Workshop Report, May 2013

Pharmaceutical Resilience

Proceedings of the Workshop on Pharmaceutical Resilience for Serious Infectious Disease, 5 February 2013

Edited by Jennifer Cole

The views expressed in this paper are the authors' own, and do not necessarily reflect those of RUSI, the Home Office, or any other institutions with which the authors are associated.

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FOREWORD

Pharmaceutical Resilience in the Response to Serious Infectious Disease

Dr Rob Jordan takes a forward look at planning for rapid access to pharmaceutical countermeasures during outbreaks of serious infectious disease.

NO MATTER how effective our ability is to monitor outbreaks of serious infectious disease and reduce their frequency, or to intercept evidence of a planned biological or chemical attack, an effective response to an outbreak or release will always be reliant on the use of medical pharmaceuticals for prophylaxis or for treatment. Maintaining large stockpiles of these drugs is expensive and distributing them to where they are needed can be logistically challenging – but there are many reasons why it is impractical to buy or produce them at short notice. On 5 February 2013, RUSI and the Office for Security and Counter-Terrorism (OSCT), part of the UK Home Office, co-convened a conference to consider how new technologies and business models could ensure that pharmaceutical countermeasures could be appropriately procured and distributed should there be an increase in the perceived biological threat.

The conference brought together key policy-makers, emergency responders, scientists and academics from the UK, US and Canada to discuss options for joint strategic approaches to pharmaceutical resilience, and included an academic poster session at which emerging scientific and technological solutions were presented. This report presents the papers from the conference and proceedings from the afternoon discussion forums.

Effective response to an outbreak or release will always be reliant on the use of medical pharmaceuticals

What is 'Pharmaceutical Resilience'?

In short, 'pharmaceutical resilience' is the principle of ensuring the public has access to appropriate medical pharmaceuticals when they are needed – even in the face of strong factors that limit the supply of these products, potentially on a global scale. At present, pharmaceutical resilience is assured by stockpiling. Around the world, the typical government response to high-impact outbreaks of disease depends on ensuring that centrally-held large stockpiles of appropriate drugs are maintained until they are required, then distributed to populations that need them. In some scenarios, such as pandemic influenza, this is based on a very large stockpile that can be distributed to the total population of an affected country. For other scenarios, such as a biological attack by terrorists, a smaller stockpile, perhaps based on the population size within a geographic area, might be adequate – but these stocks would need to be made available to an at-risk population extremely rapidly.

In the early stages of a pandemic, global demand can drive up prices and limit supply

Although considered cost-effective,[1] such stockpiles are expensive. The UK government spent more than £500 million on a stockpile of antivirals, vaccines and antibiotics to prepare for the 2009 swine flu pandemic. The UK has also been building stocks of pharmaceuticals to respond to a large-scale biological attack by terrorists as, although judged to be unlikely, the impact could be catastrophic.

Regardless of the motivation behind their retention, the pharmaceuticals in these stockpiles have a finite shelf life, typically of less than five years, meaning that they need constant renewal. But is there a better option?

Buying pharmaceuticals at times of particular threat is not a viable alternative. A response to a high-impact biological attack would need the

1. M Ruby Siddiqui and W John Edmunds, 'Cost-Effectiveness of Antiviral Stockpiling and Near-Patient Testing for Potential Influenza Pandemics', *Emerging Infectious Diseases* (Vol. 14, No. 2, February 2008).

distribution of drugs to begin in the immediate aftermath of the attack. At times of heightened concern over infectious disease, such as in the early stages of a pandemic, global demand can drive up prices and limit supply of raw materials, precursor materials and the pharmaceuticals themselves. Furthermore, the precursors for these pharmaceuticals are often produced in limited amounts by overseas manufacturers.

How Could This Change?

New technologies offer the potential to reduce our reliance on stockpiling. The development of cheap and reliable point-of-care diagnostics could make it easier to avoid unnecessary treatment, meaning smaller stockpiles could potentially be used to protect people more effectively.

Synthetic biology offers potentially massive gains to pharmaceutical security

Other technologies could have more dramatic impacts. Advances in biotechnological engineering could result in increased flexibility and production rates in pharmaceutical production plants. Developing more effective, smaller-scale, temporary production facilities could enable the production of pharmaceuticals on increasingly local levels, potentially increasing the total production capacity whilst reducing distribution burdens.

Synthetic biology offers potentially massive gains to pharmaceutical security in both the medium and long term. In the medium term, it could offer modifications to existing pathways for pharmaceutical production. In the longer term, there is the potential for self-sufficient pharmaceutical generation, reliant only on basic raw supplies, and even the prospect of developing pharmaceuticals tailored not only to specific infectious organisms but also to the host.

Scope of the Conference

The aim of the conference was to discuss these issues and to consider how the UK and US can build their pharmaceutical resilience to improve their response to high-impact outbreaks of infectious disease. It focused both on quicker wins, such as modifications to pharmaceutical infrastructure, and on the longer-term technological gains, taking a science-led and forward-looking approach which aimed to focus five-to-fifteen years ahead, looking out to the longer term where appropriate.

Dr Rob Jordan works in the CBRNE Unit at the Office for Security and Counter-Terrorism. The Unit is responsible for co-ordinating government policy that reduces the risks of chemical, biological, radiological, nuclear and explosive terrorism.

Questions considered at the conference included:

- How can vaccines, treatments and antidotes be manufactured more quickly once a threat has been identified?
- How can governments influence the speed with which such treatments can be made available?
- Stockpiling versus creation: the pros and cons
- What are the barriers to the UK being self-sufficient in the production of antibiotics and antivirals?
- What direction is the global trade in antibiotics and antivirals (and their precursors) heading in?
- Does this present opportunities to generate revenue whilst developing pharmaceutical resilience?
- Could new business models develop pharmaceutical resilience using current technology? What infrastructural changes would be required?
- What technological developments are on the horizon that could result in the rapid production of large quantities of antibiotic and antiviral pharmaceuticals?

PHARMACEUTICAL RESILIENCE: THE UK APPROACH

I. Assessing the Risk from High-Impact Disease

Felicity Oswald-Nicholls outlines how the UK government calculates the risk of biological threats and plans for specific scenarios.

THE UK's current National Security Strategy (NSS) was set in 2010 and encompasses everything that should be done to ensure that the nation, its borders and members of the public are secure. It also considers the UK's interests overseas. The NSS is informed by the National Security Risk Assessment, which looks twenty years ahead and thinks about domestic and international events, and the National Risk Assessment, which looks largely at domestic risks in a five-year horizon scan. While the National Security Risk Assessment and National Risk Assessment are classified, the National Risk Register produced from them is published openly and is available on the Cabinet Office website. New versions of these documents are produced every two years with the next review due to take place in 2014.

The National Security Strategy

Risks considered to be Tier One (the highest risk) in the National Security Strategy will drive security policy. These encompass malicious attacks and natural hazards that, were they to occur, would be likely to impact on the UK at a national level. Key pharmaceutical resilience issues include pandemic influenza and CBRN terrorism affecting the UK and its interests. International terrorism, which might include CBRN attacks, is also considered to be one of the top risks to the UK.

Following the National Security Strategy is the UK's counter-terrorism Strategy, CONTEST. This sets out the work of the Office for Security and Counter-Terrorism (OSCT), part of the Home Office, and is based on the 'four Ps': Prevent, Pursue, Protect and Prepare.

Planning the Response

In the UK, planning for both threats and hazards, whether they are man-made or natural, is based on around eighty 'reasonable worst-case'

scenarios. Around half the risks identified are malicious, such as terrorism or crime-based threats; the other half are natural hazards or industrial action-/accident-type events. A reasonable worst-case scenario is then judged in terms of likelihood and plausibility.

Pandemic disease is one of the highest-priority events on the National Risk Register

Experts are very good at determining a sensible value for the likelihood of a natural hazard occurring. However, it is harder to do that with a malicious threat, so security experts are asked to develop a measure of plausibility, taking into account the capability of threat actors, the intent they may have, and the UK's potential vulnerability to an attack. A value of one to five is determined. Impact is also scored, taking into account likely fatalities, casualties, social disruption, and economic and psychological impacts on the public.

Pandemic disease is one of the highest priority risks on the National Risk Register as it falls into the highest impact category, and is also one of the most likely risks. Catastrophic terrorist attacks and smaller-scale CBR attacks are also considered.

Resilience Planning

The majority of resilience planning in the UK is based on a generic, all-hazards approach. However, in addition to that there is also specific planning for the highest-priority risk so, for example, the Department of Health also has a specific plan for pandemic influenza. Key challenges that the UK needs to consider for the future include: how to keep up momentum and planning for infectious disease without being criticised for crying wolf? Do other risks sometimes 'hog the limelight'? Do we worry about other infectious diseases enough? With pandemics, we think about bird flu; but is that the right approach? And finally, is the public sufficiently informed to spot suspicious activity in relation to infectious disease or malicious attack, in the same way that they might be regarding an unattended bag on the London Underground?

Felicity Oswald-Nicholls is Deputy Director for Risks and Infrastructure at the UK Cabinet Office's Civil Contingencies Secretariat, where her responsibilities include overseeing the UK's National Risk Assessment, National Risk Register and risk assessment guidance for local emergency planners. This supports the resilience of the country's critical infrastructure sectors and national-level planning for those threats and hazards that are likely to have the highest impacts. Felicity joined the Civil Contingencies Secretariat in her current capacity in November 2012. Prior to this she worked in both the Home Office and Cabinet Office, leading policy development, projects and programmes on national security, counter-terrorism and policing.

II. Building Pharmaceutical Resilience: A National and International Perspective

Professor Bernard Silverman, Chief Scientific Advisor at the UK Home Office, sets out the challenges of building pharmaceutical resilience and the opportunities that can come from tackling these issues at international level.

