NEW DEFENCE AGENDA

A report of the second meeting of the

New Defence Agenda's Bioterrorism Reporting Group

Countering Bioterrorism:

With the Support of

SYMPHOGEN
Pioneering recombinant human polyclonal antibodies

Acambis

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18 OCTOBER 2004

Countering Bioterrorism:

Science, Technology and Oversight

A report of the second meeting of the **New Defence Agenda's** Bioterrorism Reporting Group

Bibliothèque Solvay, 18 October 2004

Co-organised by **Acambis** & **Symphogen**

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Introduction

Giles Merritt
Director, New Defence Agenda

The NDA is proud to present the first publication of the its Bioterrorism Reporting Group. It reflects the two meetings in June and October 2004 of an international group of experts on developments in the biological terrorism field.

The need for policies to counter the use of biological agents as weapons is not in question. The use of disease as a weapon of mass destruction (WMD) has to be considered as a low probability, high consequence instrument. For if such an event were to occur, the consequences would be so severe that preparatory action could attenuate its effects. Biological weapons have the capacity to infect thousands of people while initiating equally heavy economic disruption by destroying agriculture and infecting animal populations.

Of all WMDs, biological weapons remain the most vulnerable to diversion, and are also the most difficult to detect. It is therefore imperative governments should begin to address the threat biological terrorism poses.

The aim of this report is to make recommendations that could help accelerate the slow-moving political process governing responses to bioterrorism. The NDA plans to build upon its experience as the only regular forum in Brussels where the worlds of NATO and the EU, industry, think-tanks, academia, politics and the media gather to discuss security and defence - to deliver the expertise it sees in its meetings right to policymakers' doorsteps.

3 Recommendations following the NDA Bioterrorism Reporting Group Meeting of October 18th 2004

1. Improved national defences against bioterrorist attacks are needed – especially regarding laboratory resources and R&D.

2. There is a need for international coordination of effective crisis response.

3. A real-time reporting system needs to be developed.

Future meetings of the NDA Bioterrorism Reporting Group during 2005 will be looking at how to translate these broad recommendations into detailed submissions to governments and relevant multilateral bodies. The Bioterrorism Reporting Group's members will in each case be seeking to answer four questions.

1. Who will be in charge?

2. How long will it take?

3. What will it cost?

4. What can we build upon?

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Programme for 18 October meeting

Countering Bioterrorism: Science, Technology and Oversight

Creating Viable Infrastructures

Surveillance and laboratory capacity play key roles in containing any outbreaks of disease. But the recent increase in 'hot labs' for working on highly infectious and dangerous pathogens is controversial. Which diseases are under active surveillance, what role will the EU Communicable Disease Centre play, what is the current state of EU collaboration

Smallpox Case Study

Smallpox is often used as a model disease for bio-terrorism applications as it has been:

- Eradicated; [two repositories VECTOR and CDC still hold strains]
- It poses a serious communicable disease threat;
- If it were released it would have psychological effects associated with bio- terrorism as it is the ultimate in feared diseases;
- Has been researched as a bio-weapon and has naturally killed thousands of people across the world;
- The Soviet Union successfully developed and adapted smallpox virus for use in strategic weapons;
- Could cause massive logistical problems to manage and contain if an outbreak were to occur;
- If one state did not have enough stockpiles of vaccine, indicators suggest large numbers of people could try to acquire it in other states causing civil disruption;
- If it takes ten minutes per person to inoculate using bifurcated needles, how will rapid and massive vaccination programmes be conducted?

efforts? Vaccine research is essential yet for many bio-terror agents there is no vaccine available. Should the EU increase its own diagnostic capability or create greater capacities elsewhere? As regards the proposed Global Incident Analysis and Alerting System, where does the EU stand and where does it need to go?

Consensus building on a European vaccine policy for listed agents must be undertaken not only in the event of a deliberate disease outbreak but for natural disease response. Is it possible for the EU to build consensus around smallpox vaccine? Should the EU set a minimum requirement for stockpiling and a comprehensive European level protocol for responding to an outbreak? If it takes ten minutes per person to inoculate using bifurcated needles, how will rapid and massive vaccination programmes be conducted?

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*Observers will not be part of any recommendations made by the NDA Bioterrorism Reporting Group

An Overview

Drs. Jill Dekker-Bellamy

Bio-Defence Consultant, New Defence Agenda

Mick Garstang, Randall Hyer and Drs. Jill Dekker-Bellamy

During our last Meeting, participants discussed preventing the diversion of dangerous pathogens and select agents in transport and how to strengthen the EU's Dual-Use Export Control Regime. Participants agreed that the objective of preventing and combating bioterrorism cuts across a wide range of challenges. These include: stockpiling and harmonizing sufficient quantities of vaccines between nations; tracking shipments of dangerous pathogens, enforcing international sanctions; coordinating verification and information exchanges among key stakeholders; reorienting research and development funds toward prevention; strengthening bio-security at high containment facilities; the need to raise public awareness and improve communication and coordination between public and private actors including the interaction between civil and military authorities. These topics can be found in the first report available on the NDA website.

October 18th's sessions were developed to more fully discuss the implications of science, technology and the potential for oversight in the bio-sciences. Scientific advancement and work on bio-defence vaccines often require the use of highly secure laboratories known as European P4 'Protection Level 4' or US standard Biological Safety Level 4 laboratories. How do we balance the needs of science against the potential for abuse? Do we need more high containment facilities or are current facilities satisfactory? Is it possible for the Member States of the European Union to agree on guidelines for oversight in the bio-sciences? Should these 'guidelines' be voluntary or should we develop a system of minimum mandatory requirements? How can this be best achieved? Clearly the role of the scientific community is critical to public health security, therefore how can a system of oversight be constructed to enable legitimate science to continue unhindered? Should there be a central agency charged with undertaking and overseeing these tasks?

There are several key issues I would like participants to bear in mind throughout the ensuing debate:

I First, what type of policies should be developed and ultimately adopted to ensure the European Union is prepared for a major bio-terrorism event? Should policy planning occur at the national or European level? Several nations have run bio-terror drills and simulations and have done so in collaboration with other Member States, such simulations often test infrastructure, communication, capacity, response and containment. Coordination among two or three states or comprehensive collaboration on specific areas related to bio-terrorism does not necessarily translate into a

comprehensive or actionable policy of preparedness. If gaps exist what should be done to address potential inadequacies?

2 Second. Who will lead during a multi-state outbreak of a deliberate disease such as Smallpox? Who will be in charge and in a position of authority to consolidate information on bio-terrorism and rapidly coordinate emergency public health response? Who will allocate resources and make difficult decisions, particularly if resource allocation may not be possible due to lack of/or insufficient stockpiles of drugs and vaccines? Who will be responsible for ensuring lab capacity to process samples? Who will be responsible if deficiencies in both the number and type of medical personal trained to handle potentially thousands of victims and casualties is inadequate? Thousands is a conservative estimate... in many expert group meetings particularly within the US Department of Defense, they are discussing millions of casualties. Who will take responsibility if the current plans fall far short of our estimates and expectations? These are general questions for which we need clear and concise answers.

3 I would like to turn to the recent crisis in the United States over influenza vaccine supply. During the Chiron crisis on the 14th of October, the Oklahoma State Department of Health cancelled a mass immunization bio-terrorism exercise due to a lack of flu vaccinations which they were planning to use during what was supposed to be a mock Smallpox vaccination exercise. The exercise was halted so flu vaccinations could be diverted and saved for those considered at risk or 'immuno compromised.' The Health Department spokesman apologized for the inconvenience and said they were trying their best to deal with this surprise situation. If a smallpox outbreak were to occur today instead of an impending influenza epidemic nearly thirty percent of the population who now fall into the 'immuno compromised' or critical category would be put at immediate risk by receiving a vaccination. I will remind participants that not only do we not have mandatory regulations for the stockpiling of smallpox vaccine although the international standard is moving toward the adoption of a total population coverage policy, we also lack a standard for VIG which is used to counter adverse reactions to smallpox vaccinations (vaccinia immune globulin). This could mean the difference between life and death for that 30% of the 'at risk' population.

4 Within the European Union, the range for stockpiling is anywhere from 3% to 100% population coverage. In the absence of adequate stockpiles of both Smallpox and VIG (the current standard is considered one dose per person for Smallpox and one dose per 10,000 people for VIG although the US military recommends one dose of VIG per 8,000 people) - what needs to be done? The CDC notes that the absence of sufficient quantities of VIG to protect against adverse reactions during a mass immunization campaign would likely mean some people with adverse reactions would go untreated. We must decide if this 'collateral damage' is acceptable. Would the general public whom many of us represent find it 'acceptable?'

5 Moreover there would be no way to secure a sufficient supply of licensed vaccine on short notice. The United States is in fact experiencing heightened demand as moderate public panic over the lack of flu vaccine drives more people to ensure they are vaccinated. Every day since the announcement that the US stock of influenza vaccine has been cut in half, desperate people have been lining up in what has been termed 'vaccine lines.' People have been arrested in some instances as desperation has lead to civil unrest.

6 This particular on-going crisis should serve as a wake up call for nations and their seemingly optimistic approach to emergency public health policy in the securing of adequate stockpiles of vaccines. Given that Development of a new drug currently takes more than a decade and costs $800 million to one billion to produce, according to a recent study undertaken on Bio-Shield, what must be done for governments to offer incentives to drug makers? Limited and inconsistent funding for Bio-defence vaccine research, development and stockpiling must be urgently addressed at the policy level. Should the EU consider a system similar to the Bio-Shield plan implemented in the United States? Although many nations in the European Union do not feel perhaps placed at immediate risk from a Class A or High consequence disease by an act of terrorism, by this I am talking about the group of diseases considered the most deadly and having the potential to be used for bio-terrorism.

7 Modern travel means no nation is safe or isolated from secondary outbreaks. While many of us may feel complacent or secure with the status-quo, a mass casualty bio-terrorism event will quickly outstrip current resources even the most conservative estimates generate this outcome. Unfortunately and unlike the Oklahoma Department of Health we will not be able to apologize for the inconvenience or simply state that we tried to do our best with the surprise situation. Before a deliberate outbreak occurs we have an opportunity and I believe a responsibility to ensure we know who will lead, we have a responsibility to ensure stable and secure vaccine production, minimum and adequate standard stockpiles and we have a responsibility to ensure we will be ready to respond.

The bottom line is that ensure public health, governments need to provide pharmaceutical firms with the incentive to develop vaccines for diseases such as smallpox, anthrax, botulism, plague and influenza as well as genetically modified diseases, which have the potential to devastate the world's populations. I would venture to say that if the general public actually knew how insecure our current stockpiling system is they would demand regulations be immediately put in place. They would demand set standards for stockpiling and the secure production of bio-defence vaccines.

