restaurant salad bars with Salmonella in Oregon in1984 by the Rajneeshee cult, which sickened over 700 people but killed none; the failed attempt by the Aum Shinrikyo cult to spread anthrax in Japan involving the use of a non-pathogenic strain which could not have endangered human health (Keim 2001); and the October 2001 anthrax letter attacks in the US, which infected 17 people and killed 5. Although there were few deaths in the latter incident, the economic and disruptive impact was dramatic due the costly and lengthy process to decontaminate office buildings and postal facilities, as were the fear-inducing effects.

Notwithstanding the very low number of deaths from bioterrorism in comparison to the large mortality rates from infectious diseases, the response has been huge investment, particularly in the US, in biodefence research and preparedness, and increased legislative burden for those working with certain dangerous microorganisms (so called 'select agents'). Concerns have been raised in recent years over the potential for expanded research on diseases such as anthrax and restrictive legislation to adversely affect investment in naturally occurring infectious disease research (Russo 2002). However, approximately 70% of the biodefence-related research funded at the National Institutes of Health (NIH) is thought to be widely applicable to understanding and treatment of naturally occurring infectious diseases. In addition, beneficial countermeasures with broad applicability, such as improved face masks, have emerged from military defensive research programmes.

Concern over the potential 'insider threat' from laboratory workers has heightened since the FBI concluded in 2008 that a US government scientist was responsible for the 2001 anthrax letters (FBI 2009). This has led to a focus on the vetting of people permitted to access high-containment laboratories and 'select agents', so called personnel reliability programmes. Such programmes may include security checks and psychological testing, and have long been a feature of access to sensitive military sites. These programmes may well be expanded due to demands from governments and publics in the aftermath of the anthrax letters investigation. However, there is some scepticism of the value of personnel reliability testing, particularly since the perpetrator of the US attacks had been subject to such a programme. Any reliability programmes linked solely to research with 'select agents' would miss other potential misuse enabled by advances in science and technology.

It is important to find ways to meet these security concerns in a manner that does not hamper scientific research. It may be that current practice for employment and biosafety in academia and industry provides sufficient confidence in reliability (Berger et al 2009). Issues surrounding the assessment of overseas researchers need to be managed in way that does not constrain collaborative research and obstruct international cooperation.

4.3 New dimensions of deliberate risk

It might be necessary to consider another category of criminal biological risk, driven by financial rather than political aims. This is illustrated by the global spread of underground laboratories producing counterfeit pharmaceuticals as part of organised crime (Hileman 2003). These may be very basic laboratories in low income areas that are close to high-tech business areas, or high-end manufacturing laboratories with poor oversight. Common to both are strong underground finance and distribution networks, and low policing and intelligence capabilities to tackle the illegal manufacturing. Non-state groups operating in this trade have the production and distribution networks to produce counterfeit drugs, and could conceivably shift to production of dangerous biological agents. At the state level there might be the risk of adaptation of high-end counterfeiting laboratories for the clandestine development and production of biological weapons.

5 Implications of advances in science and technology

5.1 Adapting to emerging risks

Advances in the life sciences and the wide accessibility of associated biotechnologies may create new dual use and deliberate risks, which will need to be reassessed regularly (NRC 2006). However, likely benefits should be weighed with any potential risks since these same advances are central to developing more effective responses to the whole spectrum of biological risks including naturally occurring diseases.

Several published experiments have been highlighted as illustrations of dual use risks associated with scientific advances, including: the engineering in 2001 of a recombinant ectromelia virus (mousepox) to express interleukin-4 (IL-4) that inadvertently created a more virulent virus (Jackson et al 2001); the construction in 2002 of live poliovirus using synthetic DNA segments and the available viral genome sequence (Cello et al 2002); the reconstruction of the 1918 Spanish influenza pandemic virus in 2005 (Tumpey et al 2005); and in 2007 the illustration of genome transplantation methods to transform one type of bacteria into another using the transplanted chromosome (Lartigue et al 2007). Whilst dual use discussions have brought these scientific developments to a wider audience, prior indications of some experiments portrayed as surprises can be found in the scientific literature. For example, a 1981 paper described the recreation of infectious polio virus from DNA (Racaniello and Baltimore 1981), and there was description of the role of IL-4 on poxvirus virulence in 1998 (Bembridge et al 1998).