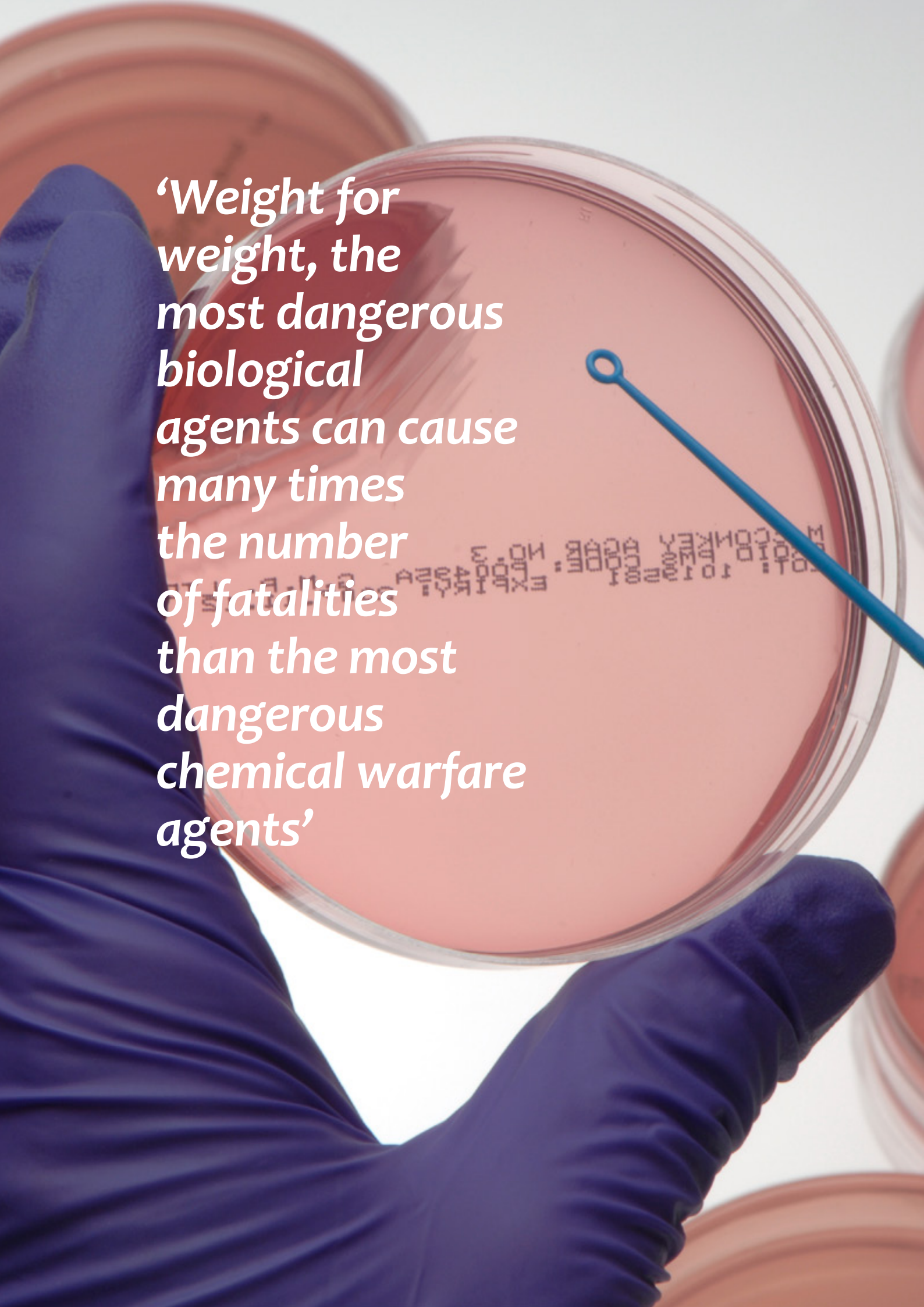
THE HOME Office leads on co-ordinating UK policy to reduce the risk of terrorist attack both in the near future and in five-to-ten years' time. The Office for Security and Counter-Terrorism (OCST), in the UK's Home Office, provides strategic direction to the UK's work to counter terrorist threats and is responsible for reducing the risks posed to the UK by CBRN terrorism.

As Chapter I explains, countering CBRN terrorism is given high priority by the UK government: there was a recent debate in the House of Lords, a lot of work was done in relation to the 2012 London Olympic and Paralympic Games, and the Government Office for Science has recently carried out a review on biodetection. We need to know that if certain threats were to be realised, we would be safe.

Reducing the Risks of Biological Attack

Reducing the risks of biological attack is given high importance for a number of reasons. A wide variety of agents could be used for an attack, with different agents causing different effects. Some will rapidly cause fatalities; others will have more delayed effects. Some can spread from person to person. Biological agents can be delivered to their targets in different ways – many causing disease if inhaled or ingested. Some can be grown in large amounts easily, while with some, only a small amount is required to effect a mass-casualty attack. Weight for weight, the most dangerous biological agents can cause many times the number of fatalities than the most dangerous chemical warfare agents. Unlike nuclear and radiological material, hazardous biological material can be found naturally in the environment, is hard to detect by law-enforcement agencies, and can easily be carried across international borders.

Countering biological threats relies heavily on scientific evidence. Immediate responses to any such attack would require some sort of medical countermeasure – usually antibiotics and, in some scenarios, vaccines. The challenge is twofold: How to produce the countermeasures and how to administer them. At the moment, it is difficult to make drugs quickly enough because of problems such as bottlenecks in the production of precursors (the ingredients used to make the drug or vaccine), so we have to have enormous stockpiles with a finite shelf life. Distribution is also a challenge – but new ways of using established technology could offer improvements, such as the ability to manufacture very large quantities of countermeasures on demand.



‘Weight for weight, the most dangerous biological agents can cause many times the number of fatalities than the most dangerous chemical warfare agents’

For these reasons, Home Office staff work closely with other departments, industry, academia and international partners to co-ordinate work to make it as hard as possible for terrorists to access the materials and knowledge needed to carry out a mass-casualty biological attack, whilst making sure that legitimate work can go ahead. The aim is to make an already-unlikely attack even more difficult. But the government needs to be realistic about its ability to prevent terrorists from obtaining a biological capability, and remember that the threat is evolving. The spread of knowledge of current scientific techniques and the development of new technologies increase the likelihood that terrorists who want to acquire a biological capability will be able to do so.

As well as malicious events, the risk of high-impact, naturally occurring disease persists and evolves. The Department of Health and Public Health England (PHE) lead work to counter this, as does the Department for Environment, Food and Rural Affairs (DEFRA). Whilst the cause may be different in the case of agricultural issues, the response challenge is similar.

Government needs to be realistic about its ability to disrupt terrorist plans

Hope for the Best, Plan for the Worst

In both cases, we hope for the best and prepare for the worst. If left unchecked, the consequences could be far-reaching, and dealing with them would require a national response. An attack involving a large release of a highly dangerous organism – such as anthrax – could cause widespread casualties and a response to such an incident would need to be in full swing within hours.

An effective response to a large-scale outbreak of serious infectious disease requires two elements. First, the ability to rapidly identify that there is a problem, in order to then initiate an appropriate response quickly enough to be effective. Plans for the London 2012 Olympic and Paralympic Games highlighted this. The biological detection system used during the Games built on business-as-usual capabilities to plan an effective response for a large at-risk population. This planning highlighted the logistical challenges associated with maintaining and distributing a strategic stockpile of drugs.

Ensuring that governments can make appropriate drugs available to those that need them *when they need them* is the principle of pharmaceutical resilience. It is a complex problem that raises questions such as:

- How might new technologies offer better ways of doing things?
- How could industry better use existing technology to achieve this?
- What could the government do better to enable this to happen?

Fully understanding emerging and future technology will ensure that new scientific developments can be fully incorporated into planning and policy. There is research and development work in the pipeline for which the precise

Key Issues for the UK Government and Industry to Consider

- What are the key challenges associated with bioterrorism response planning that piggy backs off of so many areas of 'normal' healthcare provision? How interconnected is policy on stockpiling between the health and security communities?
- How does the counter-terrorism community persuade more routine areas of healthcare provision that biological terrorism is a problem they should plan for?
- How effective is the government at communicating the risks to individuals associated with a given treatment or prophylaxis? How might or should the government do this differently in an emergency?
- What are the key challenges to increasing the shelf life of drugs and vaccines in our stockpile? Are they scientific hurdles or regulatory ones?
- How does our stockpile compare with that of key EU members? Under what situations could mutual aid work – or fail?

applications are as yet unknown, such as synthetic biology, microreactors (devices in which chemical reactions take place in a confined space) and nanotechnology. Rapid diagnosis may offer opportunities to quickly determine which individuals have been affected and which have not. These are all technologies that could potentially relate to the serious issues being discussed in this report.

Fortunately, the relationship between the UK Home Office and the US Department of Homeland Security has meant that the two countries have been thinking about these important issues together, enabling future relationships to be built and to ultimately to make genuine advances in this very important area. It was this partnership between science, industry and government that the conference on which this report is based sought to move forward. Meetings such as that held at RUSI and another planned at the Royal Society later in 2013 provide an impetus for the research and industrial communities to think about what will be useful in this sort of context, as solutions will undoubtedly have spin-offs that impact healthcare and the wider economy.

Professor Bernard Silverman is the UK's current Home Office Chief Scientific Adviser, responsible for the provision of scientific advice for the UK's Home Office and support to Home Office policy and operations in crime and policing, migration and counter-terrorism. He is also a highly cited researcher whose published work centres on computational statistics. He is a Fellow and recent Council Member of the Royal Society (FRS) and is a past President of the Royal Statistical Society and the (US-based) Institute of Mathematical Statistics.

III. The UK CBRN Pharmaceutical Stockpile

Dr Hilary Walker explains the UK's CBRN medical countermeasures stockpile, its current content and management, and considerations around the future of the stockpile as it currently stands.

IN CHAPTER I, Felicity Oswald-Nicholls outlined the procedures and processes followed regarding threats to the UK, and in Chapter IV Mark Salter will explain how people will be treated. In between these two considerations, we need to discuss what we might have in the UK's stockpile for such eventualities and ask: is it worth stockpiling?

The UK CBRN Medical Countermeasures Stockpile

The CBRN stockpile is maintained and managed by the UK government and is available to all of the UK health departments. Health is devolved in the UK to England, Scotland, Wales and Northern Ireland but they work together when it comes to managing stockpiles. There is a specific CBRN stockpile which does not include the essential stocks for more general use in the UK NHS – there are other devices used to make the pharmaceutical chain resilient regarding the provision of drugs to the NHS.

The UK government combines efficiently stockpiles which may have different primary uses. For example, during the London 2012 Olympic and Paralympic Games, a stockpile of antibiotics for pandemic flu was available, if needed, to use for CBRN issues. This enables a single stockpile to provide for pandemic flu, outbreaks of new infectious diseases, a catastrophic CBRN attack, a smaller-scale CBR attack or an industrial accident involving hazardous chemicals.

Further enhancements were made in 2002 and 2003 following 9/11

The current stockpile is based on the perceived risk – which Felicity Oswald-Nicholls described in Chapter I – and whether the supplies are generally available in the NHS. We only stockpile those which are not usually available. We also plan how to distribute these stocks in an emergency situation.

The stockpile started in the late 1970s. When smallpox was eradicated, the vaccine was retained as, at that point, there were concerns about the need to remain resilient should the disease re-emerge. In 1995, after the Tokyo sarin attacks, it was decided that the UK needed to have nerve gas antidotes in order to respond quickly if an attack of that sort happened here. Further enhancements were made in 2002 and 2003 following 9/11, looking particularly at countermeasures for anthrax and botulinum toxin.

Enhancements to the Stockpile in 2002–03

Further enhancements made after 2003 enhanced the amount of nerve agent countermeasures and personal-protection equipment. This is stockpiled out in the field to ensure it is ready for rapid use if needed.