Summary of Debates

Approximately 40 representatives from national governments, industry and EU institutions gathered in Brussels on 18 October for the second meeting of the NDA's Bioterrorism Reporting Group to review the increasing risks Europe faces, assess the adequacy of its current response mechanisms, and formulate recommendations to EU policymakers.

NDA Bio-Defence Consultant and Moderator for the event **Jill Dekker-Bellamy** opened the meeting by asking participants to bear in mind the central issues to frame their debate, such as vaccine stockpiling, harmonisation of alert-response systems, tracking the shipments of dangerous pathogens, enforcing international sanctions and coordination of national and EU-level policy in the fight against bioterrorist threats – including tighter cooperation between military and civilian authorities.

"The goal of this meeting is to present policy recommendations to the European Commission and EU member states," she said. "How do we balance the needs of science against its potential for abuse? Do we need more high-containment facilities, for example? Are the current ones adequate? Can EU member states agree on guidelines? And should these be voluntary or mandatory?"

Noting that across the EU national vaccine norms range from stockpiles sufficient to inoculate only 3 percent of a population in one member state to 100 percent in another, Dekker warned of the ensuing chaos were a serious biological outbreak to strike the EU.

"The recent public unrest in the United States over flu vaccine shortages should be a wake-up call to complacent governments on this side of the Atlantic," she said. "If the general public knew how inadequate the situation is, they would demand regulatory action."

A long, successful history of cooperation

During his opening talk, observer **Randall Hyer**, Medical Officer with the World Health Organization's Communicable Disease Surveillance and Response unit, gave an overview of the WHO's success in wiping out smallpox.

Though WHO triumphantly declared smallpox's eradication in the mid-1970s, its existence in research labs remains a source of concern he said. "Smallpox is a point of focus for terrorism. Most clinicians today, after all, haven't seen a smallpox attack and there is a steady decrease in the number of people who are immune to it. The globe has more people and more mobility of people across it than ever before. We have a fix for smallpox but it remains one of the most dreaded diseases—one suited for spreading fear, which is a primary terrorist objective," said Hyer.

An independent organization under the umbrella of the United Nations, the WHO has two focal selling points: neutral and privileged access to countries. Along with credibility, it has the ability to convey a message in the public health arena - important when confronting particularly difficult issues and problems. Using a wide range of formal and informal networks, including UN sister agencies, ministries of health, national disease control centres, regional and country offices, and military health institutions, the WHO has established the world's first network that could make a contribution to global outbreaks. Over 200 institutions can compare resources and provide assistance if needed to a member state in crisis. This is mainly done through the Alert Response Operations Unit – "like a 24 hour, 7 days a week, on call, global, kind of 911 center for disease outbreaks" – for which Dr. Hyer works.

Hyer highlighted that the disappearance of diseases such as smallpox is man-made, which does not rule out the fact that its reappearance could be man-made. When eradicating disease, two steps are needed – an eradication step and then a guarantee. "What we're here discussing, partly, is a guarantee."

An international WHO smallpox vaccine bank has been proposed. This is probably needed because of the potentially long incubation period of the virus – you would need a vaccine to contain the disease. Today, it is estimated that 500 million doses would be needed. The WHO estimates approximately a 7 month lag in mass production of a smallpox vaccine.

Risks involved in routine vaccination may be greater than the known risk of the disease itself, however. Research and development of safer vaccines and anti-viral, anti-bacterial drugs must be continued and countries must be encouraged to have a "guarantee," requiring continuous surveillance systems.

The likelihood of man-made threats is more appreciated. There is increased surveillance and research, perhaps this making us more aware of their use. Biotechnology continues its relentless search for good and unfortunately also use for nefarious reasons. We all know that world tensions remain and that the possibility for such a release of a virus is not such a remote possibility as we might want to think.

Hyer emphasised the importance of communications, both among and between the scientific communities, policymakers and the public. Speaking somewhat tongue-in-check, Hyer also admitted that the element of good luck also tends to help – as in the case with SARS, when no countries with very weak health systems were touched.

Hyer also briefly touched on the capacity of militaries to carry out impressive logistic case management and search capabilities and expertise which the WHO may want to partner with in the future.

The case for smallpox vaccines

Noting that the WHO takes smallpox vaccines seriously, **Mick Garstang**, Director of Marketing at the pharmaceutical company Acambis and Co-Chair of the day's debate, agreed. "Independently, both US and Russian scientists agree that smallpox is the highest risk. It kills a third of the people it infects, and we have a relatively 'naive' [vulnerable] population compared to the situation 30 years ago," he said. "There's a virtual stockpile across world of only about 200 million doses."

There is a great need for bioterrorism preparedness, when we look at issues such as alert response protocols, as well as vaccine stockpiles. We should consider what percentage of a population stockpiles should cover – countries such as the US, France and the UK have a policy of 1 dose per citizen whereas other countries can have policies for 1 dose per 3 citizens.

Garstang advocated persuading national and EU authorities to build up their stockpiles of vaccines, prefaced by a white paper on bio-terrorism to identify shortfalls and emergency response deficiencies.

"Different EU member states have different response protocols," he observed. What would happen if there was a smallpox outbreak in Spain, and France proceeded immediately to vaccinate while Italy waited for an identifiable case? This would produce potential panic, with Italian citizens crossing the border to get black-market vaccines. It could very easily lead to a political crisis and unrest. Consensus is needed here. But unfortunately, he noted, we are nowhere near a consensus in Europe.

The case for VIG

John Haurum, Chief Scientific Officer at the Danish biotech company Symphogen, spoke of new technology aims to produce target specific recombinant human polyclonal antibodies. During research in drug development programmes for infectious diseases, Symphogen realised the application for their technologies are suited to the biodefence sector as well as emerging infectious disease areas.

According to Haurum, the only active remedy for most bioterror agents as well as emerging infectious diseases is the natural immune system. The immune system has evolved over the centuries to deal with emerging diseases – mostly viruses. This is also the mechanism of use for vaccines, using a modified weakened version of pathogens prior to exposure, creating an immune resistance towards future exposure. Vaccination requires a certain time of activation. Effective immune response can take up to a week to appear. But if it was possible to administer the reaction that comes from the natural immune response to vaccination, you would have immediate protection.

This natural immune response to vaccination mimics what occurs in antibodies in natural infection – with the pathogen circulating freely around the vaccinated person. Up to millions of antibodies can all recognize the pathogen differently, creating a significant diversity. Previous developments to recognize these pathogens were restricted since they could only recognize one aspect of the pathogen. This means that if the pathogen manages to develop different strains, it can very quickly escape recognition.

Vaccina immune globulin (VIG), is the only known agent reported to be effective in treating adverse reactions to vacaccina vacinations which occur in about 1 per 10,000 of the population vaccinated against smallpox. Haurum pointed out that VIG works to treat side effects of the smallpox vaccine, especially in cases of pregnancy and underlining disease. Pathogen specific polyclonal antibodies (pAbs) have also successfully been used for postexposure therapy against botulinum in animal models. This technology is believed to be suitable for prophylactic and therapeutic use agaisnt all CDC category A agents which could be used for bio-terrorism or bio-warfare. The technology is also highly promising for developing counter measures against avian influenza and other possible pandemic emerging diseases.

Most importantly for the day's meeting perhaps, was Haurum's statement that unfortunately current VIG manufacturing is based on blood sampling from people with a high vaccinia virus titer and purification of immunoglobulin, making VIG extremely expensive to produce. Of each donor sample of blood used to extract immunoglobulin, only 1% can be effectively used to protect against the intended virus. All other antibodies are defending against all the other infectious agents individuals have encountered. He stressed the need to discuss further the possibilities of a vaccine pathway for polyclone antibodies where an existing compound is approved, allowing for updates every two years on specificities on new strains. Symphogen is developing a second generation recombinant VIG.

Haurum emphasized the importance of government funding to finance projects of this kind, stating that Symphogen is currently working with the Health Protection Agency to develop a vaccinia hemoglobin to be used specifically for bio-defence purposes. "What we would benefit from, however, is a clear statement from governments about what they want from industry and how they intend to fund it."

Smallpox, stockpiling and the difficulties of consensus

Marion Koopmans of the Rijks-instituut voor Volksgezondheid, the Netherlands' national public health authority, also called for a more inflected approach. "There is need for stockpiles but, just as importantly, we need an EU approach to stockpiling. This is a public health issue. We need to

build a bio-defence agenda into the public debate - here I mean the European CDC and its mandate."

Florin Paul, Deputy Surgeon General at the Romanian Ministry of Defence, was of the opinion however, that how we manage and shift around supplies and capacity — sharing vaccines — is more important than building up huge stockpiles of them.

Not all participants were convinced that highly virulent agents such as smallpox or anthrax pose the scale of risk commonly assumed today.

Guy Collyer, of the UK's National Counter Terrorism Security Office in London expressed he was a bit sceptical when he saw that smallpox is always sorted out as the main hazard.

In a similar vein, **Richard Guthrie**, Project Leader for Chemical and Biological Warfare at the Stockholm International Peace Research Institute, opined that risk in general is difficult to speculate about. "Very few of these kind of diseases in the last 60 years have killed a lot of people at one blow. Access to these pathogens is not the issue because they are so difficult to deliver to the intended target." He pointed out that luckily, there isn't much expertise in the spread of deliberate disease around the world. Indeed, it is dissemination of the material that is the main challenge.

Tim Brooks, Director of Public Health Affairs at the UK's Health Protection Agency at Porton Down, reminded the group, however, that smallpox transmits very easily from one person to another. "One primary case will cause 6-8 secondary cases. That is why everyone fears it so much. Case in point: in 1972 one person came back to Yugoslavia with the disease and it infected over 100 people in three waves before the situation was finally brought under control."

The changes needed

Shifting discussion to prevention, **Magnus Ovilius**, Senior Administrator at the European Commission's Directorate General for Justice & Home Affairs, insisted that whatever pathogen is used, "the effects are the same. It is the events leading up to the crisis that we need to address." Ovilius pointed out that in the event of a crisis, which agent is used is not the most important factor, since reactions to any bioterror attack should be the same. Are new member states' facilities up to date? What about third world countries? How easy is it to get a hold of these agents for illegal purposes?

Brooks concurred, but cautioned that it is important that Europe's response infrastructure not separate bioterrorism from the natural outbreak of other diseases. "If you have already established networks and vaccines to cover all diseases, then you already have the infrastructure in place to deal with bioterrorism." The reality is that natural disease is the most likely candidate – for example, influenza.

Paul supported that view, stating we have to use what we have in place. We also can't forget about animal and agricultural impacts as well. Numbers in stockpiling address very specific areas – more of regional and international concern. But the day's discussions should focus on how we can build up European and international support, such as drugs, vaccines or personnel among the 25 Member States, more than on how many vaccines we should stockpile. We must build more capabilities in terms of sharing vaccines between states.

A serious problem brought up by participants is the lack of consensus among Member States who don't necessarily consider that resources available can be shared, since this is a highly sensitive matter of national security. Even if they were shared, questions arise as to how vaccines are transported from one state to another, where are they kept, and how are they distributed evenly?