It has been suggested that advances in science and technology expand the scope for deliberate misuse of biological agents, and ultimately decrease the threshold for the use of biological weapons by both states and non-state groups or individuals (Petro et al 2003). In the near term any state interest in biological weapons would present a significant risk given available resources and access to science and technology. Over time the risk from non-state groups and individuals may increase as the access to relevant technologies broadens and associated costs decrease, thus lowering the barriers to deliberate misuse. In the near term, greater focus should be given to the possibility of non state groups or individuals misusing naturally occurring pathogens or exploiting mature bioprocessing technologies rather than emerging technologies, such as synthetic biology.

5.2 Beyond lists of agents

Attention to biological risks should not be constrained by lists of agents. Non-pathogens can be engineered to be pathogenic and advances in DNA synthesis may enable development of novel pathogens. The US NRC has recommended a '*broadened awareness of threats beyond the*

classical "select agents" and other pathogenic organisms and toxins, so as to include, for example, approaches for disrupting host homeostatic and defense systems and for creating synthetic organisms' (NRC 2006).

Increased understanding of the molecular basis underlying biological processes is blurring the boundaries between chemical and biological agents. In the context of deliberate misuse, this will enable interference with specific biological processes to exert a wide range of effects, resulting in a shift from a focus on particular agents to specific targets in the human body.

Peptide bioregulators are responsible for regulating a wide variety of biological processes and can have profound effects in very small quantities on immune response, blood pressure, and nervous system function. These include neuropeptides that modulate cognition, perception, mood, motivation, and consciousness, and are of great interest to the pharmaceutical industry in addressing depression, anxiety, and other disorders. Such agents might be used deliberately for harmful purposes and this dual use risk may be exacerbated by advances in drug delivery technology that allow for use of peptides as drugs (NRC 2008).

5.3 DNA sequencing and synthetic biology

Developments in DNA sequencing and synthesis technologies demonstrate the overall pace of change and spread of biotechnologies, where the speed and productivity are increasing whilst costs are reducing (Carlson 2003, 2008). These developments are particularly relevant to the advancing field of synthetic biology, the deliberate design of novel biological systems (Royal Society 2008c).

The technology and knowledge to emerge from these advances will raise dual use concerns over the potential risks, both unintended and deliberate (Royal Society 2008c). The wide availability of sequencing technology, providing the knowledge of pathogenic genomes, and synthetic biology, providing the tools for synthesis of pathogens will facilitate wider access to the development of dangerous pathogens that could be used for harmful purposes, and ultimately may enable the development of new man-made pathogens. Furthermore, as these technologies are made more 'user-friendly' and portable, the manipulation of genomes may require less scientific and technical knowledge.

However, it is important not to exaggerate the risk of misuse of these technologies. Much remains to be understood about the mechanisms underlying virulence and links to transmissibility in microorganisms, and it would currently be very difficult to design a novel pathogen that would cause disease but that will also be easily transmissible

The new generation of DNA sequencers has enabled the sequencing of an entire genome for around $60,000 and this is expected to decrease to $1,000 in the coming years. In early 2008 an international consortium of researchers in the UK, China, and the US announced plans to sequence the genomes of 1,000 individuals (1000 Genomes Project 2009). In less than 10 years the genomes of at least 1 million individuals and nearly all the other major organisms may have been sequenced. DNA sequencing is the most reliable and fastest tool for identifying pathogens and is therefore central to the future development of effective vaccines and drugs, as well as utility in assessing individual susceptibility to disease.