There is also a more central stockpile containing antibiotics for bacterial biological agents, in a similar fashion to that which is held in the American stockpile. It includes products to deal with elements of radiation exposure, including potassium iodate, which was already in place for the UK's nuclear installations but a further stockpile has been generated nationally. More smallpox vaccines have been brought in to supplement the stores stockpiled previously and there are some specific antidotes to deal with particular types of chemical poisoning. Additional products including specialised needles and syringes, if required, have also been added.

There is quite a considerable stockpile available for use in the UK

Where the UK is Today

The current main stockpile includes twenty-four products not including items that are already used by the NHS for routine applications. Over the next five years, the costs to maintain that level of stockpile will be in the order of £71 million. There are additional storage costs of £8.4 million. The total replacement value is about £147 million – so there is quite a considerable stockpile available for use in the UK.

There are protocols for release, and these depend on the need and speed of wanting them in place. There are items that can be distributed to particular areas within five hours, and there are others which can be distributed within twenty-four hours. An advantage of the UK being relatively small is that it is possible to get items around the country within five hours if needed. This is in contrast to countries like the US.

Medical Countermeasures Stockpile Review

We recently reviewed the countermeasures stockpile, looking at whether the stockpile is proportionate to the anticipated threats or hazards and whether it remains consistent with clinical guidelines or requires updating. The review also looked at whether it is realistic in terms of the timescales allowed for managing the logistics and distribution of stocks and whether it represents value for money within the risk appetites of each of the UK administrations.

It is possible to get items around the country within five hours

There are a number of issues that need to be tackled, and we need to readdress the stockpile content and management in light of the changes being undertaken currently in the NHS generally. We also need to consider

and develop our public-health information strategy in this area and we are looking forward to working to meet these challenges in the future.

Dr Hilary Walker is currently responsible for managing health policy regarding health impacts from CBRN threats and environmental hazards. Previously, she was the Deputy Director for Emergency Planning. She has contributed to the scientific aspects of planning and dealing with emergencies including pandemic flu, volcanic ash and more recently the Fukushima accident. She joined the Civil Service in 1986, a few months after the Chernobyl accident when there was a need for more radiation expertise in the government scientific civil service.

IV. Options for Response

Mark Salter of the Health Protection Agency (now part of Public Health England) explains the options available for responding to a sudden outbreak of serious infectious disease.

IN RECENT years, a number of major international events have put the HPA and the UK government on their toes. In 2002–03, the SARS (Severe Acute Respiratory Syndrome) virus raised awareness that infection can spread rapidly across international borders. This prompted a major change to international health regulations: countries around the world are now required to have effective surveillance systems and to report new threats to the international community so that appropriate measures can be put in place. It was around this time that the HPA was formed and it has since dealt with the threat and actuality of influenza pandemics, in particular concentrating on the newly emergent H5N1 'Bird Flu' and, four years ago, the H1N1 'Swine Flu' pandemic.

These events have led public-health groups across the world to work together to develop rational responses in relation to risk assessments. There are a number of ways in which these threats might be addressed.

Response Option 1: Do Nothing

In the case of a minor disease, the best response option may be to do nothing in the first instance and treat only those people who actually become unwell. Even if 50,000 people were affected, managing those individuals as they present clinical illness may be more efficient than trying to put anything in place to prevent them from contracting the illness. In reality, this may be the only practical approach if a significantly large proportion of the population is affected and it is difficult or impossible for those who are actually infected to be identified early.

During the London 2012 Olympic and Paralympic Games, the HPA worked on a number of scenarios where an agent might be released. Through reverse epidemiology and advanced modelling, it would have been possible, within twenty-four to forty-eight hours of detecting a release, to have to have distributed medical countermeasures to an at-risk population. Depending on the timing between detection and running the models, however, there were scenarios where anywhere from 200 to 200,000 people might be affected by the time the countermeasures could be made available. Potentially, these people could have dispersed all across the world in that time. In such cases,

Events have led public-health groups across the world to work together

responding to the overt clinical consequences may be the only pragmatic way to manage the incident.

Prophylactic medicine is potentially the most cost-effective method

Response Option 2: Use a Prophylactic Medicine

Using a prophylactic medicine is potentially the most cost-effective method of preventing symptoms developing in those who have, or who are likely to have, come into contact with the agent. This could be achieved relatively quickly.

Such a response is most important where the outcome of treatment is poor and when clinical disease has become established. There will, however, be side effects: some people are allergic to drugs, even common ones such as paracetamol. If 100,000 people are given a drug and only one per thousand is severely affected by side effects, this is still a significant number. Administering the treatment becomes a balancing act, depending on the severity of the disease and the likelihood and impact of any side effects that might materialise.

This option is generally only feasible for bacterial diseases; with antiviral drugs, the imbalance between effectiveness and availability is likely to be too large and, often, the methodology of delivery is different from the tablet or capsules that are normally used for antibacterial drugs.

Compliance is also a limiting factor, particularly when a course of treatment is required. How long does the treatment need to be given for? Is there sufficient evidence to take the prophylactic? This knowledge may have to be accumulated as the incident progresses, and there may not necessarily be an effective exit strategy at the start of the prophylactic intervention.

Response Option 3: Use a Vaccine

In theory, the use of a vaccine is the most attractive option. There are relatively safe vaccines and equally unsafe vaccines; the latter can cause significant side effects. Most recently, smallpox vaccination was considered an important requirement for military recruits; the US embarked upon a large-scale vaccination of military personnel but the one-in-a-million side effects that had been observed during the mass smallpox

Issue for Consideration

How much of this information and the understanding of the generic systems should be disseminated to the wider population, so that when the government is called upon to provide advice to the public on emergency countermeasures, the population has some perception of why they are being asked to act in a certain way? Would this go some way to saying ‘Don’t panic’?

eradication programmes proved a considerable underestimation of the side effects seen by those who were inoculated in the US.

There may not necessarily be an effective exit strategy at the start of the prophylactic intervention

The delivery of vaccines is complicated and there may be a very short period of time in which to vaccinate large numbers of people. The provision of the vaccine is a major problem as is the provision of the technology to deliver it, such as syringes. It may be difficult to get people with the right skills to the right places at the right time. The UK has a 'train the trainers' system, so there would be a cascade of the teaching ability but this would be slightly more complicated in the case of smallpox, as the mechanism of delivery is more complicated. Vaccines can rarely be used as the sole intervention.

Response Option 4: Mixed Approaches

The most useful and most sensible approach is one of a mixed intervention

Probably the most useful and sensible approach is one of a mixed intervention: establish those who have had the greatest exposure and who are therefore at the greater risk of developing the symptoms of the disease; provide prophylactics for those who have yet to develop symptoms and treatment to those who have overt symptoms; and, if the risks are understood and considered to be acceptable, administer the appropriate vaccines at the appropriate time.

Dr Mark Salter is a public-health physician with extensive experience of dealing with complex health emergencies at national and international level. He has a close relationship with the World Health Organization (WHO) and was the WHO clinical lead working on SARS. He is currently the Global Health Consultant and senior medical adviser within Public Health England on issues of Global Health Security and Response to CBRN(E)-related events.

PHARMACEUTICAL RESILIENCE: THE US APPROACH

V. Pharmaceutical Resilience: The US Perspective

The US has recently reviewed its strategy relating to emergency medical countermeasures and continues to develop its stockpile. Dr Gerald Kovacs outlines the new strategy and specific projects aimed at helping the US become more resilient in pharmaceutical product development.

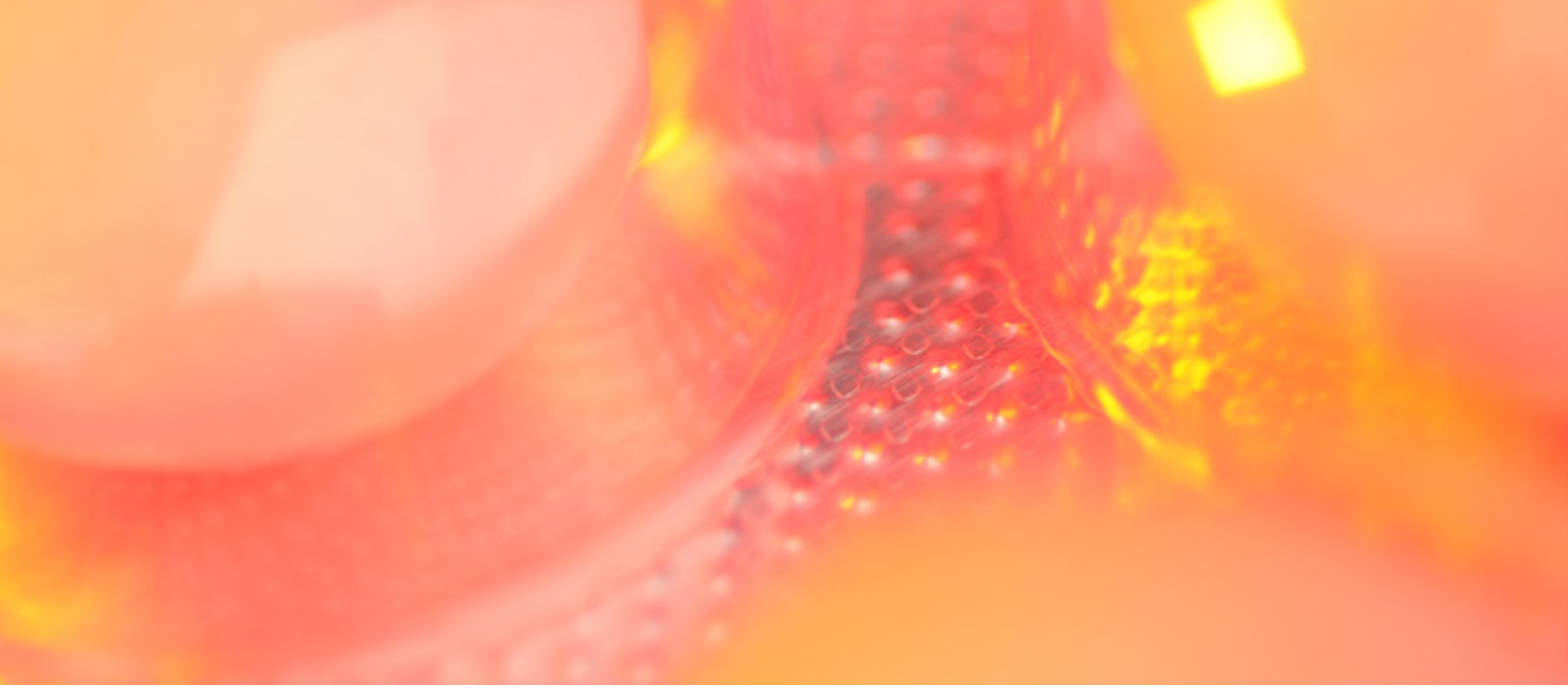
PHARMACEUTICAL RESILIENCE is a topic with a wide scope; in the US, resilience to serious infectious disease is embedded within the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Diseases (NIAID), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC).