Giles Merritt, Director of the NDA, then intervened to steer the debate's emerging themes., noting the debate was throwing out more questions than answers:

- Participants clearly stated the wheel should not be reinvented in existing networks to deal with disease exist. But are we talking about strengthening these networks? Or of rationalizing a whole set of overlapping networks?

- Funding is certainly a concern, especially at the EU level. Are we talking simply about more money or about different rules? Merritt heard talk during the debate of a billion euro proposal for security research awaiting ratification by EU Member States, but noticed that Jill Dekker-Bellamy mentioned the creation of a new vaccine could cost up to a billion euros alone…

- Decision making remains flux, both in speed and in nature. The whole question of how Member States support each other is interesting since we are dealing with very sensitive matters of national security and more specifically, authority. Who has the authority to transfer one sovereign nations' pool of vaccines to another? How far in advance do two leaders have to shake hands for the vaccines to reach an infected country in time? To what extend do resources and logistics need a centralized mechanism?

This provoked a lively exchange of views around the table.

What to recommend?

There are different standards of biosafety among European Member States. Several participants, including Dr. Koopmans, Drs. Dekker-Bellamy and Dr. Brooks, addressed the different standards of biosafety among European Member States.

Brooks stressed the importance of pathogen results coming out of one lab in a new Member State being the same as one from an old Member State. "What is needed is a syndronic, real time surveillance system – with real time reporting, requiring a very significant investment in infrastructure, as well as extensive training so that people know what to report and when. The challenges are considerable, but the benefits are enormous for any disease." He called on the example of the UK's influenza sentinel network – where general practitioners report not true laboratory cases of influenza, but system complexes that relate to it. These reports are used to plan health care provisions for any given current year.

Dr. Hyer jumped in to make two key observations regarding public health infrastructure and communication. Public health infrastructure will face everything: from daily illness to a bio attack, and it is something the Commission can fund and support. Looking at the American response after the anthrax attacks of 2001, the US government funded public health infrastructure. People found out what the phone number was of the state lab next door, labs got more phone and fax machines – what was missing was actually remarkable. The WHO's consistent message has been that investment, though difficult to sustain overtime as its not as visible as bioterrorism, is best. He also brought up communication, suggesting that the antidote to terror was most likely communication. A problem we're seeing right now is the lack of influenza vaccines in the United States, yet Hyer did not know of a serious influenza case in the US at that time. Yet people are cueing for hours, paying ten times the price. It's a question of terror.

Merritt brought the questions back to who's in charge of some of these different areas?

Koopmans stressed the need, along with Richard Guthrie, for a current crisis response system. When do you switch to a supranational system? Koopmans took the example of a situation such as the SARS outbreak in China, what do you do if you know something is going on, but the information is not being shared? What would have happened if that situation took place in Europe. Can you impose quarantine? When would procedures switch from a national to European authority?

It was then suggested that perhaps the European Council should take on the same structure as the Commission to be able to make these decisions – needing to be able to close borders or down air traffic. The Commission needs to be able to bring in all the networks from the member states to circulate them within the Union itself, working as a focal point of communication for the 25 countries. Bilateral relations are not enough.

How is an event of international consequence to be handled without a supranational body that has the public's confidence? As long as one event can be isolated, fine. But what about something that takes place along a border or involving 3-4 Member States. A terrorist attack on the port of Rotterdam might kill only a few people but the psychological impact would shut down Europe.

Noting that the European Commission has just adopted a recommendation to set up a new EU alert-crisis centre to coordinate emergencies affecting two or more Member States, Ovilius said the forthcoming centre "doesn't replace individual systems; it builds on them. There will be an interface to channel the alerts so that all participants are aware that an alert is there."

Brooks cautioned that whatever the EU sets up, "it has to be credible. If you think there's going to be a hand-over of sovereignty, well that is not going to

happen. I think the WHO model is the one to follow: something voluntary, but with strong pressure for nations to respond to its appeals."

Florin Paul warned that "it is important that bioterrorism notification and prevention be split into its scientific, technical and political aspects."

Guthrie suggested a recommendation reminding Member States that despite the deeply sensitive nature of this subject, by the time consensus on an issue is taken in a time of emergency, it may be too late.

Merritt also pointed out existing entities that could help in a crisis situation that might be overlooked. NATO, he alluded, is often associated with "hardware" and things obviously military, rather than civil protection. This is a view Merritt was not sure NATO would share.

Merritt wrapped up the session by summarizing the broad recommendations that emerged from the workshop debate, outlining three main aims for recommendations.

"It seems that our recommendations should include the need for a real-time reporting system. But should this be European only – or global? Also, advocating some form of supra-national crisis response system seems evident. But this raises other questions: how to share resources; how authority is delegated, and the extent to which one country can demand help from another," he observed.

As a final framing point, he asked: "Are researchers doing the right things? If not, what incentives are needed to prod them to move in the right direction—i.e., toward developing the right kind of vaccines? If we can come up with just four or five clear points that we can agree on, then we have the beginning of a set of recommendations."

Analysis
October 18

Drs. Jill Dekker-Bellamy

Bio-Defence Consultant, New Defence Agenda

Drs. Jill Dekker-Bellamy

Countering Bio-Terrorism: Science, Technology and Oversight

"Four points of view prevalent among national policy circles and the academic community at various times have served to dismiss biological terrorism as nothing more than a theoretical possibility. 1) Biological weapons have so seldom been deployed that precedent would suggest they will not be used. 2) Their use is so morally repugnant that no one would deign to use them. 3) The science of producing enough organisms and dispersing them is so difficult that it is within the reach of only the most sophisticated laboratories. 4) Like the concept of a "nuclear winter," the potential destructiveness of bio-weapons is essentially unthinkable and so to be dismissed. Each of these arguments is without validity."

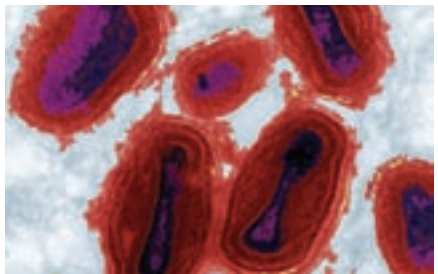
D.A.Hendersen,

the Johns Hopkins University

[1] Henderson, D.A., "Bioterrorism as a Public Health Threat", *Emerging Infectious Diseases*, Vol. 4, No.3. Centers for Disease Control and Prevention, Atlanta, July-September 1998.

Preface

On 18 October, the New Defence Agenda presented the second in its new series of quarterly Expert Group Meetings on Bio-Terrorism. The Brainstorming session on 21 June opened the debate on the use of disease as a weapon of mass destruction. This latest meeting saw the official launch of the Bio-Terrorism Reporting Group. While the primary intention of the session was to follow on the recommendations and suggestions developed from the Brainstorming Meeting, new areas for debate were opened up; deepening the content and our understanding of the many facets of public health protection, security and defence, intrinsic components for preparing to counter biological terrorism. Participants were reminded that the goal of the Bio-Terrorism Reporting Group is to make policy recommendations to decision makers. This report therefore presents the key policy recommendations experts agreed formed the critical areas vital to preparing for and addressing mass casualty bio-terrorism.



Introduction

The last New Defence Agenda Bio-Terrorism Reporting Group on 21 June discussed the need to strengthen our ability to identify diseases. In our latest meeting, disease surveillance was sighted as a crucial component of any national public health security system. However one of the newer challenges of disease surveillance in the post 911 environment is to determine if an outbreak is natural or if it is *deliberate*. Should a deliberate attack be prepared for and responded too in the same way as a natural outbreak? Or does the nature of bio-terrorism, the fact that there is a well thought out planning period, the potential for greater spread due to either advanced dispersal techniques, or the potential for a simultaneous release, mean that in countering a deliberate disease we may be required to engage in more extensive rapid assessments and interventions? Should we place more diseases under active surveillance? Should we build in a system embedded within our existing capacity to identify and respond to deliberate disease outbreak?

Building upon the last Bio-Terrorism Report we take a deeper look into the issues and the structure of European surveillance, capacity, bio-security and the problems of variation in standards, practice, regulation and technology. The original Member States which comprise the European Union have largely enjoyed advanced capability and capacity to conduct rapid, accurate diagnostic and reference testing even for select biologic agents likely to be used in a bio-terror attack. New Member States still face tremendous challenges in building their infrastructure for disease surveillance, capacity and collaboration. It is important to remember that wide variation exists and to account for this in preparing for a regulatory approach to counter bio-terrorism.

Designating and detecting the intentional use of disease

In 2002, the Chief Medical Officer of the UK reported that anthrax, botulism, bubonic plague, smallpox and tularaemia are the agents that have been most extensively studied and used in scenario plans[2]. These have the highest priority because of their ability to spread rapidly, cause high mortality and for which many have no vaccine or prophylactic intervention available. Many Class A[3] diseases initially present with symptoms associated with influenza. It is therefore essential we train medical professionals to identify potential cases of smallpox, anthrax, plague, botulism and tularemia among other highly infectious diseases which could be suitable for bio-terrorism. At the same time it is important to have the technical and scientific capacity to conduct accurate diagnostics on possible agents.

It was deemed important to develop standard diagnostic tests so results in one state can be interpreted in another. At the European level developing a "common" list of select agents should be undertaken. Many Member States have lists which are variable even among the national institutes; listed select agents can vary from one laboratory to another. While most list the above select agents, some laboratories drop botulinium toxin for their lists and do not include viral haemorrhagic

[2] The Select Committee on Science and Technology, "The Scientific Response to Terrorism", The United Kingdom Parliament, House of Commons, Session 2002-2003, Science and Technology Committee Publications, 6 November 2003.
URL: http://www.publications.parliament.uk/pa/cm200203/cmselect/cmsctech/415/41502.htm

[3] See table 1. Charles Kemp, Infectious Diseases, 2001-2004.