The rapidly developing field of synthetic biology may enable applications in diverse fields such as medicine, energy, environment, and materials. Further development will draw upon advances in automation and smaller size of DNA synthesis and genome assembly technologies. Technological advances are enabling significant achievements as illustrated by the Massachusetts Institute of Technology (MIT) International Genetically Engineered Machine competition (iGEM), which is an undergraduate synthetic biology competition where students design their own novel biological

systems using a 'kit' of biological parts (iGem 2009). Meanwhile, lower costs and increasing access to technology mean that biotechnology is becoming an amateur pursuit amongst a developing community of so called 'biohackers' or DIY biologists (Bloom 2009, DIYbio 2009). Even toys are available for children as young as 10 that introduce methods to extract and map DNA (Baker 2003, Dyson 2006).

At the forefront of increasing understanding of disease is the inter-disciplinary field of systems biology, which is the analysis of the interactions of the components of biological systems to determine the properties of those systems. Advances in this area will therefore lead to greater predictive understanding of the possibilities and consequences of synthetic biology. Whilst data acquisition is expanding, there is an analytical gap in deciphering these data and a need for inter-disciplinary collaboration with computing and data specialists.

Some participants considered whether more emphasis should be given to technical fixes for risks associated with rapidly developing technologies such as DNA synthesis. It was noted that commercial DNA providers have already started to screen their orders to avoid supplying potentially dangerous DNA sequences (ICPS 2009). However, as DNA synthesis technology becomes cheaper and more widely accessible this screening would not be effective. It was suggested that the DNA synthesis machines of the future might be designed in a 'proliferation resistant' manner that prevents them producing particular sequences (Nouri and Chyba 2009).

Others take the view that it would be very difficult to regulate the use of DNA synthesis machines in this way. Technical screening for particular sequences of DNA may not be effective because it is possible for the same sequence of DNA to appear both in a pathogenic virus and a harmless virus. Furthermore, introducing technical controls and limitations on DNA synthesis runs the risk of slowing down and increasing the costs of legitimate research.

6 Common approaches to biological risk assessment

6.1 Overall biological risk assessment

Current methodologies for assessing biological risks at different parts of the spectrum would benefit from harmonisation, both within nations across sectors and industries, and internationally to enable more effective policy making, resource allocation, international cooperation and sharing of best practices in tackling global biological risks.

Development of an overall methodology to inform biological risk assessment would require multi-disciplinary involvement and wide international representation, drawing on the existing work of national and international organisations. One approach would be to develop a systems analysis of existing risk assessments in a number of geographically representative countries to assist in: analysis of best practices; understanding how and why existing methodologies diverge; and identifying the elements upon which a common international biological risk assessment methodology might be developed.

Risk assessment models should recognise the variety of viewpoints and uncertainties with consideration given to the assumptions that are used to frame the risk assessment. These 'framing assumptions' may include a variety of socio-economic, security, and political factors. Different assumptions will lead to differing assessment of the risks, and so it is important to delineate the scope of the risk assessment to define what risks are included and how they are traded against the benefits. These assumptions inform scientific risk assessment, which in turn informs risk management. At the latter stage additional technical, economic, social, and political factors are taken into consideration. A characteristic of this dynamic model of risk assessment is that the risk management approaches and considerations also feed back into the scientific risk assessment,

and the initial framing assumptions, as shown in Figure 2.

An important consideration in developing a risk assessment for overall biological risk is that it is comprehensive, and its' scope set by risk managers. It should both draw on multiple disciplines and have cross-disciplinary application. Key features of a comprehensive assessment process include: examination of a wide range of uncertainties and possible scenarios; a precautionary approach with a deliberate search for gaps in knowledge and divergent views; attention to proxies for possible harm; consideration of indirect effects (eg those that accumulate or are synergistic); taking account of individual and institutional behaviours; drawing on multi-disciplinary knowledge and experience; a systematic approach to modelling; targeted scientific research to address unresolved issues; and consideration of the reversibility, flexibility, diversity and resilience of the model (Stirling 2007).

The value of diverse expert input is supported by lessons from recent experience in the financial and insurance worlds. Modelling catastrophic risks, such as hurricanes, has benefitted significantly from multi-disciplinary contribution from economists, scientists, and others.