The 2012 Strategic and Implementation Plans

Threat determinations are made by analyses of intelligence information and risk assessments

In 2012, the Department of Health and Human Services (HHS) published the 2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan.[1] Available online, this provides a great resource for understanding the US approach to medical countermeasure development and use. The 2012 Strategy and Implementation Plan is a revised version of the one published in 2007, which was written after a major law, the Project BioShield Act 2004,[2] was passed in the US. Project BioShield was primarily intended to: facilitate CBRN medical countermeasure development; allow the FDA to implement emergency use authorisation of medical countermeasures prior to their approval; and provide an incentive to manufacturers to develop CBRN medical countermeasures ($5.6 billion over ten years was appropriated by Congress). The 2007 Strategy and Implementation Plan was developed subsequently to provide a roadmap for

1. See <http://www.phe.gov> and <www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx>.
2. See <www.gpo.gov/fdsys/pkg/PLAW-108publ276/html/PLAW-108publ276.htm>.



Project BioShield. The 2012 PHEMCE Strategy and Implementation expands the breadth of the original document by including everything from research and development, to the regulatory processes that it uses to license its products, to effective deployment.

Priority will be for programmes that provide the broadest capability to known and unknown threats

There are four main goals in the 2012 PHEMCE Strategy and Implementation Plan. Goal 1 is to identify, create, develop and procure critical medical countermeasures, and is the responsibility of BARDA and the NIAID. Goal 2 is establishing and communicating clear regulatory pathways to facilitate MCM development and use, and primarily relates to the FDA's work. Goal 3, regarding logistics and operation plans, is in the hands of the CDC and the Office of Preparedness and Emergency Operations with the ASPR Office. Goal 4 addresses the need for MCMs for all sectors of the American population and is the responsibility of all agencies.

The 2012 plan not only articulates the responsibilities and plans of the respective agencies aligned through the PHEMCE, but also provides a framework for identifying priority investments in medical countermeasures:

- Threat: only the highest-priority threats for which MCM capabilities do not already exist will be addressed; threat determinations are made by analyses of intelligence information and risk assessments, many of which have been identified by the Department of Homeland Security
- Multi-functionality: investments will be prioritised for programmes that provide the broadest capability to known and unknown threats. BARDA is moving away from a 'one bug, one drug' paradigm and addressing countermeasures that have multiple uses, or are broad spectrum
- Operational capacity: focus will be to adapt MCM distribution and utilisation methodologies to existing infrastructure to facilitate their use in the event of an emergency. Product development and product improvements will focus on facilitating their utility as well.

In addition there are three moderating criteria:

- At-risk population needs: addressing the needs of all segments of the US population by considering alternative formulations and delivery routes for MCMs
- Time: balancing rapid acquisition of current materials versus gains in longer-term capabilities. Consideration is always given to the development, procurement and stockpiling of products that have the most cost-effective lifecycles
- Cost: balancing considerations of MCM lifecycles, by considering the entire spectrum of capability development and sustainment.

Centres for Innovation in Advanced Development and Manufacturing

There are two programmes that BARDA has started over the last three or four years to help build resilience in pharmaceutical product development. One is run by Novartis in Holly Springs, North Carolina, and is licensed to manufacture pandemic flu vaccines. It can be used at any given time when a pandemic is declared but throughout the year, when there is no pandemic, it will primarily be used to manufacture seasonal flu vaccine. The other is the Emergent BioSolutions facility, in Lansing, Michigan. This facility is used to manufacture large quantities of the anthrax vaccine, AVA.

BARDA has started two programmes to help build resilience in pharmaceutical product development

More recently, large contract awards were made to three partners: Novartis, the Texas A&M University System and Emergent BioSolutions. These are public-private partnerships not only in terms of resources, but also in terms of the financial partnership. Partners either build or retrofit manufacturing facilities that can be used to manufacture vaccines for pandemics or other CBRN purposes. These centres provide technical expertise at the highest level. The personnel and organisations have been involved in pharmaceutical product development for a long time; they are very experienced. The facilities provide flexible manufacturing systems and also serve as countermeasure development centres for the next-generation workforce. The capabilities they offer include the manufacture of recombinant proteins, antibodies, vaccines, blood- and plasma-derived products, mammalian-cell, insect-cell, microbial, live-virus, small-molecule and antibody-like biologics (synthetics). No one facility offers all capabilities but collectively they offer everything that is needed.

Collectively, facilities offer everything that is needed

Tackling Antimicrobial Resistance

A particular challenge to pharmaceutical resilience is the rise of antimicrobial resistance, or AMR (see the box above for more information) – the emergence

The Spread of Drug-Resistant Organisms

The spread of Carbapenem-resistant Klebsiella is one example of the threat to the US from drug-resistant organisms. First recorded in 1996 in North Carolina, by 2011 it had spread throughout the country and has now been recorded in at least thirty-seven states.

During natural disasters there is a significant amount of mortality and morbidity associated with multi drug resistant (MDR) organisms. Three examples of recent events in the US during which MDR pathogens have played a major role include the aftermath of Hurricane Katrina in 2005, when 18 per cent of hospitalised victims were infected with either Gram-positive MDR pathogens (MRSA and VRE) or Gram-negative MDR pathogens. During the 2009 H1N1 pandemic, bacterial co-infected patients were characterised by high mortality rates, more frequently presented with shock, required mechanical ventilation, and required longer periods under ICU care. And in the aftermath of the 2010 Haiti earthquake, 77 per cent of sampled wound infections were polymicrobial, with 89 per cent of infections involving Gram-negative pathogens.

MDR infections continue to rise and biological agents could, in theory, be deliberately engineered to be multi drug resistant. The antibiotics that BARDA is helping to develop, although not necessarily tested with MDR organisms, may serve in that role if necessary. There is a prerequisite that when BARDA partners with pharmaceutical companies on these different types of projects, they build a biodefence indication into the label – that is, the drug must not only be effective against MDR pathogens, but also against one or more of the high-priority threats.

It is expected that new antimicrobials will have sufficient penetration in the marketplace so that BARDA does not necessarily have to maintain large stockpiles of these antibiotics in the Strategic National Stockpile.

of new, drug-resistant diseases or drug-resistant strains of known diseases. While there are antibiotics in the stockpile for anthrax and other biological threat agents, there is a danger that multi drug resistant pathogens may emerge. This danger is exacerbated by the fact that pharmaceutical companies have, for the most part, stopped developing new antibiotics as there is very little opportunity for profit compared with other areas of drug development and manufacture.

To address this, BARDA is partnering with pharmaceutical and biotechnology companies to help them develop antimicrobials for treating not only

multidrug resistant pathogens, but also infections caused by bio-threat agents such as anthrax, tularemia and plague.[3]

Core Services

MCM development differs from traditional drug development in that efficacy data cannot ethically be accrued by testing these products on human subjects. The FDA Animal Efficacy Rule of 2002 enables the approval of products through testing in qualified animal model systems. BARDA has established partnerships throughout the world to develop animal models to test product efficacy.

BARDA remains committed to developing countermeasures for the civilian sector

This Nonclinical Development Network is also being used to evaluate the efficacy of marketed products not intended for biodefence purposes. Qualified animal models are being used to test these products with the expectation of expanding their licensed indications. The animal model network is also used for countermeasure readiness. All the data is shared with sponsors and is publicly available, with contract research organisations located throughout the US and with a couple also in the UK.

Conclusion

BARDA remains committed to developing and providing countermeasures for the civilian sector, working collaboratively and sharing information and resources with partners in the Department of Defense, which develops countermeasures with slightly different indications for armed forces personnel. However, BARDA no longer relies exclusively on contracted relationships. Instead, it partners with industry on many of the aspects that it funds and the portfolio has more than 170 MCM (including CBRN and pandemic influenza) in development at this time. The PHEMCE's biggest challenge is developing the safest and most efficacious products, whilst sustaining this capability in the long term.

Dr Gerald Kovacs is the Director of the Division of Chemical, Biological, Radiological and Nuclear (CBRN) Countermeasures in the Office of the Biomedical Advanced Research and Development Authority (BARDA), within the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response. Since joining BARDA in 2005, Dr Kovacs has expanded the organisation's portfolio of CBRN programmes from four to over fifty. He has led five programmes through Phase II clinical testing, and has delivered five first-in-class medical countermeasures to the Strategic National Stockpile. Most recently, his group has achieved FDA approval on two products (anthrax antitoxin and heptavalent botulism antitoxin).

3 See <https://respond.niaid.nih.gov/conferences/amdw/Pages/default.aspx>.

VI. The Strategic National Stockpile in the United States

Dr Ali Khan and Greg Burel set out the approach to medical countermeasure stockpiling and distribution in the US, highlighting the shared strategic vision of the UK and US and the opportunities for collaboration this brings.

IN THE US, there are five national preparedness goals: prevent, protect, mitigate, respond and recover. These are supported by thirty-one capabilities. There is an all-hazards approach to public health that includes preparedness for natural events, bioterrorism and antimicrobial risks, as well as for natural disasters and pandemics of all kinds. Public health is dynamic; on any given day the US is responding to all sorts of threats all of the time.

The Strategic National Stockpile (SNS) is the US repository of antibiotics, antitoxins, antivirals and medical devices that are designed to intervene in a positive way in various disease conditions and other natural-hazard events. Its mission is to prepare and support state and local partners to provide the right material at the right time to secure the nation's health. It also supports private partners that are outside of the traditional healthcare and public health-arena and participates in the PHEMCE to determine US MCM requirements.

In the US, there is an all-hazards approach to public health

SNS's current portfolio value is estimated at $5 billion and it receives approximately $500 million in annual appropriations. Approximately 250 CDC staff members carry out SNS work across the US for all fifty states, as well as for all US territories and freely associated island nations. All activities revolve around supporting the nation to increase its ability to rapidly and effectively respond to new and emerging disease threats, CBRN threats and other threats across a wide spectrum.

The Strategic Approach

Stockpiled countermeasures cannot reach everywhere in the US in five hours as they can in the UK but SNS plans and processes have been refined to ensure the timely delivery of MCM within clinically relevant timeframes for each type of threat. High bars have been set for movement and transportation to meet clinical needs, even in the Southern Pacific. In particular, a lot of work has been undertaken during natural events such as hurricanes. The SNS has also worked on the H1N1 outbreak, the World Trade Center attack and the response to the anthrax letters sent to high-profile targets in the US thereafter.

The SNS is 'a whole lot more than the stuff'. SNS staff develop and support federal, state, local and private sectors to use its material effectively. They

There is a thirty-day backlog of any drug in the pharmaceutical supply chain

create guidance and policy and provide training. They teach about 2,000 people annually, based throughout the US, what would happen if the SNS were called into play and they provide subject-matter expertise from CDC in all phases of surveillance, diagnostics formulary design through the PHEMCE, and acquisition and utilisation of its material.

They strive to maintain an understanding of the normal pharmaceutical supply chain in the US in order to include products in the stockpile that the market cannot deliver, either in the right quantity or in the desired timeframe during an emergency. Due to commercial pressures, there is approximately a thirty-day backlog of any drug in the pharmaceutical supply chain. That expands a little for some and contracts for others but certain drugs are often in shortage. SNS staff work with both the big distributors in the US and the FDA to understand requirements for federal intervention.