Disease & Agent Type	Probable BW Route	Incubation (days)	Signs & Symptoms (incomplete)	Treatment of mass casualties	Prophylaxis	Vaccine
Anthrax: Spore-forming bacteria	Aerosol; no person-to person	1-7 days (or more)	Febrile flu-like; then severe respiratory distress	Ciprofloxacin or Doxycycline	Ciprofloxacin or, if susceptible, Doxycycline	Available, but short supply
Smallpox: Virus	Aerosol; then person-to person	7-17 days	High fever, prostration; then rash & pustules	Supportive only	None	Available but short supply
Plague: Bacteria	Aerosol; then person-to person	1-6 days	Fulminate pneumonia; then sepsis	Doxycycline or Ciprofloxacin	Doxycycline or Ciprofloxacin	Not now available
Botulism: Toxin from bacteria	Aerosol; no person-to person	2 hours to 8 days	Bulbar nerve palsies; descending flaccid paralysis	Passive immuni-zation (antitoxin); supportive care	Passive im-munization (antitoxin)	Antitoxin in short supplyv
Tularemia: Bacteria	Aerosol; no person-to person	1-14 days	Febrile, flu-like; respi-ratory; sepsis	Doxycycline or Ciprofloxacin	Doxycycline or Ciprofloxacin	Not widely available & incomplete protection

Table 1. Summary of Selected Class A Biological Warfare Agent

fevers. A system which rates factors such as likelihood for weaponization, ease of delivery and the threat of mass casualty is probably a more accurate reflection of probable threat agents. However given the potential outcome of a Class A agent and/or smallpox strike, while the probability may be low, the outcome of such an attack would be so devastating we cannot fail to account for the most deadly diseases. What should be done at the policy level to encourage harmonizing a list of select agents, strengthen laboratory capacity, increase disease surveillance and standardize tests? How best can we achieve these crucial components of public health security for the prevention and containment of deliberate disease? Is the focus on public health security missing the point? Should we also strive to balance the strengthening of emergency public health policy and the current health infrastructure with security, intelligence and military infrastructures to create a more comprehensive approach to bio-defence?

Stockpiling and Vaccine Research

A central theme in the discussions was the need to ensure Member States have adequate and consistent stockpiles of drugs used to prevent (prophylactic) and treat post exposure casualties of a bio-terror attack. As there is no way to estimate return on research and development costs for producing 'orphan' drugs , participants discussed ways to encourage incentives and the potential for setting minimum standards for government support.

On a similar front legislation to increase bio-defence vaccine research was designated as a significant function of preparing to meet emergency public health challenges into the 21st Century. Experts opened the discussion on problematic areas related to orphan drugs[4], government support for research into drug development on diseases for which there can be no projection of return. How can we maintain our defensive bio-tech edge without sacrificing highly advanced research into some of the most devastating diseases which have the potential to kill millions of people? We touched upon the Bio-Shield legislation in the United States where governmental guarantees for drugs which may not return the investment might be considered within a European framework.

Bio-shield

Bio-Shield is a 10 year, 6 billion dollar plan to increase research and drug development for bio-defence vaccines. A number of bio-defence analysts and industry experts polled on Bio-Shield were less optimistic about the ability of governments to offer incentives for the pharmaceutical industry to continue research and development into orphan drugs. This they concluded could have significant and detrimental effects when coping with large scale epidemics such as SARS or influenza, and would not be enough to induce development of counter measures nations need for effective bio-defence. Moreover the lack of stockpiling of bio-defence vaccines and vaccines for naturally occurring diseases could compromise not only public health but civil order; as nations with 1 dose per person smallpox stockpiled, verses nations with no or low smallpox vaccine stockpiles may try to acquire vaccines in other states.[5] The point was made that it is easy to be moderate when your nation has 100% coverage. Many east European states only have a virtual stockpile of smallpox and VIG[6] (Vaccinia Immune Globulin), if smallpox

[4] The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 people. The Orphan Drug act was adopted in the United States as a means to encourage research and development of counter-measures for rare diseases. Regulation (EC) No 141/2000 of 16 December 1999, sets out a Community procedure for designating drugs as orphan medicinal products. The Regulation establishes the Committee for Orphan Medicinal Products (COMP), within the EMEA, which is responsible for examining applications for orphan medicinal product designation.

were to break out the populations in these states would probably not take a moderate approach and there exists the real risk of civil breakdown. Discussions then focused on vaccine availability to nations who can not stockpile. The sharing of vaccine stockpiles and the potential for the World Health Organization to moderate in such a crisis would be highly advantageous.

An area often overlooked but key to any pubic health emergency is the communication of the risk. Public perceptions and opinions often determine the resolution of high concern, high stress or emotionally charged issues.[7] The intentional or unintentional introduction of a pathogen in an urban setting presents severe communication challenges.[8] Public perception can have a profound impact on the successful outcome of a public health emergency. The media can play a positive and central role in how the threat is managed. Risk communication during a public health crisis is therefore an essential tool in preventing and reducing panic which could result during smallpox or naturally occurring epidemic for which there are limited supplies of vaccine available.

The European Communicable Disease Center and Wider Collaboration

The Reporting Group discussed the European Communicable Disease Center (ECDC) as a possible choice in leading during a deliberate disease strike.[9] However given that intelligence and security sector agencies from a number of Member States would likely be involved, it was unclear how such agencies would liaise with the ECDC. Moreover although the European Union has a system for the Europe-wide epidemiological surveillance of infectious diseases (see: MEMO/03/155) cooperation on investigating and controlling disease is largely ad hoc.[10] For example, the small EU team sent to help the WHO investigate avian influenza in Vietnam (see IP/04/165) is part of an EU project to train disease investigation experts[11]. The EU expert group on SARS created during the outbreak in spring 2003 was put together under the European Communicable Disease Network.[12] While these have been good short term solutions, they are not sustainable in the long term.[13] The ECDC is on course to become operational in 2005. The EU summit in December 2003 decided that the ECDC will be based in Stockholm, Sweden.

Epidemiology Surveillance

As appeared in the first Bio-Terrorism Reporting Group report, the European Union has many well established programmes for detecting and reporting outbreaks of disease.[14] While the European CDC will likely increase disease surveillance capacity in states with existing collaboration such as among the 8 P4 reference labs, it is essential to strengthen the ability of the new Member States to participate in such programmes. This can best be achieved through strengthening technical and scientific capacity throughout the new Member States. The new Member States were invited to participate for example in Enter-Net prior to Accession. At that time several eastern national reference labs lacked the computer systems needed to collaborate; in a few labs test results were still being written on paper. While an ECDC will hopefully support surveillance programmes across the EU, participation by *all* Member States must be addressed. When a lab struggles to identify salmonella, a common foodborne disease; advanced technologies required to rapidly processes and confirm samples in the event of unusual clusters or multiple mass outbreaks, may mean some labs would not be able to successfully identify or rapidly process samples. This could mean the difference between rapid containment or mass casualties from widespread communicable disease.

Participants identified a number of gaps and lack of infrastructure. It was noted improved surveillance efforts should

[5] The halving of the US supply of influenza vaccine with the closure of Chiron production in the UK, has lead to civil unrest in some US states. US citizens are now crossing the boarder to Canada to receive vaccines. Some people have died waiting all night for inoculations and the US reports several arrests due to civil disorder. Aventis Pasteur the only other US supplier has recently found another 2.4 million doses but this continues to leave the US short of approximately 50 million doses.

[6] The European Union Commission recommends access to VIG to supplement smallpox stockpiling programmes. In the US the Centers for Disease Control and Prevention (CDC) is supplementing its smallpox stockpiling strategy through the stocking of Vaccinia Immune Globulin (Human) Injection (C-VIG). Recommended stockpiling is at a rate of 1 dose of C-VIG per 10,000 doses of stockpiled vaccine. Acambis URL: http://www.acambis.com/default.asp?id=622

[7-8] Covello, Vincent, T., Richard G. Peters, Joseph G. Wojtecki and Richard C. Hyde, "Risk Communication, the West Nile Virus Epidemic and Bioterrorism: Responding to the Communication Challenges posed by the Intentional or Unintentional Release of a Pathogen in an Urban Setting", Journal of Urban Health: Bulletin of the New York Academic of Medicine, Vol. 78, No.2. June 2001, p382-392.

[9] The Council of Ministers agreed on the Commission's proposal to create a new European Centre for Disease Prevention and Control (ECDC European Commission Press Release, "New EU Centre for Disease Prevention and Control adopted", Ref.: IP/04/427; 31/03/2004. Accessed at: http://europa.eu.int/rapid/pressReleasesAction.do?reference=IP/04/427&format=HTML&aged=0&language=EN&guiLanguage=en

[10-14] European Commission Press Release, "New EU Centre for Disease Prevention and Control adopted", Ref.: IP/04/427; 31/03/2004. Accessed at: http://europa.eu.int/rapid/pressReleasesAction.do?reference=IP/04/427&format=HTML&aged=0&language=EN&guiLanguage=en

be instituted with as close to real-time data gathering as possible.[15] All facets of surveillance should be used, to include emergency visits, laboratory data, pharmacy use, school absenteeism, or any other data that correlate with an increase in infectious disease.[16] Robust surveillance systems are essential to detecting any emerging or reemerging disease; quick recognition of any change in disease patterns will facilitate determining the source and preventing further exposure, which should be the key driving force behind any epidemiologic investigation.[17] Through strong epidemiologic training, a close attention to disease patterns, and a healthy respect for the threat of biological terrorism, potential problems can be discovered rapidly, and actions can be taken to decrease the impact of disease, regardless of its origin.[18]

Within the Member States it is important to build upon existing assets. To increase disease surveillance capacity particularly in states which lack this, while structuring an approach which takes bio-terrorism into consideration when emerging or reemerging diseases occur. Should we also be working toward a stronger response capability? Strengthening the infrastructure of coordination and leadership in areas critical to identifying and containing an emergency public health crisis? Who should lead? Should the Ministries of Public Health from each Member State agree on a rotation of leadership? Should simulations be routinely conducted to test the preparedness of this leadership?

Hot labs: Why the Controversy?

concepts and considerations

The meeting touched upon the issue of high containment facilities or what are commonly referred too as 'hot' labs. National Reference and bio-defence laboratories are critical aspect of public health infrastructure and bio-defence. Bio-safety labs are categorized into four levels based on the level of danger associated with the diseases they conduct research, analysis and diagnostics upon.[19] The US Bio-Safety Level (BSL) 3 and 4 or European standard Protection 3 or 4 (P3/P4) are highly specialized facilities.[20] The potential to increase capacity in new states of the European Union was discussed within the wider framework of capacity strengthening. Policy recommendations for standardizing bio-safety regulations as well as the number of available P3 facilities were areas considered to be significant for increasing preparedness.

The ability to diagnose Class A or select agents requires the use of advanced laboratories. As mentioned in our previous Report, P4 laboratories are rare. There are 8 within the European Union. P3 laboratories are more common yet the challenges to undertake diagnostics on a potentially unknown pathogen make the use of such facilities imperative. Concurrently, while accidents in these labs are rare, they do occur. P4 in many Member States are associated with or conduct research in collaboration with defence. Biological defense laboratories study organisms categorized as potential agents of bio-terrorism. Much of the work in these facilities falls into one of the following six categories:

- Research on the basic biology and mechanisms of disease causation in select pathogens;
- Identification of intervention into human immune responses to toxicity and infection;
- Creation of systems to rapidly detect the presence of select agents in the environment;
- Development of methods for more effectively diagnosing human exposure to and infection from bio-terrorism agents;
- Creation of new therapeutic interventions for specific as well as broad categories of pathogens; and
- Production of vaccines against specific agents.[21]

Controversy over bio-defence research result from both the secrecy associated with these facilities and the often dual-use nature of the research. As previously mentioned it can be

[15-18] Pavlin, Julie Col., "Epidemiology of Bioterrorism", Emerging Infectious Diseases, Centers for Disease Control and Prevention, Vol.5 No.4, July-August 1999, Accessed at: http://www.cdc.gov/ncidod/EID/vol5no4/pavlin.htm

[19] Labs that deal with organisms that would not typically cause disease in a healthy human, such as E. coli, are given a Biosafety Level 1 designation. Biosafety Level 3 includes viruses, bacteria, and fungal agents.