In creating a model, and formalising risk assessments, it is necessary to have a clear understanding of where different data inputs are most appropriate and the impacts of the choices of data on the quality of the model output.

In order to ensure user friendliness for policy makers, factors to consider include: usability for non-mathematical users, costs of maintaining the model such as data collection, and simplicity through focusing on critical variables. Key issues in terms of the utility of any model will be the timeliness of the output, how feasible it is to act on the output, and the level of confidence in the model's output.

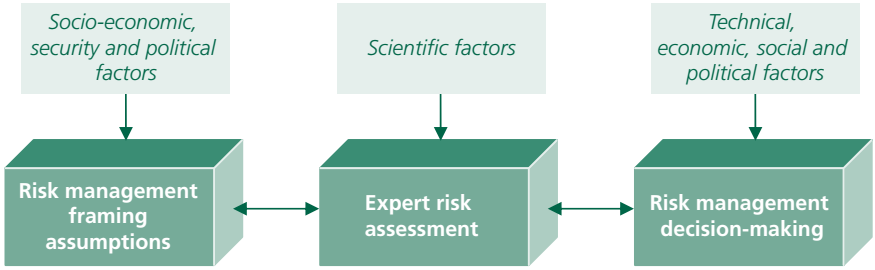
An important dimension to incorporate into any risk assessment is the timescale. Whilst extrapolations are required for naturally occurring, unintended, and deliberate parts of the spectrum, over long timescales the scope for new risks may increase most markedly in the context of deliberate misuse, particularly given the pace of technological change.

There may also be a need to include political consequences in any risk assessment. That is, incorporating the consequences of a particular biological incident that are not related to the direct affects in terms of loss of life. This might include any political and military responses to a deliberate biological attack. One dimension to this issue is analogous to the concept of 'catalytic attack' in nuclear proliferation, where one country or other non-state group might use a disguised biological attack in an attempt to induce conflict between other countries or groups.

6.2 Addressing uncertainty

Communicating clear scientific advice about biological risks to policy makers is paramount.

Figure 2: Dynamic model of risk assessment (van Zwanenberg and Millstone 2005)



One problem that can arise when the scientific community is not able to provide definite conclusions in their policy advice is that drastic but ineffective measures, such as closing airports and borders, can be introduced due to pressure from the public and the media, or a political desire to respond.

However, a major issue in overall biological risk assessment is the extent to which reliable estimations of risks can be formed due to uncertainty. Given the different nature of the risks across the spectrum and varying availability of data against which to derive or test mathematical models, a common approach should incorporate a range of specific assessments at points on the spectrum coupled with an overarching model to unify the resultant risk assessments. For naturally occurring diseases there are historical data available to inform risk assessment. There are also data available for unintended risks such as laboratory accidents, although less so for unintended consequences of dual use research. However, for deliberate misuse of biological agents there are very limited data and significant uncertainty.

Nevertheless, an overall risk assessment model would build on the similarities across the spectrum, and might focus on common characteristics of uncertain risks, both naturally occurring and deliberate, such as the specific properties of biological agents posing the greatest risk. This would require ensuring openness and transparency in the flow of available information on the range of risks to strengthen any assessment. This approach is supported by lessons from the financial world on the problems associated with restricting the flow of information available to inform risk assessment.

Traditional approaches to assessing the probability of different risks that incorporate subjective judgements and uncertainty include surveys and sampling of experts. As regards the latter, some participants suggested that subject area experts (ie in biosecurity) might enhance the accuracy of risk assessments through training in probability-related mathematical judgements.

A further possibility raised was the potential of using prediction markets to assess risks due to the incentive to assess the risk correctly regardless of bias. Prediction markets function best when applied to known issues but this might be improved with distribution of relevant information to assess unanticipated risks. It was noted that the forecasts generated by prediction markets do not predict the probability of a given event. Rather they provide a risk weighted or risk adjusted assessment of the probability.