Regarding scenarios that are difficult to predict, SNS staff look at how material that is already held in the stockpile can be repurposed for other things should a new threat arise. This has created an infrastructure that is capable, in the face of such events, of taking rapidly developed products, or material acquired from the private sector, and moving them forward more quickly.

Challenges

Defining MCM requirements is complex. Prior to 2001, the SNS was rather small but since then it has benefited from significant investments to try to deal with a broad range of terrorist activities, primarily CBRN-based. During the early days of expansion, the SNS invested heavily in certain products. This created huge spikes in product expiration in inventory, which SNS is currently looking to resolve through strategic procurement.

The main challenges to the matured stockpile now centre around sustaining the assets and continuing to align its capabilities with SNS partners. Maintaining a $5 billion portfolio of countermeasures and devices considered critically important is difficult as annual funding declines. This has led to novel modelling approaches to balance the existing inventory and formulary.

Another challenge is in effectively dispensing material to large populations

Another challenge is in effectively dispensing material to large populations in a mass drug campaign. For example, New York City and its suburbs has a population of around 15 million people. There is a narrow timeframe to move 15 million regimens of a certain material into the city and hand it out to 15 million people. Initially, this operation was to be

conducted in twenty-four hours, but CDC staff have been challenged to think of ways of reducing federal delivery times to six hours.

The goal in the end is to get safe, effective products to people when they need it

The goal in the end is to get safe, effective products to people when they need it, wherever they need it. None of this happens until initial detection, which may significantly reduce the time available to act once the incident has been confirmed.

The US strategy encourages innovation in how such challenges are addressed, through research, financing models, manufacturing models, reassessment of the platforms used to develop different drugs, in the regulatory science and in dispensing and distribution practices.

This has established a means of getting drugs out into the cities, placing them in fire departments and ambulances at hospitals. There are different approaches for different agents which, combined, are increasing the preparedness of the US.

The shared strategic vision between the US and UK regarding preparedness is a reminder of the shared threat. This may offer opportunities for shared investment in countermeasures as well as shared learning and shared collaboration more broadly.

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Greg Burel currently serves as Director of the Strategic National Stockpile (DSNS) at the Centers for Disease Control (CDC), a division of the US government's Office of Public Health Preparedness and Response.

DISCUSSION FORUMS

Future Technologies for Pharmaceutical Resilience

Dr Gerald Kovacs set the scene for the conference discussion session by explaining BARDA's role in advancing medical countermeasure development, prompting delegates to discuss and debate the advantages and disadvantages offered by current manufacturing processes and emerging biomedical technology.

PHARMACEUTICAL PRODUCT development needs to be approached with a sense of reality: it takes a very long time and it is extremely unusual for a scientist working in this area to see even one pharmaceutical product developed and licensed during his or her lifetime.

Secondly, it is extremely expensive. Each new drug or vaccine costs an average of $800 to $1,500 million to develop and there is no assurance at the start of the investment that the new product will get to the finish line. There is only a 20–30 per cent chance at best that something in Phase I testing will make it to licensure. Therefore, it is important to keep in mind that if pharmaceutical resilience requires flexible and cheap products to be available quickly after an event has occurred, the traditional path may need to be reassessed.

New ideas are needed for how the current pipeline for new products can change and how it can have more flexibility. To do this, scientists and pharmaceutical companies need to understand one another better. Policy-makers need to make sure they do not make promises, most importantly to politicians, that imply the current situation can be changed overnight or that something that may take years to develop can be delivered immediately.

In the US, BARDA is involved in two phases of pharmaceutical product development to help address this. During the very early development stages, BARDA helps to get products out of the pipeline as quickly as possible, by making quick decisions on whether to stop or continue trials at key steps along the path. Once the drug gets to clinical testing, BARDA will help it through as quickly and as cheaply as possible. This process then becomes incredibly

expensive and economically risky as manufacture starts to scale up.

Regulatory agencies in the UK, Europe and America take a very different approach to flexible manufacturing than the manufacturers and the policy-makers. Everything has to be done according to preset specifications, which themselves take years to put in place.

Anthrax vaccines and smallpox vaccines already exist, but new and better ones may be needed; for example, ones that have faster-acting immunogenicity. Many current vaccines need people to come back for two, three or more doses over a period of weeks before the vaccine is effective. In the event of an attack, immunity would need to be immediate. Antimicrobials may need to be developed in as broad spectrum as possible.

Drugs are also needed for viral haemorrhagic fevers, radiation countermeasures, volatile nerve agents and – a new area that is gaining increasing interest – countermeasures for blast burns. While in the event of a CBRN incident, the N (nuclear) would result in blast injuries and burn injuries, such a product is also likely to have applications during more everyday incidents and this offers opportunities for CBRN industries and the general pharmaceutical industry to work together more closely to develop such products.

The Phases of Pharmaceutical Testing

New pharmaceutical products go through four phases of clinical trials (plus a 'Phase 0', in which very small doses of the drug are given to between ten and fifteen test subjects to test how the human body reacts to the drug and vice versa), in order to be approved and licenced for use.

Each phase is treated as a separate clinical trial and the entire process can take several years.

Phase I: Treatment is given to a small group of test subjects to evaluate whether the drug is safe to use, to determine the appropriate dose and to check for side effects.

Phase II: If the drug passes Phase I trials, the process is repeated on a larger group of people (typically up to 300) to further evaluate safety.

Phase III: In the final testing stage, the drug is given to a much larger group of test subjects (1,000–3,000) and compared with commonly used treatments for the same condition to see how it performs. Safety and side effects are also considered further. If a drug passes Phase III trials, it will usually be licensed for use.

Phase IV: Post-approval studies determine any additional risks and benefits of use, and the optimal use of the drug.

Building resilience needs a long-term approach

BARDA has been thinking about issues such as these for a number of years but its funding will end in September 2013, after which its work will stop or be handed over to CDC and FDA.

Funding is already scarce in innovation: the US's National Institutes of Health (NIH), one of the world's foremost medical research centres, is seeing only the top 5 per cent of proposals they receive being funded. It is not enough. Building resilience needs a long-term approach: it could take five-to-ten years to get a new product into a national stockpile, and the new generation of scientists coming up through school and university need to know there is funding available for their work if they choose medical countermeasure production as a career.

These are the issues that need to be borne in mind throughout discussions on how pharmaceutical resilience can benefit from future technology.

Dr Gerald Kovacs is the Director of the Division of Chemical, Biological, Radiological and Nuclear (CBRN) Countermeasures in the Office of the Biomedical Advanced Research and Development Authority (BARDA), within the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response. Since joining BARDA in 2005, Dr Kovacs has expanded the organisation's portfolio of CBRN programmes from four to forty-eight. He has led five programmes through Phase II clinical testing, and has delivered five first-in-class medical countermeasures to the Strategic National Stockpile.

Business Factors Affecting Pharmaceutical Resilience

Dr Gigi Kwik Gronvall examines the challenges facing pharmaceutical resilience, such as maintaining a skilled workforce, sourcing medical countermeasures not available commercially and addressing manufacturing shortages. She also looks at the steps that could be taken to minimise the effect of a supply shock.

MEDICAL COUNTERMEASURES, including vaccines, therapies and diagnostic tests, will be required in the event of an epidemic to treat and protect people affected and at risk. However, whether a nation is able to offer its population appropriate countermeasures at the time when they are most useful – that is, if there is *pharmaceutical resilience*[1] – is not solely a matter of whether governments have previously made correct decisions about investments or stockpiling. There are additional business factors which

1. For the purposes of the conference, pharmaceutical resilience has been defined as the principle of ensuring access to countermeasures when they are needed.

may have a profound impact on the pharmaceutical resilience of nations but which are not directly controlled by them. This section briefly outlines some of these factors, and points to actions governments need to take to increase their nation's pharmaceutical resilience.

'Normal' Shortages

Pharmaceutical shortages have been common in recent years; patients have had to confront critical shortages of pharmaceuticals including antibiotics, cancer therapies and influenza vaccines. While these 'normal' shortages have not been caused by deliberate or nefarious acts, they demonstrate the types of supply shocks that could result from an attack, and also illustrate the general vulnerabilities of the pharmaceutical supply chain.[2]

There are myriad reasons for the shortages, including manufacturing errors, scarcity of ingredients, natural disasters, regulatory issues, poor planning and contamination but the cumulative effect prompted President Barack Obama to issue an executive order on 31 October 2011 declaring that 'shortages of pharmaceutical drugs pose a serious and growing threat to public health'.[3] The US Food and Drug Administration (FDA) was given broadened authorities, requiring additional reporting that would help to predict shortages and to provide expedited regulatory reviews of substitutes. While prediction of shortages, and thus stockpiling, may increase as a result, the shortages still present an ongoing public-health crisis.

Pharmaceutical shortages have been common in recent years

Shortages Specific to Biodefence

There is a wide range of pathogens that could potentially be used in a biological weapon attack – as well as the possibility of engineered pathogens – but there is a lack of tested medical countermeasures which could be available in sufficient quantities to distribute if necessary.[4] The possibility of generating a novel countermeasure in a short period of time, in order to be useful in a crisis, is remote[5] – some of the reasons for this have been discussed in Chapter IV.

2. A A Adalja, S B Wollner, T V Inglesby and G Poste, 'The Globalization of US Medical Countermeasure Production and its Implications for National Security', *Biosecurity and Bioterror* (Vol. 10, No. 3, September 2012), pp. 255–57.
3. Barack Obama, 'Executive Order: Reducing Prescription Drug Shortages', 31 October 2011.
4. National Biodefense Science Board, 'Optimizing Industrial Involvement in Medical Countermeasure Development', February 2010 and 'Where Are the Countermeasures? Protecting America's Health from CBRN Threats', 2010.
5. J A DiMasi, L Feldman, A Seckler and A Wilson, 'Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs', *Clinical Pharmacology and Therapeutics* (Vol. 87, No. 3, March 2010), pp. 272–77; J A DiMasi, R W Hansen, H G Grabowski, 'The Price of Innovation: New Estimates of Drug Development Costs', *Journal of Health Economics* (Vol. 22, No. 2, March 2003), pp. 151–85.

A strong manufacturing base is desirable for pharmaceutical resilience

In the event of a biological attack, it is possible that already stockpiled and available antimicrobials will be appropriate to treat those affected. Depending on the biological agent used, however, this may not be an option; a specific vaccine or therapy may be required and unless the government has already taken steps to develop, produce and stockpile that medical countermeasure, it is unlikely to be available in a crisis. Most vaccines and therapies require up to ten years to develop. There is also a substantial cost per product—up to and exceeding $1 billion—which may need to be borne by a government if there is no commercial market for the product.[6]

There is little commercial market for medical countermeasures specific to such diseases as anthrax, ebola or glanders, for example, so it falls to governments to be able to stockpile to make them available – and only a few governments take those steps.[7] Even with substantial investments, there are critical gaps in medical countermeasure availability for most of the pathogens considered to be potential weapons.[8]

Company-Specific Decisions which are Detrimental to a Nation

A strong pharmaceutical manufacturing base is desirable for pharmaceutical resilience to supply shocks, whatever the cause. The potential for the US to suffer from influenza-vaccine shortages during a pandemic in spite of pre-negotiated contracts, for example, led to US government investment in a domestic vaccine-manufacturing capability.[9] However, just as companies may decide to relocate due to attractive tax breaks or a qualified workforce, there may be reasons internal to the company that lead it to shut down capability, which nevertheless affects national pharmaceutical resilience.