[20] Bacterial usually include: tularaemia, pulmonary and nonpulmonary tuberculosis, glanders, melioidosis, typhoid fever, paratyphoid fever, plague (bubonic, pneumonic, and septicaemic), Q fever, typhus (scrub and epidemic), and Rocky Mountain Spotted Fever. Viral agents usually include over 160 arboroviruses such as West Nile, Yellow fever, encephalitis (Dengue fever, Hantavirus various others); lymphocytic choriomeningitis(LCM) (neurotrophic strains), Hepatitis B and C, HIV, and Rift Vally Fever. Fungal agents in BSL3 include: Coccidioides immitis (causes pulmonary disease), pulmonary histoplasmosis, and North American Blastomycosis. BSL 4 covers a more limited group of exotic pathogens that pose a high risk of exposure and infection ratio to personel, the community and the environment if released. Includes" filoviruses, arenaviruses, arboroviruses such as Junin, Marburg, Congo-Crimean, hemorrhagic fever, Omsk Hemorrhagic fever, Lassa, Machupo, Ebola, Sabia and Encephalmomyltis.

[21] Boston University Biodefence, A project of the Council for Responsible Genetics. Cambridge, Mass. 2003.

difficult to distinguish between offensive and defensive applications.[22] Almost all of the requirements of Level 4 facilities deal with preventing accidents; and then the focus are almost exclusively on accidents from within the Lab (preventing infections) not from outside forces. For example, what happens in case of massive power failure, fire, and explosion? Although there are a number of examples of laboratory accidents involving select agents, the increased investment in bio-defense funding has created many more research sites. The present complexity of shipping, handling, and research has increased the risks of accidents that can pose harm within and beyond the laboratory. These are all areas which the European Union Member States must consider when developing regulations to prevent accidental and deliberate exposure.

Accidents do happen

The concern and controversy surrounding P4 facilities and to a more limited extent P3 are the result of accidents which heightened public awareness to the risk of bio-defence research. Four cases of SARS-CoV were laboratory acquired.[23] While the last case of endemic Smallpox occurred in Somalia in 1977, the last recorded case in humans occurred in England in 1978; this case was a Laboratory Acquired Disease (LAD). Should we be concerned not only about the protection level under which such high consequence diseases are held[24] but the bio-safety standards and practices which can vary widely from one lab to the next? The four confirmed laboratory acquired SARS outbreaks reflect the dangers to public health security that arise from accidental laboratory acquired disease and the potential release of biological pathogens which may only exist in a laboratory setting. In 1977 an influenza virus not reported for 27 years inexplicably reappeared and circulated worldwide this too may have been a laboratory release or LAD.[25] How safe are the most dangerous pathogens held in high containment facilities?

Should the Member States of the European Union move toward a system of laboratory accreditation to standardize bio-safety and bio-security? Should we build consensus on bio-safety and set minimum criteria which each lab must demonstrate in order to transport, hold and conduct research on high consequence Class A and B pathogens?

The following example noted by the Massachusetts Institute of Technology, Security Studies Programme reflects the growing public concern of laboratories engaged in bio-defence research and the potential need for a system of certification. While this incident occurred in the United States such 'accidents' have happened in a number of facilities. A European approach which standardizes procedures and requires laboratory certification on a wider set of criteria than currently employed may reduce the risk of such accidents. It may also help reduce the risk of diversion and the potential for bio-terrorism. The following is an account of one such accident.

"The shipping of deadly, live bacteria is in theory controlled by regulations and permits and it might typically be handled by courier rather than sent through the mails. These safety provisions should work. In June 2004, it was discovered that researchers at the Children's Hospital Oakland Research Institute in Oakland, California, were working with deadly, live anthrax bacteria when they thought they were using only a non-hazardous, dead bacterium. Six researchers, who were involved in a project on anthrax vaccine, handled the deadly bacteria and others may have been exposed."[26]

"That a deadly strain had been sent was not immediately reported. Researcher's injected mice with what they thought were dead anthrax bacteria. It was only after several days, when all the mice in the experiment died, that the lead researchers were told there might be a problem. Then a second batch of mice was inoculated and cultures obtained from a dead mouse revealed virulent anthrax."[27]

[22] Boston University Biodefence, A project of the Council for Responsible Genetics. Cambridge, Mass. 2003.

[23] On 17, December 2003, a 44 year-old male researcher was confirmed to have SARS in Taiwan. The patient is a senior scientist in the Institute of Preventive Medicine, National Defense University in Taipei, conducting SARS Co-V research. He was working on the SARS study in a Level 4 Laboratory in Taiwan. On the fifth of May 2004, WHO reported two researchers working at the National Institute of Virology in Beijing contracted SARS although they were not working directly on active SARS. On 8 September Singapore confirmed a laboratory acquired SARS case. The patient was conducting research on the West Nile virus in a laboratory that was also conducting research using active SARS-CoV (coronavirus).

[24] There is a significant difference between fist and secondary barrier methods for a P3 compared to those of a P4.

[25] Unintentional release of extinct human-adapted viruses arguably poses a serious threat to global health as bioterrorism or a natural outbreak. Again an example from influenza is instructive: Genetic sequencing of the global pandemic 1977 H1N1 influenza virus has shown it to be identical to an H1N1 strain that became extinct outside laboratories in the 1950's. The most plausible scenario is that the 1977 virus was one stored for decades in a laboratory freezer and thawed for experimental study during the 1976 swine influenza scare. See: Donald S. Burke, "Ignoring Deadly Viruses", Johns Hopkins Bloomburg School of Public Health, Baltimore, January 2004. URL: http://www.jhsph.edu/Press_Room/Press_Releases/PR_2004/Burke_WSJ_viruses.html

[26-27] Massachusetts Institute of Technology, Security Studies Programme, Level Four Bio-Safety Laboratories: Public Information and Risk Analysis (High Risk Scenarios). Accessed at: http://web.mit.edu/ssp/twg/level4/scenarios.html on 20, October 2004

"The source of the virulent bacterium was the Southern Research Institute of Frederick, Maryland, an affiliate of Fort Detrick. This company maintains two "hot labs," one in Frederick and another in Birmingham, Alabama. Thomas Voss, in charge of the company's emerging infectious disease program, initially said that "We receive [select] agents on a routine basis. But on our end, we ship very infrequently. I don't even recall shipping live agents." The deadly agent was shipped via FedEx, double-boxed. The California Department of Health Services was called in, as were the FBI and the CDC. Samples of the anthrax bacterium were sent to CDC in Atlanta for testing. The local community was not informed about research on anthrax vaccine. The institute is not registered for work on live select agents. Before the 2001 anthrax letters, there were around 12 facilities working with the anthrax bacterium. Now it appears that there are 350."[28]

A wider concern to both the European Union and international community as a whole is the reporting not only of research on dangerous pathogens but the reporting of accidents which occur in these facilities. On May fifth of 2004 a senior researcher at the State Research Centre of Virology and Biotechnology known as Vector died after a sharps accident involving hemorrhagic Ebola. There is no requirement to report such accidents so World Health Organization was not informed until nearly two weeks later. They could not therefore provide treatment which may have saved her life. The secrecy surrounding select agent research continues to be controversial.

Policy Options and Considerations

Should we be concerned? Each of these statements and examples may help to better define a European approach to bio-defence, how we conceive of 'acceptable risk' in the bio-sciences and ultimately the regulatory approach to encourage bio-defence research while reducing the risk associated with this research. Mediating the threat posed either by naturally occurring or deliberate disease is a delicate issue.

- Should regulations be established to certify P3 and P4 laboratories on an annual basis using standard criteria and independent audits?
- Should the EU require the reporting of accidents in P3 and P4 laboratories which could result in Laboratory Acquired Diseases such as SARS?
- Should the EU set standards on what constitutes a P3 and limit application of plus practices?
- Should the EU require and standardize security screening for personnel working on select agents?

The Bio-*Terror* Debate

The meeting witnessed debate on whether or not bio-terrorism actually poses the threat some believe it does; or whether this threat was more marginal and should be considered to have a low probability and low priority. There was also debate on the type of biological pathogen (disease) most likely to be deployed or used in material or weapon form. While Class B diseases and emerging disease pose a tremendous challenge to public health, the bio-terror potential of such organisms is considered within the European Union's RAS-BICHAT programme.[29] Although emerging and multi-resistant strains of salmonella and e-coli may pose a significant health risk if released and their natural occurrence greatly impacts public health and economic sectors annually, lab capacity to identify foodborne pathogens such as e-coli, salmonella, listeria and campylobacter is fairly well established both within the EU under the Enter-Net[30] programme and Salm-Gene.[31] While the public may have cause to be concerned about an act of terrorism using foodborne or Class B diseases, the focus of this reporting group, similar to other bio-defence forums is to discuss the more widely feared Class A group for which there are fewer interventions and for which the human and economic costs would most certainly be higher.

[28] Massachusetts Institute of Technology, Security Studies Programme, Level Four Bio-Safety Laboratories: Public Information and Risk Analysis (High Risk Scenarios). Accessed at: http://web.mit.edu/ssp/twg/level4/scenarios.html on 20, October 2004

[29] Rapid Alert System for Biological and Chemical Attacks and Threats.

[30] Enter-net is the international surveillance network for human gastrointestinal infections. The participants in the network are the microbiologist in charge of the national reference laboratory for salmonella and E. coli infections, and the epidemiologist responsible the national surveillance of these diseases. The network involves all 15 countries of the European Union (EU), plus Australia, Canada, Japan, South Africa, Switzerland and Norway. The newly associated states of Eastern Europe will formally be able to join the network in 2003, although an informal working relationship already exists with the Czech Republic, Hungary, Latvia and Poland. The network is funded by the European Commission (EC) DG Health and Consumer Protection, and conducts international surveillance of salmonellosis and verocytotoxin producing Escherichia coli (VTEC) O157, including antimicrobial resistance.

[31] Salm-Gene is a project funded by the European Commission (DG-RESEARCH) aiming to strengthen international Salmonella surveillance through molecular strain typing and differentiation

World Health Organization among other major health centers such as the Centers for Disease Control and Prevention in Atlanta list the specific diseases associated with bio-terrorism as: anthrax, botulism, plague, smallpox, tularaemia.[32] The World Health Organization has recognized threats to food safety in it's "Terrorist Threats to Food: Guidance for Establishing and Strengthening Prevention and Response Systems." While discussions on probability of a Class A event are relevant and the potential of a Class B or foodborne pathogen attack may be more likely, this forum is designed to address Class A major biological attacks. Class B may be better served within a special focus on agro-industrial threats with public health consequences.