A key issue with deliberate misuse is the need to assess and model intent. This needs to encompass an assessment of what informs the decision to acquire and use a biological weapon, the target selection, and the scale of an attack. An assessment is also needed of how the risks of acquisition and use vary according to different factors such as: the scale of the attack (ie from individual poisoning to mass casualty); targets (ie from an individual to a large area); objectives (eg terror, disruption, mortality), and actors (ie state, non-state group, or individual). It should also take into account the potential reactions of a malign actor in adjusting according to responses and countermeasures put into place to mitigate deliberate biological risks.

6.3 'Net assessment' of countermeasures

In any risk assessment it is important to incorporate an assessment of the consequences of different countermeasures (ie risk reducing strategies) to ascertain whether they have reduced risks or potentially created new or exacerbated existing risks. This approach would also highlight the most effective countermeasures across the whole spectrum and show where responses to risks at one part of the spectrum can mitigate risks at another. An overall cost-benefit analysis of different countermeasures would feedback to strengthen the risk assessment process and risk management options and inform a mutually-

reinforcing patchwork of measures to reduce risks. While no single countermeasure can be a 'silver bullet', there is a need to prioritise certain responses that will have the most impact on the full spectrum of biological risks on a global level.

Due to limited data there will be low levels of certainty around assessments of the risk associated with the deliberate misuse of biological agents as weapons. This presents difficulties in assessing the effectiveness of countermeasures. For this reason, countermeasures that can be applied across the full range of the biological risk spectrum are likely to be less risky investments as their effectiveness can be better determined. Such countermeasures include preparedness measures (eg stockpiles of therapeutics), early detection measures (eg disease surveillance and diagnostics), and rapid response measures (eg genome sequencing and rapid vaccine production). In addition, considerations of how countermeasures put into place for naturally occurring disease and unintended consequences might minimise the attractiveness of deliberate misuse of biological agents would further strengthen overall response to risk across the whole spectrum.

6.4 Socioeconomic factors

An overall lesson for biological risk assessment across the spectrum is the need to link epidemiological modelling of disease, economic modelling, and qualitative social science modelling of human behaviour.

Public perceptions and media reactions play an important role in driving policymakers' decisions on biological risks, particularly in the context of risk management and communication. Therefore, any risk assessment methodology needs to encompass assessment of human behaviour and motivations, and any model needs to incorporate feedback loops to address the public's reaction to government risk management policies.

Lessons from the modelling of pandemic flu in the UK, stress the importance of understanding social and economic factors, and particularly their interconnectedness, on the progression of a pandemic, in order to inform response measures. For example, whilst shutting schools might be considered a good response to limit person to person contact, the resultant chain of events could be significant. Shutting schools could increase people's fear of illness, which might result in staff shortages. These could lead to food and fuel shortages, which would encourage panic buying and hoarding. The latter could ultimately result in civil unrest and a breakdown in law and order.

Linking epidemiological modelling to socio-economic models can help minimise the economic impact of a flu outbreak. Based on the assumption that the case fatality rate will have a greater impact on public perception of risk than the infection rate, at a low fatality rate the best approach might be to promote a 'business as usual' message. However, as the fatality rate rises there will be a point at which the dominant response will be public alarm. If this point can be ascertained through socio-economic analysis then it can be used to inform the response. For example, recommending social distancing before this point is reached in order to minimise the infection rate and number of deaths, combined with adjustment in other elements of contingency planning such as replenishment of drug and vaccine stocks, might enable maintenance of overall control and avoidance of social breakdown.

For naturally occurring diseases public behaviours and perceptions are important in affecting the assessment and response at the level of groups and populations. However, for deliberate misuse there is the need for attention to behaviours at the level of the individual, as illustrated by the 2001 anthrax letters. With the dispersal and wider availability of emerging biotechnologies, understanding behaviours at the level of the individual may become increasingly relevant to assessing deliberate biological risks. In this context, the analogy of cyber security may be useful, particularly with regard to the motives and behaviour of computer 'hackers' and insights this may give for an emerging community of 'bio-hackers' (Chyba 2002).

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