According to Pfizer, the closing of the research laboratory in Sandwich, Kent, in February 2011 was a matter of corporate restructuring, and was undertaken for the continued health of the company.[10] Their decision put nearly 2,400 people out of work. The loss of manufacturing capability and skilled workers was seen as a national security issue, leading to investigations and

6. DiMasi, Hansen, Grabowski, 'The Price of Innovation'.
7. B T Smith, M Mair, G K Gronvall, J Matheny, 'Developing Medical Countermeasures for Biodefense', *Biosecurity and Bioterrorism* (Vol. 7, No. 1, March 2009), pp. 42–43; J Matheny, M Mair, A Mulcahy, B T Smith, 'Incentives for Biodefense Countermeasure Development', *Biosecurity and Bioterrorism* (Vol. 5, No. 3, September 2007), pp. 228–38.
8. P K Russell, G K Gronvall, 'US Medical Countermeasure Development since 2001: A Long Way Yet to Go', *Biosecurity and Bioterrorism* (Vol. 10, No. 1, March 2012), pp. 66–76.
9. Novartis Media Release, 'Novartis Receives FDA approval for Flucelvax, the First Cell-Culture Vaccine in US to Help Protect against Seasonal Influenza', 12 November 2012.
10. B Barrow, 'Drugs Giant Pfizer Lays Off up to 2,400 as it Shuts Down Viagra plant', *Daily Mail,* 2 February 2011.

renewed calls for boosting the country's attractiveness for pharmaceutical investment.[11] While there are many options available to governments to increase the desirability of the pharmaceutical industry to invest in a particular location, there is still the possibility that corporate objectives may diminish a nation's overall resilience to pharmaceutical supply shocks.

Availability of Skilled Workers

Some governments have made great strides in creating a pharmaceutical-friendly environment by investing in technologies and training skilled workers, which should act as an enticement for investments by pharmaceutical companies. For example, China, Brazil, Russia and India have been investing heavily in biotechnologies, perceiving them to be engines of twenty-first-century economic growth. Russia is embarking on plans to have a 5 per cent share in the global biotechnology market by 2020.[12] Brazil has undertaken an ambitious workforce-training programme, costing $2 billion, to make available 75,000 scholarships in science and technology for study abroad, in order to increase the workforce available for skilled pharmaceutical industry jobs.[13]

Conclusions

There are many factors which may threaten pharmaceutical resilience, including those which are under a government's control (such as investments

11. *Ibid*.
12. G Bryanski, 'Russia Targets 5 pct of Global Biotech Market by 2020', *Reuters,* 1 April 2011.
13. E Gardner, 'Brazil Promises 75,000 Scholarships in Science and Technology', *Nature News,* 4 August 2011.

in a skilled workforce, medical countermeasures which will not be developed commercially, and other enticements to private-sector investment); as well as external factors such as corporate decision-making and problems due to limited manufacturing. It is possible that synthetic biology will offer paths to distributed manufacturing, which could alleviate potential shortages due to problems at one particular manufacturing plant.

While there are likely to be many areas affecting pharmaceutical resilience that are outside of a nation's control, there are still steps that could be taken to minimise the effect of a supply shock, no matter what the cause. The critical pharmaceutical vulnerabilities need to be determined so that the shocks do not come as a surprise and can be planned for; the workforce needs to be kept at a high level of training; and government needs to guide industry through either research projects that are precompetitive and beneficial to companies, or through direct investments. In other words, a balanced approach is required so that areas of the pharmaceutical industry which are important for resilience are maintained, especially where the likelihood of a commercial market developing is minimal.

Discussions

Chaired by:
Professor Joyce Tait, Scientific Advisor of the ESRC Innogen Centre
Dr Stephen Morris, BARDA
Dr Gigi Kwik Gronvall, Senior Associate, Center for Biosecurity of UPMC
Dr Richard Bax, Transcrip Partners

1. Regulation and Legislation of Countermeasures

TAKING NEW products through the regulatory regimes required to get them to market is a long, complicated and expensive process. This is seen as a particular challenge to pharmaceutical resilience. There are benefits to be had from setting up new regulatory regimes that can operate more quickly and more flexibly following an outbreak or incident. Regulations need to be in place that will allow early access to products currently in development, while normal development times and the length of time required to undergo clinical trials may need to be shortened.

The US has an integrated stockpiling programme with input from different sources, including the Department of Homeland Security (DHS). There is an established technological base in universities and other areas as well as funding sources for development. The overall development process is well-defined and once the product has reached a reasonably advanced stage, BARDA gets involved. The product then has to meet regulatory requirements before being licensed for use.

In the UK, stockpiling is based more on consideration of the risks; the products that are stockpiled have to be already available on the market and applicable to an identified threat. Very little UK government resource is spent on development specifically for stockpiling.

Regulation and Mutual Aid

There are potential pitfalls in using drugs that have not been pre-licensed, or drugs that have not been licensed specifically for use in the country experiencing the incident, and this could be a particular issue when considering mutual aid. It is also important to note that there are different regulations relating to the use of an existing product licensed for one disease for a different application and the use of something completely innovative. The adaptive medicine licensing scheme, in which work has been done within existing regulations to find a way to enable early access, is one option for change.

The US and Canada have an agreement with regard to medical countermeasures that gives each the authority to provide medical countermeasures to the other. In the US, the protection of the American population would be considered the highest priority in the event of a serious infectious outbreak and any issues associated with using pre-licensed products would be dealt with after the event.

Very little UK government resource is spent on development specifically for stockpiling

Regulation should not be circumvented altogether in order to get new products through faster, however: it is there for a reason. Nonetheless, if a product is good, it should be able to be picked up and used quickly in any country rather than having to go through the regulatory processes of each state.

Gaining Final Approval

The biggest hurdle for any new product to get over is often final approval and in the US there are moves to make this process faster. In particular, there is the Critical Path Initiative (C-Path),[14] which was developed following the publication of a report that recognised the increasing difficulty and unpredictability of medical product development. The report concluded that collective action was needed to modernise scientific and technical tools as well as to harness information technology to evaluate and predict the safety, effectiveness and manufacturability of medical products.

Some of the knowledge gained from C-Path will be shared with the European Union's Innovative Medicines Initiative (IMI),[15] which is still in its very

14. See <http://c-path.org/CPI.cfm>.
15. See <www.imi.europa.eu>.

early days but has a €1 billion budget over the next several years. The two organisations have signed a memorandum of agreement to share information in order to accelerate the development of safer, more effective medicines. There are also fast-track mechanisms within the EU for conditional approval, even where there are issues with the product.

These mechanisms tend to exacerbate demands at the post-product stage, however, which are often more rigorous than the Phase III testing, and regulators have been accused of slowing approvals by asking for more information and safety guarantees than would normally be required for a Phase III development licence. Nonetheless, the development of a fast-track system for EU patents is likely to see a licence granted within days rather than months and this has already paid dividends in the case of seasonal inflenza vaccines, where four licences were recently given in a day. Global harmonisation of testing standards for pharmaceuticals is also moving forward.

Legislation, as well as regulation, has a key role in building resilience

A good example of circumventing the issue of different regulatory regimes in different territories, and mitigating many of the problems of country-to-country mutual aid, is the stockpiles of smallpox vaccines that have been donated to the WHO under the Global Health Security Group Initiative. A centralised international collection-and-redistribution mechanism may be of benefit during an international incident, although the increased perception of threat following a biological attack may result in states wanting to keep hold of their pharmaceutical stockpiles rather than share them, to ensure that they are able to respond to a potential future attack on their territory.

Regulating Synthetic Biology

Regulation is a particular issue in the case of synthetic biology. There is a need to build capability, particularly in the development of vaccines and antibiotics, and there is potential to operate much faster on a niche scale, but certain techniques currently have way of being approved through regulation. Uncertainty in the regulatory system around synthetic biology creates a huge disincentive for investment.

Synthetic biology needs standard parts, the achievement of which is a long way off. It also needs to be model-driven: good metabolic models are necessary in order to know how to engineer mechanisms and predict or indicate what will happen, and what side products will occur. Funding for further research is vital if this is to be taken forward.

Legislation

Legislation, as well as regulation, has a key role in building resilience and supporting markets for new products. To give an example from the environmental sector, legislation on emissions control created an overnight market for low-emissions vehicles. Could the healthcare sector create guaranteed markets for pharmaceuticals? The seasonal influenza vaccine industry, for example, has already been a major driver for industry stability.

Issues for Further Consideration

1. The clinical management of an exposed population following a mass-casualty biological attack might, by necessity, be very different from the management of more normal outbreaks of the same disease. Novel therapeutics may have differing utility in the response to different outbreaks of the same disease.

2. Co-operation at all stages in the development of pharmaceutical solutions among states and international organisations is vital in driving the development of innovative solutions to pharmaceutical resilience. This spans everything from a common appreciation of the requirements for a particular therapeutic right through to a thorough understanding of the regulations governing the acceptance into service of a new pharmaceutical.

2. Accelerating and Facilitating the Development of New Products

It is important to foster co-operation in pharmaceutical resilience so that efforts are not duplicated. QuaDPharma[16] is one organisation that facilitates this, and there is also a role for the WHO. In the UK, the Technology Strategy Board[17] issues challenges across academia and industry to map issues and solve them, while the Medical Research Council (MRC)[18] and the National Institute for Health Research (NIHR) [19] take a strategic overview to ensure that there is no duplication in development work being undertaken. More co-operation in applied research, rather than funding *per se,* might also provide benefits. On the other hand, the duplication of stockpiles may increase, rather than adversely affect, overall resilience.

The US has a clearly laid-out process for applying for funds to carry out research directly related to stockpiling countermeasures, but there is confusion as to how the same process might be attempted in the UK – there is no clear funding route or procedure for applying for funds in order to invest in this area.

16. See <www.qdpharma.com>.
17. See <www.innovateuk.org>.
18. See <www.mrc.ac.uk>.
19. See <www.nihr.ac.uk>.

The above is particularly important as development must effectively use the funds that are currently available. In general, a broad-spectrum approach is seen as better than a more focused one, as the development of a product for only one infectious disease can be too expensive. SMEs (small- and medium-sized enterprises) can be hugely innovative but may not be able to take high risks during the development stages, when economic returns are particularly low. The US experience of developing Raxibacumab (for the clinical management of advanced anthrax) demonstrates that the development of pharmaceuticals for dealing with a single infection can be resource-intensive, with limited gains compared to broad-spectrum approaches.