Loosing sight of Terrorism?

Often when discussing "bio-terrorism" and the need to implement policies to prevent it, we loose sight of the terrorist component. It is not abstract or unknown. It is quantifiable and it is on-going. While public health security is vital to this equation so too is an understanding of the nature of the threat and the vital role security, defence and intelligence agencies play toward preventing bio-terrorism.

The potential for al Qaeda to use biological weapons has and continues to be a focus of concern within expert defence and intelligence circles. It has been documented that al Qaeda training camp (abu-Khabab) outside Jalalabad, Afghanistan, named after al-Qaeda's Egyptian born chemical and biological expert Midhat Mursi who goes by the alias Abu Khabab, ran chemical and biological training programmes. Moreover al-Qaeda's manual "Encyclopedia of Afghan Resistance" distributed on CD-ROM includes sections on making chemical and biological weapons.[33] Al Qaeda poses a threat as their top leadership not only actively recruits from within European states but many of their top leadership hold Ph.D., d.Phil. and M.D. degrees. For example Ayman Al-Zawahri comes from a family of doctors and scholars. He graduated from Cairo University School of Medicine in 1974 and obtained a masters degree in surgery. He is an optical surgeon. His father was a professor of pharmacology. He has lived in Denmark and Switzerland.

Within the EU several cases have come to light which would appear to support intelligence claims that al Qaeda is seeking biological capability. In December 2002, French counter-terror agents arrested four suspected terrorists and seized two phials of substance (unidentified) along with "Hazmat" (hazardous materials) suits. The four suspects were thought to have spent time in Chechnya. Terrorist factions from the Groupe Islamique Armé[34] (GIA) have been notably involved in Albanian organized crime and have strong ties to the Chechen conflict with the Russian Federation. Chechnya is viewed as a training ground for Muslim terrorists. In January 2003, Spain arrested 16 Islamic terrorists with connections to the four French suspects and the British suspects found in possession of Ricin. The Spanish authorities believe the suspects, of mainly Algerian decent, were preparing to send communications equipment to Chechnya and Algeria. Six of the previous detentions involved suspected members of the Salafist Group for Call and Combat, which formed in 1998 as a faction of Groupe Islamique Armé (GIA).

Four Islamic terror suspects arrested in 2003 in France identified as Merouane Benahmed, Mourredine Merabet, Menad Benchellali and Ahmed Belhout had lived in Spain and was closely associated with the suspects arrested in Italy. Merouane Benahmed is an expert in bio-chem and explosives. Common denominators among these men and their associates include: Training in chemical and biological weapons at a camp in the Transcaucus (Pankisi and Korda Gorges); training in Afghanistan and Pakistan. At the time of the London arrests it is believed the Ricin found at a London flat was partially refined in the Pankisi Gorge.

Preventing terrorism and in particular bio-terrorism requires security and intelligence cooperation with those responsible for ensuring public health security. Both aspects must be brought into the equation

[32] For more information see: World Health Organization, Communicable Disease Surveillance and Response (CSR), "Specific Diseases Associated with Biological Weapons", World Health Organization, Geneva, 2004. URL: http://www.who.int/csr/delibepidemics/disease/en/

[33] de Rugy, Veronique and Charles V. Pena, "Responding to the Threat of Smallpox Bio-terrorism", No. 434, Cato Institute, Washington D.C., 18 April 2002. p.2.

[34] Previous conventional GIA terrorist attacks in France has led to the exposure of an extensive GIA infrastructure in various European countries, particularly in France, Belgium, the U.K., Germany, Italy, Sweden, and Spain. Logistics, financial and operational ties were found to exist between the members of the small terror cells operating in these countries. The main objective of this European network is to smuggle funds and weapons to their comrades in Algeria and support Chechen Islamic terrorism. The later is partially funded through the massive heroin trade run through Albania. Other Muslim organizations helping the Chechens are affiliated with the Saudi Wahabi Movement and Al Qeada. Moreover ranks of Chechen terrorists have increased with foreign fighters. Some from Afganistan, headed by Ibn-ul-Khattab, whose extensive combat and leadership skills, acquired in Afghanistan and Tajikistan, have proved of great service to the Chechens. See: Shaul Shay and Yorum Schweitzer, "The Afghan Alumni Terrorism", International Policy Institute for Counter Terrorism, Herzlia, Israel. 6, November, 2000. URL: http://www.ict.org.il/

in order to prevent and deter acts of deliberate disease. A European orientation to preventing bio-terrorism must therefore carefully center regulations on criminal law as well as health protection and emergency public health regulations.

Policy Options

As with planning for any other type of potential attack nations generally don't wait until they have an ample number of such events occurring before they begin preparing for it. For example although there has not been a mass casualty strike against the European Union using advanced tactical weapons, national security planners still invest billions to prepare for such an attack. Is the EU prepared today to cope with a major mass casualty bio-terrorism event?

- Should we create a bio-defence team that can liaise between security and the scientific community during an emergency and conduct contingency planning?
- What role should Member States counter-terrorism organization play?
- How can we strengthen the existing infrastructure and increase communication to prepare for a deliberate public health emergency?
- Should we structure a European approach to criminalizing the possession and development of select agents into biological weapons?[35]
- Clearly a key challenge appears to be to build an infrastructure which balances the science of bio-defence with the need for a wider security agenda.

Scenario[36]

Several fictitious scenarios have been created to explore the ways in which the public may be better protected from both bioterrorism and accidents involving infectious diseases.[37] A couple examples are provided to help conceptualize the risk, outcome, and basic policy framework which may serve to reduce the risk. How can the European Union apply some aspects presented to create a moderate policy on bio-terrorism which suits a broader European level consensus? How can we bring together science and security to develop policies which fill the gaps and strengthen our bio-defence posture? "Over a period of at least three millennia smallpox was second to none in inflicting human pain, suffering and death; by some estimates, smallpox killed as many as 500 million people during the twentieth century alone."[38] As recently as 30 years ago, smallpox was endemic in 31 countries, and of the 10 to 15 million people who contracted the disease each year, it killed two million.[39]

Drawing on concerns about possible bioterrorism, consultants from four different organizations devised a fictional contagion scenario called "Dark Winter" which described three U.S. states being attacked. The Center for Strategic and International Studies, the Johns Hopkins Center for Civilian Bio-defense Studies, the ANSER Institute for Homeland Security, and the Oklahoma National Memorial Institute for the Prevention Terrorism, hosted the senior-level war game examining the national security, intergovernmental, and information challenges of a biological attack on the American homeland.

In July 2001 "Dark Winter" was enacted to demonstrate the roles of the US President and other officials who would have to respond to a bioterrorist attack by Iraqi agents. The presumption was made that Iraq either had the smallpox virus or could obtain it from Russia. One of the political goals of the scenario was to underscore the need for national stockpiles of smallpox.[40]

Dark Winter

The following scenario was drawn from Tara O'Toole, Michael Mair, and Thomas V. Inglesby, "Shining Light on Dark Winter" from the Center of Civilian Bio-defence Strategies, Johns Hopkins University:

In Dark Winter world supply of smallpox vaccine doses is estimated at 60 million, with half in South Africa. There are

[35] For example French public health legislation effectively criminalizes non-authorized persons from possessing and transferring select agents may provide a roadmap for general EU guidelines as it comprehensive and concise.

[36] This scenario is provided to better understand the threat a biological attack may pose. It is based on The Plague Makers: The Secret World of Biological Warfare by Wendy Barnaby. While this scenario reflects the potential of deliberate disease it must be noted that experts who attended the Reporting Group in general opted for a moderate approach to bio-terrorism and the current risk was generally perceived as low.

[37] Massachusetts Institute of Technology, Security Studies Programme, Level Four Bio-Safety Laboratories: Public Information and Risk Analysis (High Risk Scenarios). Accessed at: http://web.mit.edu/ssp/twg/level4/scenarios.html on 20, October 2004.

[38] Koplow, Daniel, A., "Smallpox: the Fight to Eradicate a Global Scourge", University of California Press, Berkeley, CA 2003, p. 1

[39] Acambis. "The History of Smallpox and Vaccination", URL: http://www.acambis.com

[40] The ANSER Institute for Homeland Security, "Dark Winter", Arlington, VA, http://www.homelandsecurity.org/darkwinter/index.cfm

concerns that some non-U.S. vaccine may be ineffective, and may also have a higher rate of side effects[41] which would require intervention such as VIG.

Initially 100,000 doses of vaccine are released for Oklahoma, with the same amounts prepared to be sent to Pennsylvania and Georgia, pending lab confirmation of suspected cases in those states. Because of the limited vaccine stock, the decision is made to ration vaccine. The only civilians to be vaccinated are close contacts, healthcare personnel and investigators in case states. 2.5 million doses are reserved for the military and the National Guard. As the scenario progresses, two weeks after the presumed attack there are 2000 cases in 15 states, with 300 deaths. A total of three million doses of smallpox vaccine have been sent to Oklahoma, Pennsylvania and Georgia. Shipments of 500,000 doses delivered to each of 12 affected states. Five days after the first case was diagnosed only 1.25 million doses of vaccine remain.

By day six of the crisis, vaccine supplies are dwindling. An additional supply, from the United Kingdom (500,000 doses) and Russia (4 million doses), last for only a couple of days. The NSC develops a plan to use private pharmaceutical facilities in the U.S. to produce about 12 million doses of an unlicensed smallpox vaccine per month. But first delivery would be 5 weeks from the current time.

Near the end of the role-playing exercise, about three weeks after the fictional bioterrorism attack, a second generation of cases begins to appear. During the past 48 hours, the number of cases has skyrocketed with 14,000 new smallpox patients confirmed in 25 states, among them the large population centers of New York, California and Florida.

Smallpox is an extremely contagious disease. A single case can infect 10 to 20 others, and this can go on for generation after generation (or wave after wave), with a rapidly increasing number of infections at each step. The second generation, outlined in this exercise, would be followed by a third, a fourth and so on.

With a vaccine supply enough to immunize less than 5 percent of the population (2001), the infection rate would continue to increase tenfold every two to three weeks, according to medical experts. Continuing this grim calculation, that would mean 30 million cases, with 10 million deaths in the fifth wave. And then, two to three weeks later, a final wave sweeping the nation and killing off nearly one out of every three citizens. Of the smallpox importations analyzed, the importation into Yugoslavia in 1972 is particularly instructive because that outbreak encompassed many of the attributes that would be expected if a smallpox outbreak occurred today (e.g., a large number of susceptible people, delayed diagnosis, both hospital and community transmission, wide geographic dispersion of cases, difficulty in contact tracing). Given the low level of herd immunity to smallpox and the high likelihood of delayed diagnosis and public health intervention, the authors of this exercise used a 1:10 transmission rate for Dark Winter and judged that an exercise that used a lower rate of transmission would be unreasonably optimistic, might result in false planning assumptions, and, therefore, would be irresponsible.

"We are used to thinking about health problems as naturally occurring problems outside the framework of a malicious actor....If you're going against someone who is using a tool that you're not used to having him use disease and using it toward quite rationally and craftily an entirely unreasonable and god-awful end we are in a world we haven't ever really been in before" (James Woolsey).

The 'learning points' presented by ANSER (Analytic Services) developed for the Dark Winter scenario reflect wider issues which are applicable to the European Communities and developed nations alike. In summary these 'points' have been adapted for consideration in their application to the more general issues which would immediately face most developed nations:

- An attack on a western nation with biological weapons could threaten vital national security interests. Massive civilian casualties, breakdown in essential institutions, violation of democratic processes, civil disorder, loss of confidence in government and reduced strategic flexibility abroad are among the ways a biological attack might compromise national security;[42]

[41] BioHazard "Smallpox Scenario", URL: http://www.biohazardnews.net/scen_smallpox.shtml

[42] The ANSER Institute for Homeland Security, "Dark Winter", Arlington, VA, http://www.homelandsecurity.org/darkwinter/index.cfm

- Current organizational structures and capabilities are not well suited for the management of a BW attack. Major "fault lines" exist between different levels of government, between government and the private sector, among different institutions and agencies, and within the public and private sector. These "disconnects" could impede situational awareness and compromise the ability to limit loss of life, suffering, and economic damage; [43]

- There is no limited surge capability in health care and public health systems, or the pharmaceutical and vaccine industries. This institutionally limited surge capacity could result in hospitals being overwhelmed and becoming inoperable; could impede public health agencies' analysis of the scope, source and progress of the epidemic, the ability to educate and reassure the public, and the capacity to limit causalities and the spread of disease; [44]

- Dealing with the media will be a major, immediate challenge for all levels of government. Information management and communication (e.g., dealing with the press effectively, communication with citizens, maintaining the information flows necessary for command and control at all institutional levels) will be a critical element in crisis/consequence management; [45]

- Should a contagious bio-weapon pathogen be used, containing the spread of disease will present significant ethical, political, cultural, operational and legal challenges; [46]

Confronting gaps in policy

After a bioterrorist attack, leaders' decisions would depend on data and expertise from the medical and public health sectors. In Dark Winter, even after the smallpox attack was recognized, decision makers were confronted with many uncertainties and wanted information that was not immediately available. [47] The general lessons of Dark Winter [48] may be applicable to policy issues on both the international and European front.

Points and Observations to Consider:

- "It isn't just [a matter of] buying more vaccine. It's a question of how we integrate these [public health and national security communities] in ways that allow us to deal with various facets of the problem." (James Woolsey). [49]

- Federal and state priorities may be unclear, differ, or conflict; authorities may be uncertain; and national-regulatory issues may arise; [50]

- In Dark Winter, tensions rapidly developed between state and federal authorities in several contexts. State leaders wanted control of decisions regarding the imposition of disease-containment measures (e.g., mandatory vs. voluntary isolation and vaccination) what can be applied to European vs. national jurisdiction issues? [51]

- Leaders in states most affected by smallpox wanted immediate access to smallpox vaccine for all citizens of their states, but the federal government had to balance these requests against military and other national priorities;

- How will nations holding a 1:1 ratio of vaccine respond when demand in another Member State with no stockpile occurs? Will they protect their own population or share their stockpile?

- There were problems cited over jurisdiction on both quarantine, transport, closing airports and borders;

- Will Member States be inclined to go against European level regulations as has happened in the past with emergency animal disease outbreaks?

[43-46] The ANSER Institute for Homeland Security, "Dark Winter", Arlington, VA, http://www.homelandsecurity.org/darkwinter/index.cfm

[47] O'Toole, Tara, Mair, Michael, and Inglesby, Thomas V., "Shining Light on Dark Winter", in Clinical Infectious Diseases Confronting Biological Weapons, Donald A. Henderson, Thomas V. Inglesby, Jr., and Tara O'Toole, (eds.), Vol. 34:972-983, 2002.

[48] Criticisms of "Dark Winter" emerged. Experts thought that the high rate of contagion in the scenario, which allowed each one person infected to infect another 12 to 15 other people, was an exaggeration of what would happen in real life. They also criticized the way in which the scenario left out the active role an informed public could take in preventing the spread of the disease, by hand washing, staying at home, and wearing a simple mask. In the 1947 smallpox outbreak that threatened New York City, the public and the media worked together to allow vaccinations to take place with great efficiency and without the public panic and violence that were part of "Dark Winter." These criticisms and other criticisms are found in journal articles by scientists and physicians in Emerging Infectious Diseases, volume 7, number 1, (2001); Nature, volume 414, number 13 (2001) and New England Journal of Medicine volume 348, number 5 (2003). It is important to emphasize that the purpose of the Dark Winter exercise was not to make the case that smallpox is the weapon most likely to be used in a bioterrorist attack (it is impossible to make such predictions) but to demonstrate that the use of a contagious pathogen as a weapon of bioterrorism can have devastating effects.

[49-51] O'Toole, Tara, Mair, Michael, and Inglesby, Thomas V., "Shining Light on Dark Winter", in Clinical Infectious Diseases Confronting Biological Weapons, Donald A.

- The Dark Winter exercise offers instructive insights and lessons for those with responsibility for bioterrorism preparedness in the medical, public health, policy, and national security communities and, accordingly, offers insights on future options.

The consequences of an attack with smallpox are potentially catastrophic. Therefore, even if the likelihood cannot be established, the effects of smallpox as a weapon of bioterrorism warrant taking the threat seriously in order to understand the efficacy of potential response options.[52] Also, preventive measures, which might act as a potential deterrent, reduce the risk, and mitigate the consequences of an attack, need to be examined and evaluated.[53] Should we decide on a limited system of indicators and warnings? Well constructed scenarios and simulations can indicate how well or ill prepared public health institutions, security infrastructure and civil defences are for a major biological attack. We can then better assess the gaps and coordinate a policy response.

Smallpox Case Study

The smallpox virus is specific for humans and non-pathogenic in animals. Smallpox is one of the two most dangerous BW agents (the other being anthrax) because of its high case-fatality rate (>30%), ready person-to-person transmission, lack of population immunity (possibly including persons immunized 25+ years ago), and lack of treatment[54] As a result of a worldwide eradication campaign, the last endemic case of smallpox was reported in 1977. Russia and the U.S. are the last two known repositories of smallpox virus (with Russia having virus at several sites). Plans to destroy the virus by 1999 were delayed and it is not known when or if they will be destroyed.[55]

Smallpox is the result of infection by the variola virus, which belongs to the genus Orthopoxvirus in the family Poxviridae. The variola virus is a large brick-shaped double-stranded DNA virus that serologically cross-reacts with other members of the poxvirus family, including ectromelia, cowpox, monkeypox, vaccinia, and camelpox. Smallpox infects only humans and does not exist in a carrier state. In the 20th Century approximately 110 million people died in war. An estimated 300 to 500 million people died of smallpox; several times the number of deaths from all wars combined.[56]

The Yugoslavia outbreak of Smallpox in February 1972 reflects the chaos that a few cases can create. Yugoslavia's last case of smallpox occurred in 1927. In 1972, a man returning from Mecca became ill with an undiagnosed febrile disease. Friends and relatives visited from a number of different areas; 2 weeks later, 11 of them became ill with high fever and rash.[57] The patient's physicians (few of whom had ever seen a case of smallpox) failed to make a correct diagnosis.[58]

One of the 11 patients quickly became critically ill with the hemorrhagic form, a form not readily diagnosed even by experts. The patient was first given penicillin at a local clinic, but as he became increasingly ill, he was transferred to a dermatology ward in a city hospital, then to a similar ward in the capital city, and finally to a critical care unit because he was bleeding profusely and in shock.[59] He died before a definitive diagnosis was made and buried 2 days before the first case of smallpox was recognized.[60]

The first cases were positively diagnosed 4 weeks after the first patient became ill, but by then, 150 persons were already infected; of these, 38 (including two physicians, two nurses, and four other hospital staff) were infected by the second patient.[61] The cases occurred in widely separated areas of the country. By the time of diagnosis, the 150 secondary cases had already begun to expose yet another generation, and, inevitably, questions arose as to how many other yet undetected cases there might be.[62]

Health authorities launched a nationwide vaccination campaign. Mass vaccination clinics were held, and checkpoints along roads were established to examine vaccination certificates. Twenty million persons were vaccinated. Hotels and residential apartments were taken over, cordoned off by the military, and all known contacts of cases were forced into these centers under military guard.[63] Some 10,000 persons spent 2 weeks or more in isolation. Meanwhile, neighboring countries closed

[52-53] de Rugy, Veronique and Charles V. Pena, "Responding to the Threat of Smallpox Bio-terrorism", No. 434, Cato Institute, Washington D.C., 18 April 2002. p.4.

[54] Henderson, D.A., "Smallpox: Clinical and epidemiological features", Emerging Infectious Diseases, Vol.5, No.4, Centers for Disease Control and Prevention, Atlanta, 1999.

[55] Henderson, D.A., Inglesby, T.V., Bartlett, J.G., Ascher, M.S., Eitzen, E., Jahrling, P.B., Hauer, J., Layton, M., McDade, J., Osterhoim, M.T., O'Toole, T., Parker, G., Perl, T., Russell, P.K., & Tonat, K., (1999). "Smallpox as a biological weapon: Medical and public health management", JAMA, The Journal of the American Medical Association, Vol. 281, No. 22, 1999.

[56] Shepard, H.R., and Peter J. Hotez, "The First Great Terror of the 21st Century", Sabin Vaccine Report 3, No.2 (Winter 2001).

[57-63] Henderson, D.A., "Bioterrorism as a Public Health Threat", Emerging Infectious Diseases, Vol. 4, No.3. Centers for Disease Control and Prevention, Atlanta, July-September 1998.

their borders. Nine weeks after the first patient became ill, the outbreak stopped. In all, 175 patients contracted smallpox, and 35 died.[64]

What might happen if smallpox were released today?

The current ring containment strategy of administering smallpox vaccinations only after an outbreak in the hope of containing the spread of the virus favored by the US Federal Government and some European Member States is appropriate for dealing with a natural outbreak of smallpox, but it is likely to be woefully inadequate for countering a direct attack by a thinking enemy intent on inflicting mass infection, death and panic.[65] If smallpox were released today across several member states simultaneously or staggered with interval releases every few days the outcome could be devastating. As with the index case in Yugoslavia, few practitioners could differentiate smallpox from the flu in the initial stages. Training, for first responders and medical practitioners could increase vigilance. Moreover educating and informing the public of the potential for unusual disease outbreaks may reduce the risk of panic or civil unrest during an attack. While most Member States as well as the US government have decided upon a ring vaccination strategy, the public should be informed of what this means, why it is the dominant policy and what steps to take during an emergency public health crisis.