Protecting the Manufacturing Base

Pharmaceutical manufacture may benefit from government subsidies in the UK and across Europe that could protect an individual country's manufacturing base and certain research and development capabilities. Innovative manufacturing processes offer novel ways of guaranteeing a population access to pharmaceuticals by potentially increasing the speed of production and by decreasing reliance on centralised production machinery, and an assurance on the international uptake of any resulting products would significantly minimise the risks associated with development.

Whether development should be driven by big pharmaceutical companies or be a more collaborative process with SMEs is an important question, as is the extent to which government should be involved. Pharmaceutical companies in the US tend not to want to engage with the FDA until later on in the development process, and the FDA also tends to see its involvement as more important during Phases II and III, but it has to be involved from the very beginning in projects where the company is working with, or directly for, the US government.

Co-ordination during planning phases does have benefits, of course: the extensive pre-pandemic influenza planning from the WHO enabled a very quick, Europe-wide approach. Using modelling and producing products available for a 'normal' influenza season can make it possible to produce and distribute products to combat a new pandemic strain very quickly.

The demand for seasonal influenza vaccines is a major driver for industry stability and, similarly, guaranteed markets for other pharmaceuticals could help to create confidence within industry. Multi-use manufacturing plants, which are able to produce one widely used product, such as paracetamol, for 80–90 per cent of the time but to whom the government would pay a small tariff to switch to another product as needed in an emergency is another potential model and would provide facilities ready to meet sudden requirements. There may not be enough flexibility in the regulations for this at present, however (switching from biological to non-biological and back, for

example, would raise regulatory issues), and how to ensure the availability of the raw materials needed for the production of non-routine drugs is unclear, including when and how ensuring their availability and supply should be built into the resilience plan.

Economic Challenges

The current economic climate is proving problematic for pharmaceutical resilience, particularly at the national level, as Pfizer's move out of Kent demonstrates. With 'big pharma' unwilling to invest in the UK, should SMEs look more towards the NHS, the MRC or central government for funding? The long timescales involved in the regulatory framework is a particular challenge to investment, as it means there is a long wait for return on investment. Any shortening of the timeline would be an advantage.

Some areas of pharmaceutical production need to be profitable in order to fund the continued production of less profitable drugs. Capital investment costs are high for niche markets in particular, and there are few funding opportunities for novel, small-scale production in the UK. A specific problem is the EU procurement process, which means that contracts worth £100,000 or more have to be put out to tender across Europe, with a few exemptions relating to national security or products that have niche, UK interest only. Finding a national security application for a product in development may help to 'reserve' the contract for a UK-based manufacturer.

In the US, the government is the sole financial sponsor for the production of some drugs, which helps to protect the manufacturing base, surge capacity and the ability to stockpile drugs. The US is already seeing some supply-chain problems: however, numbers are low for products including benzodiazepines, sterile injectables and frequent-use antibiotics.

A particular economic challenge is patent expiry, which leads to the outsourcing of production to the cheaper labour markets of China and India. This brings with it a 'haemorrhage of talent' as scientists move to countries that are investing more heavily in the pharmaceutical industry, such as Singapore. If government could be persuaded to provide guaranteed markets in the West, this would encourage pharmaceutical companies to invest more heavily in research and development.

A more flexible patent regime with longer patent periods, or other sweeteners such as corporation tax cuts, might also have a positive impact. While many patents have a twenty-year life, half of this can be used up during the development stage before any return on investment has been made. New European legislation is looking at either a longer patent life, or the ability to shift the years of one patent to another, within the company's range. As the average time from set-up to Phase III is more than ten years, there is a

IP tends to be seen as sacrosanct by both researchers and industry

danger that the patent will already be void by the time the product comes to market.

One option would be to forego patents altogether for some products, or for academics to be paid directly by government for the research they conduct (and potentially for the government to also pay for the development of any products emerging from the research). The UK research councils are already shifting towards this model, particularly for synthetic biology. Such a model raises issues, however, over who would own the IP rights over the resulting products.

Open-Access Research versus Patenting

The open-source software movement, which has many benefits for innovation and collaboration, is percolating into the biotechnology field (particularly with regard to synthetic biology) but it is unlikely that the majority of pharmaceutical researchers will be willing to give up intellectual property (IP) rights to a product in which they have invested fifteen years' development.

IP tends to be seen as sacrosanct by both researchers and industry, though it is also the case that a number of vaccination products make very little money and are produced under corporate-social-responsibility obligations; a drug for river blindness, made by Merck, is one example of this; another is antimalarials developed at Fort Worth.

It is important to remember that neither patents nor open-source issues are obeyed by terrorists or nature. In the event of a global pandemic or a deliberate biological release, it will be necessary to be prepared and to share.

Future Developments

In terms of trends in manufacturing countermeasures, Novartis is looking at cell culture for influenza vaccines, perhaps indicating a trend towards biologicals, and there are industrial biotechnical and biological processes that could be used to produce high-end chemicals. There is also a trend towards relying on multipurpose drugs that treat rather than prevent diseases, where insufficient research has been carried out on the cost of developing a vaccine and delivering it pre-outbreak or release, versus the cost of treating those affected in the aftermath of the event.

More rapid biological-production systems are needed. Plant-based protein expression systems and insect cell cultures both the have potential to produce drugs much faster than cell-culture methods – they have a two-three month time-scale, as opposed to the more usual year-long one – but these are only just starting to come through the regulatory process.

Issues for Further Consideration

1. There are clear parallels between preparedness for pandemic influenza and preparedness for dealing with the aftermath of a mass-casualty biological attack. There are also significant differences. Pandemic flu planning assumes that a small number of early cases in a population will increase in time as the disease spreads throughout the population. Response planning for a mass-casualty biological attack needs to assume that there is no prior warning, and that a very large number of cases occur simultaneously. How can the two sectors best work together?

2. The expansion of pharmaceutical production capabilities in rapidly growing economies interacting with market forces in the West presents considerable challenges to ensuring pharmaceutical resilience – but also opportunities. How might these be exploited?

3. Rejecting large-scale batch production and instead focusing on small-scale batch production will entail less waste if the product is rejected. What are the barriers to this – is capital investment the issue? Is there is a need to build facilities which can switch product lines with ease if one line falters?

4. Developing solutions tailored purely for biological terrorism or other niche areas will always be costly. Public-private partnerships in this area offer considerable potential to use the power of commercial industry without replicating it.

3. Risk Perception and Education

Policy in the UK is based on risk, but often these risks are not communicated well, nor discussed with the public either before an event (when reactions are more likely to be intellectual and logical) or during and after an event (when reactions are more likely to be clouded by emotions).

It is very difficult for governments to encourage or direct industry to do something without public support, and there is also a danger that drugs which are stockpiled but never used will be seen as a waste of taxpayers' money. Governments may have to lead on producing or stockpiling countermeasures, however, because of inherent problems, seen in other areas of resilience, of expecting the public to mitigate risk at a personal or family level.

Policy in the UK is based on risk, but often these risks are not communicated

Better communication of risk assessment undertaken at national and international level, is needed and would benefit from being applied to the product-development stages as well as in response to an actual event, particularly as the public seems to have an inherent reluctance to

embrace innovation in drugs and pharmaceuticals that is very different to the way in which they will happily embrace new IT technology. This appears to be influenced by negative attitudes towards the pharmaceutical industry in general and to synthetic biology in particular. Changing public perceptions with an education programme to make people more comfortable with novel scientific processes should be a priority for the future.

Governments need to understand the perception of the threat as well as the threat itself: the reason that vaccination is so difficult may be due to the public's dislike or fear of needles as much as to genuine concerns over the safety of the vaccine. Would it make sense to look more broadly at how vaccines might be delivered differently?

Risks from Animal Disease

Insufficient consideration is currently being given to the threat of crossover disease from animals, both in terms of the risk to human health posed by such diseases and also the potential economic cost to the UK of responding to serious outbreaks. Biomedical, bioterrorism and pharmaceutical experts broadly agree that the UK government's response to the foot-and-mouth epidemic of 2001, which largely consisted of slaughtering all animals from infected herds, was an over-reaction, as is regulation that prevents meat from cattle that have been vaccinated against the disease being sold in the UK or US. Many countries, such as Argentina, follow vaccination programmes with no obvious associated risks. In theory, if antivirals and antimicrobials – whose regulation is managed by the WHO – could be created cheaply, then it might be possible for them to be added to animal feed, thus preventing the jump from beast to human; however, this encourages over-use of such drugs and eases the emergence of drug-resistant strains, which raises a different set of problems.

Governments need to understand the perception of the threat as well as the threat itself

The above issues highlight the need to balance one risk against another, and to ensure that focusing on one does not result in more serious risks being ignored or receiving little attention. For example, has sufficient international concern been given to the Indian government's concealment of NDM-1 (New Delhi Metallo-beta-lactamase-1) – an enzyme that makes bacteria resistant to a wide range of antibiotics, including carbapenems, which are used to treat drug-resistant infections? Up to 60 per cent of chickens from Thailand now contain the NDM-1 gene, but the implications of this for antimicrobial resistance (AMR) and, in turn, the risk AMR poses to public and animal health in general is only beginning to be given sufficient attention.

Issues for Further Consideration

1. Rapidly delivering drugs when and where they are needed is a large logistical challenge to improving the preparedness of a population. A clear understanding of the relative benefits of vaccination, both ahead of an incident and in response to an incident, is important to all aspects of response planning.

2. How does government justify to the taxpayer large amounts of public money spent on stockpiling a product that might never be used? It is accepted that governments may stockpile weapons in the hope that they will not actually be used in war, but does the public see the government stockpiles of medications in the same way?

4. Potential Benefits from Synthetic Biology

Synthetic biology is hugely effective and has made certain tests much more feasible. Its techniques offer potential ways to improve access to existing pharmaceuticals, to produce modifications of existing pharmaceuticals, and to develop entirely novel treatments. The potential for current technologies – or the business models they operate within – to be adapted to improve pharmaceutical resilience should not be underestimated.

The move towards single-use purification systems that can be bought off the shelf, used once and thrown away could, for example, be seen as a positive trend towards multitasking. So, too, can the convergence of techniques such as the production of animal proteins using animal stem cells, which could be combined as a very useful manufacturing base for making novel molecules on a large scale.

Synthetic biology offers huge benefits for creating new and complex molecules in particular, though there are concerns about bio-containment. More research is needed to ensure current developments are not hampered. A particular challenge is the failure so far of the US to ratify the Convention on Biodiversity,[20] and specifically the Cartagena Protocol on Biosafety[21] (though the US has at least signed it), which aims to reduce any adverse effects of importing potentially dangerous organisms from another country for research-and-development purposes. The Protocol includes built-in genetic restrictions, which originate from the debate around genetically modified (GM) food, and might potentially allow a veto on research into synthetics.

There is, however, some concern that using animal models is a poor predictor of the safety of new synthetic drugs; general product development might benefit from more predictive elements, whilst still relying on empirical

20. See <www.cbd.int>.
21. Cartagena Protocol on Biosafety, October 2000, <www.cbd.int/doc/legal/cartagena-protocol-en.pdf>.

testing. There are additional concerns over how synthetics might interact with other medicines such as those used in chemotherapy, and how the ability to sustain 'batch upon batch consistency' can be maintained when stepping up to large-scale production particularly if production is split between more than one plant or facility. It may be the case that while these are modern products, they are currently constrained by old ways of developing them.

The power of the non-government organisation (NGO) lobby to prevent research on GM crops and synthetic biology is a serious concern. Diagnostic techniques in synthetic biology are at risk of being challenged by NGOs, which have a tendency to see synthetic biology as nothing more than an offshoot of GM modification. This threatens to negatively influence UN legislation and therefore ways to engender a better understanding of the science behind synthetic biology may be needed; promoting its successes, when they happen, might be one way to address this.

Summary of the Discussions

There are a number of factors affecting the provision of pharmaceutical resilience, many of which are unlikely to be quick fixes or easy answers. Developing, building and maintaining resilience is dependent on a balance of activities, and is not solely dependent on government. The public sector, pharmaceutical companies and international agencies such as WHO need to work together for mutual gain. There is currently a lack of will and funding to take the necessary steps to ensure resilience; more money is needed, but so are smarter ways of working to ensure that the resources currently available are used to the greatest effect.

Developing more flexible manufacturing techniques and regulatory frameworks, which might provide the ability to switch production lines in times of need, might help to ease bottlenecks, encourage more financing and enable a baseline of manufacturing and skills to be maintained. The potential loss of jobs – and the skill set required to undertake those jobs – that will come with the loss of a manufacturing base in the UK is seen as a particular risk to the UK's pharmaceutical resilience in the future, especially when considering the knock-on effect this will have on the ability to attract the next generation of scientists to work in this sector.

Finally, the complex social factors surrounding risk needs to be more fully understood by the general public, politicians, policy-makers and the pharmaceutical industry itself, in order to ensure risks are perceived and mitigated appropriately.

Conclusions

As the conference drew to a close, Professor Bernard Silverman of the Home Office summed up the day's proceedings and outlined the opportunities he sees for working together in the future to take pharmaceutical resilience forward.

BRINGING TOGETHER the people who participated in the Pharmaceutical Resilience Conference and surveying the field in this way produced a very good baseline for what should be done in the future.

One important point arising from the day is the issue around communicating risk. The general public need to be reassured that appropriate measures are being taken, which cannot just be done by informing them of the choices being made, even if we would wish to, but also requires that they can make proper judgements about the risks underlying these options and choices. Their elected representatives particularly need to understand the issues, as it is they who will ultimately drive policy, strategy and action forward.

The general public need to be reassured that appropriate measures are being taken

The Royal Statistical Society's statistical literacy campaign is aimed to help policy-makers understand the empirical data on which decisions should be based. The evidence is that there is room for improvement, though of course many politicians and officials are extremely statistically literate. However, to give a trivial example, only a minority of Members of Parliament were able to answer correctly the following question: if you toss two coins, what is the probability they both come up heads?

Equally, a bio-literacy campaign would help the issues discussed at the conference to be addressed from a position of knowledge and understanding – and not just those issues discussed at this conference, but also issues such as genetically modified material.

Communicating understanding of pharmaceutical resilience is particularly difficult because it involves both science and issues of national security. Politicians and policy-makers need to understand the risks, what can be done to mitigate them and what sort of awkward choices this would require. This is a very important topic for consideration in the future.

ANNEX I

Anthrax Counter Measures 2013 International Conference

4 February 2013

On the day prior to the OSCT-sponsored Pharmaceutical Resilience Conference, RUSI co-convened with the Health Protection Agency (now part of Public Health England) the Anthrax Counter Measures 2013 International Conference. This was the fourth in a series of international conferences about anthrax held by the HPA approximately once every decade.

THE INTENTION of this event was to bring together government and healthcare policy-makers, scientific experts and academics from the UK and North America to share knowledge, exchange research findings and discuss ongoing challenges to counter the threat of anthrax. Deliberate, terror- or criminal-inspired releases were discussed as well as the risks associated with a natural outbreak of the disease in the human or animal population.

The conference was a closed event, strictly by invitation only, to enable full and frank discussions to take place on this sensitive topic. Speakers and chairs from the UK represented the Department of Health (including the HPA and its successor Public Health England), Home Office, London Fire Brigade, Ministry of Defence/Defence Science and Technology Laboratory (DSTL), Metropolitan Police and the Police National CBRNE Centre, as well as the Universities of Cardiff and Southampton. North American speakers came from the Biomedical Advanced Research Development Authority (BARDA), Centers for Disease Control (CDC), Food and Drug Administration (FDA), Public Health Agency of Canada (PHAC), and the University of Pittsburg Medical Center (UPMC).

Key takeaways from the conference included:

- Anthrax is still a high-threat biological agent, with atmospheric dispersion models predicting between tens of thousands and several million deaths in the absence of a public-health response
- The interplay among reverse epidemiology, syndromic-surveillance, and dispersion models will help target a rapid prophylaxis strategy involving both antibiotics and vaccines
- Much has been learned from the investigation of multiple outbreaks among heroin users in Denmark, England, France, Germany and Scotland since 2009

- There is now advanced understanding of the interplay between reverse epidemiology, syndromic surveillance and dispersion models to help target a rapid prophylaxis strategy involving both antibiotics and vaccines
- Successful containment is heavily dependent on rapid identification after the smallest number possible of early cases, immediate and accurate statistical assessment of its geographic extent based on case histories, and a rapidly targeted prophylaxis strategy that considers antibiotics, vaccines and other countermeasures
- Post-Amerithrax, there have been significant achievements by US government agencies such as BARDA (notably, Project BioShield and its first licensed product, Raxibacumab), the CDC (especially strengthening its Strategic National Stockpile), and the FDA (for instance, Animal Rule, Medical Counter Measures Initiative, and others)
- Formation of the Medical Counter Measures Consortium (MedCMs), under which partnerships are being forged in the health and defense portfolios of Australia
- Canada, the UK, and the US are also helping to take work forward
- There is immense value in conducting such meetings periodically, because they are likely to advance the ongoing MCMs dialogue between quad countries.

Proceedings from the conference have been summarised by:

G K Gronvall, 'UK Examines Anthrax Threat', *Biosecurity and Bioterrorism* (Vol. 11, No. 1, 2013), pp. 8–9.

S S Vasan, 'Anthrax Counter Measures', *Military Medical Science Letters* (Vol. 82, No. 2, 2013).

Poster Session Prize Awards

A focused poster session ran alongside the conference, presenting nineteen academic posters on this topic from the UK and the US. Prizes were awarded to the following two posters selected by a panel of judges (FDA's Dr Luciana Borio, PHAC's John-Francois Duperre, UPMC's Dr Gigi Kwik Gronvall and Department of Health's Dr Hilary Walker):

Jennie Latham, Erin Price, Paul Keim et al., 'Molecular Characterisation of Bacillus Anthracis Responsible for Outbreaks Of Anthrax in Injecting Heroin Users'.

Kelly Lowings, Ian Davison, Sara Fraser et al., 'New Life for an Old Vaccine: Implementation of Single Use Technology for Production of the UK Anthrax Vaccine'.

ANNEX II

Tackling Antimicrobial Resistance: Identifying Future Research Themes

6 February 2013

The OSCT-sponsored Pharmaceutical Resilience Conference was followed by a workshop on Antimicrobial Resistance funded by the Science and Technology Facilities Council, part of Research Councils UK (RCUK), under its Defence, Security and Resilience programme.

THIS WORKSHOP was part of an ongoing series STFC funds at RUSI that aim to help inform its future calls by identifying areas of research which are currently underfunded and to identify new areas where funding is needed. There is a focus on identifying research that will help to implement current or future government policy. The topic for this workshop was Antimicrobial Resistance (AMR), which has garnered growing interest as a security and resilience topic in recent months, including attention given to the topic in the most recent World Economic Forum report. The Department of Health's new Five Year Strategy and Action Plan for tackling AMR is due to be published in summer 2013 and there are a number of existing strategies and policies within the Department of Health and NHS to address AMR and reduce the overuse of antibiotics, which considerably exacerbates the problem.

Approximately eighty delegates attended the workshop, from organisations including the Department of Health, the Health Protection Agency, Imperial College London, Home Office, DSTL, Royal Centre for Defence Medicine, Birmingham Public Health Laboratory, World Health Organization, Cabinet Office, Department of Homeland Security (US) and the Parliamentary Office of Science and Technology.

The keynote address was given by the Chief Medical Officer, Dame Sally Davies, who stressed the seriousness of Antimicrobial Resistance, and called for it to be included on the National Risk Register. Further presentations were given by speakers from the World Health Organization, the Health Protection Agency, the Advisory Committee on Antimicrobial Resistance and Healthcare Related Infection, University College London School of Pharmacy and the Royal Centre for Defence Medicine.

The afternoon broke down into small discussion groups to address specific themes: changing behaviour in antibiotic prescribing; data collection and

sharing; use of social media and online services; improving diagnostic techniques; and media and political barriers to implementing strategy.

The key takeaways from the conference were as follows:

- The workshop provided a unique opportunity for doctors, health policy-makers, pharmacists, microbiologists, nurses, emergency planners and academics to discuss issues and brainstorm potential solutions in a cross-disciplinary approach. Facilitation of similar opportunities in future would be welcomed
- Data on infection is currently collected widely but there are no set standards, making it difficult to amalgamate and interrogate different data sets
- Diagnostic techniques need to provide quick results at the bedside in order to confirm the presence of infection so that antibiotics can be administered only where necessary and discontinued early when infection is ruled out. Early detection and characterisation of antimicrobial resistant strains is a particular issue
- Better antibiotic stewardship will rely on changing behaviours that have become embedded over decades; this in turn will rely on strong messages and communication strategies. Better understanding is required regarding public-health campaigns and those which have been more and less successful in the past and why
- Enhanced surveillance and monitoring of the spread of AMR, over a variety of distance and timescales (from within single hospitals for infection control to internationally for the purposes of planning and ensuring robustness of national provision), is required
- The supply chain needs to be stimulated to make new classes of therapeutic agents available. This is currently being inhibited by commercial rather than technical factors, and new and innovative business models need to be developed
- Research that will help with the implementation of policy would benefit from smaller studies that yield quick results (for example, £25,000–30,000 grants for studies over three months) rather than larger, three-to-four-year research programmes.

The workshop was singled out for special mention in Volume 2 of the Chief Medical Officer's Annual Report 2013, published a month after the event, as a good example of the collaborative approach that is needed to address the challenges faced by antimicrobial resistance.

RUSI and the STFC intend to carry on their work in this area throughout 2013. A full workshop report will be published in the summer.