Points to Consider:

- Should the EU develop a separate public health response plan to bio-terrorism than its current reliance on the natural disease outbreak paradigm?

- Flexible and responsive bio-manufacturing infrastructures are an essential part of an effective overall strategy for bio-terrorism preparedness[66] ; what role can national and European level policies play toward ensuring the research and development on select agents for counter-measures to prevent and treat deliberate diseases receives priority as a preparedness option?

- In the event of a bio-terrorism attack should national governments offer the public vaccination on demand?

- What needs to be done to ensure new Member States are prepared (sufficient vaccine stockpiles, adequate and standard laboratory capacity and the ability to participate in surveillance programmes) to counter a major bio-terrorism event?

We need to be as prepared to detect, diagnose, characterize epidemiologically, and respond appropriately to biological weapons use as to the threat of new and reemerging infections. In fact, the needs are convergent. We need at international, state, and local levels a greater capacity for surveillance; a far better network of laboratories and better diagnostic instruments; and a more adequate cadre of trained epidemiologists, clinicians, and researchers. [67]

On the immediate horizon, we cannot delay the development and implementation of strategic plans for coping with civilian bioterrorism. The needed stocking of vaccines and drugs as well as the training and mobilization of health workers, both public and private, at state, city, and local levels will require time. Knowing well what little has been done.[68]

Summary

A range of proposals were presented as advantageous to European policy for increasing public health security, improving our preparedness and response to bio-terrorism. The vexing questions which remain are who should lead? Who will take responsibility during an actual attack? Which institution will coordinate these efforts and delegate specific activities to be undertaken rapidly? Who will be in charge of both the security and public health response? One example of the problem and possible solution is reflected in the Select Committee on Science and Technology Eighth Report to the United Kingdom Parliament. Herein the Select Committee stated:

[64] Henderson, D.A., "Bioterrorism as a Public Health Threat", Emerging Infectious Diseases, Vol. 4, No.3. Centers for Disease Control and Prevention, Atlanta, July-September 1998.

[65] de Rugy, Veronique and Charles V. Pena, "Responding to the Threat of Smallpox Bio-terrorism", No. 434, Cato Institute, Washington D.C., 18 April 2002. p.4.

[66] Kocik, Janusz, "Preparedness against bioterrorism and reemerging infectious diseases: regional capabilities, needs and expectations in Central and Eastern European Countries", NATO Advanced Research Workshop, Warsaw, Poland, January 15-18 2003. p.12. URL:http://www.onrglobal.navy.mil/reports/csp/2003/2003CSP1011.doc.

[67-68] Henderson, D.A., "Bioterrorism as a Public Health Threat", Emerging Infectious Diseases, Vol. 4, No.3. Centers for Disease Control and Prevention, Atlanta, July-September 1998

"There seems to be a range of risk assessments, particularly within the Department of Health (DoH). It is not clear who in Government is responsible for determining what threats the UK should be responding to, and with what priorities. We have not established how risk assessments are informing Government policy and thus the scientific response. There should be a single assessment, informed by science and intelligence, which is communicated clearly to all those who need to make strategic decisions on funding allocations. We hope that the Joint Terrorism Analysis Centre can fulfill this function." [69]

This statement would seem to reflect the very basic dilemma which faced experts at the Bio-Terrorism Reporting Group. If each Member State cannot answer such questions then there could be problems which would lead to breakdown in response and preparedness. A breakdown during a major bio-terror event could devastate populations not only in Europe but compromise international health security. It is therefore imperative we determine exactly where the gaps are and what needs to be done to close those gaps now.

Key Points

- It was difficult to determine who should and would lead during a major bio-terrorism attack;
- Fragmented infrastructure was sighted as obstructive to strengthening collaboration:
- Standardizing a range of bio-safety and bio-security measures was promoted as advantageous;
- Variation in bio-defence vaccine stockpiling could pose a serious problem and lead to civil unrest if standards are not set to harmonize policies on stockpiling and production;
- The ability to conduct research on Class A select agents is necessary and increasing P3 level capacity could strengthen the existing laboratory capacity;
- The World Health Organization could play a key role in communication of disease outbreak in real-time; provide expertise on containment and control and epidemiology support to national and European level efforts to stamp out a disease caused by bio-terrorism. WHO could also assist in rapidly obtaining vaccines, bifurcated needles and VIG in the event of a smallpox outbreak.
- WHO recommends each country prepare a Smallpox Preparedness Plan; as Europe is now an open border area should we prepare a European Plan to counter the threat of Smallpox?

Conclusion

Contemporary threats are of an entirely different nature and scale than hitherto.[70] Moreover the current responses to such threats appear increasingly inadequate. Weapons developed to counter threats at the end of the last millennium will not sufficiently meet the challenges of the 21st Century.[71] Yet beyond specific technologies, fresh thinking is required to cope with the new environment.[72] We must be careful when considering the nature and type of threats likely to occur in the future that we do not position such threats based on a limited or culturally pre-conceived concept. We must be careful not to transfer how we think governments or individuals will act onto the potential actions of the enemy.

A new approach is critical because terrorism is just one of many, non-traditional security challenges.[73] Such threats - where conflict and crime often merge - respect no boundaries; all too often, there are no leaders or legions against which to focus attention or target a response.[74] Given advances in science and technology and the potential for biological pathogens to rapidly cross borders and infect thousands of people, how can we best prepare for biological terrorism and the possible use of Weapons of Mass Destruction?

Facing 'next generation' challenges will require wider thinking both in terms of the potential for biological terrorism and increasing our ability to respond from multiple platforms i.e. regulatory, scientific, technical and security levels. Despite current emphasis on non-state actors, it is important to remain cognoscente of the threat posed by state actors as well. The so-called 'listed' states still pose a real threat

[69] Henderson, D.A., "Bioterrorism as a Public Health Threat", Emerging Infectious Diseases, Vol. 4, No.3. Centers for Disease Control and Prevention, Atlanta, July-September 1998

[70-74] Hall, Robert and Carl Fox, "Rethinking Security", NATO Review, Vol. 49, No.4, Winter 2001, pp. 9-11. URL: http://www.nato.int/docu/review/2001/0104-02.htm

to international security. A recent report on biological weapons by the National Intelligence Council stated that more than a dozen states are known to possess or are actively pursuing offensive biological capabilities.[75] The European Union is at a very definitive crossroads. We can choose to prepare to respond and hope to never face mass casualty bio-terrorism, or we can fail to prepare and accept the risks that come with this decision. Given the possible outcome, a moderate approach would be to hope for the best and prepare for the worst. We must now put policies in place to ensure proper response and reduce the risk of bio-terrorism.

[75] Cilluff, Frank J., and Daniel Rankin, "Fighting Terrorism", NATO Review, Vol. 49.No.4, Winter 2001, pp.12-15. URL: http://www.nato.int/docu/review/2001/0104-03.htm

The need for EU consensus to deal with a bioterrorist attack

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The experts participating in the NDA meeting on October 18th are in a unique position to be able to influence and facilitate the development of a consensus view on bioterrorism preparedness within the EU. It is essential that there is agreement within the EU on policies such as alert response protocols and stockpiling of vaccines to counteract a bioterrorist attack. Without a co-ordinated plan, an attack or even a suspected attack could lead to civil unrest.

The scenario of a smallpox attack provides a good model to outline the potential problems of an uncoordinated approach within Europe. Smallpox and anthrax are the only two Category A bioterror agents for which there is a vaccine. Of the two, smallpox is considered to be the more complex to deal with because it is transmissible from person to person, there is no proven treatment and it is difficult to distinguish from less serious diseases such as chickenpox. However, there is a vaccine known to prevent the disease and the vaccine can be used up to four days after exposure to the virus.

The basic outbreak control response for bioterror agents where there is no vaccine or treatment is simply detection and isolation of cases. For smallpox and anthrax, this basic control response is required but there is the additional control option of vaccination available. At present, EU Member States appear to

have different alert response protocols in place. Recent international exercises such as Global Mercury highlighted some of the difficulties in co-ordinating a response. Member States have different approaches to stockpiling of smallpox vaccine, ranging from stockpiles of one dose per citizen through to stockpiles of one dose per 30 citizens. There are also difference in the type of vaccine held, with some countries stockpiling modern, licensable cell culture vaccines and others stockpiling old animal lymph derived vaccine which is not now licensable.

Example scenario:

Country A has sufficient smallpox vaccine to provide a dose per citizen. The preparedness response plans state that it will begin vaccination of first responders once there is a confirmed case of smallpox anywhere in the world.

Country B has only a limited stockpile of smallpox vaccine, insufficient to provide a dose per citizen. The policy in Country B is not to start vaccinating first responders until there is a confirmed case of smallpox in their country.

Scenario:

1 There is a confirmed case of smallpox in neighbouring Country C

- Country A begins to vaccinate first responders
- Country B does not begin to vaccinate first responders

2 There is public concern and demand for vaccination in Country B

- The public in Country B are aware that there is only enough vaccine for a small percentage of the population
- It is known that Country A has a stockpile large enough to provide a dose of vaccine per citizen
- Citizens start to cross from Country B to Country A

This scenario is likely to be much worse if we were to consider the situation where one country moves to implement a policy of mass vaccination rather than ring vaccination during an outbreak. The response needs to be coordinated across EU to prevent civil unrest.

In summary, the EU needs to act as one to deal with a bioterror attack. For this to happen, there needs to be consensus on when to move to the next alert level, what the response protocol should be and, in the case of smallpox, when vaccination will begin. With specific regard to smallpox, if countries within the EU have an agreed stockpiling strategy, even just an agreed base level coverage of the population, this should provide more public reassurance in the event of a smallpox release.

Recombinant Vaccinia immune globulin (VIG) for biodefense use

Dr. John Haurum
CSO, Symphogen

Dr. John Haurum

Although smallpox was eradicated in 1980, bioterrorism has reintroduced smallpox as a potential threat to public health. The US and some of the European governments are for this reason ordering large quantities of vaccines for stockpiling with the aim of having up to one dose per citizen.

Smallpox is caused by airway infection with the orthopox virus Variola. Serum from Smallpox convalescents have used to treat smallpox infection. Endemic smallpox has been eradicated as a consequence of worldwide prophylactic vaccination programs using the related orthopox Vaccinia virus.

Unfortunately, Vaccinia virus vaccination results in moderate to severe adverse reactions in approximately one in every 10,000 vaccinated, and this is too high a frequency to allow mass vaccination of the general population. Anti-Vaccinia virus serum has previously been reported to be efficient in treating the vaccine-related adverse effects and the protective effect of neutralizing pAb against Vaccinia virus has been established in mice. Monoclonal antibodies have also been shown to block Vaccinia virus infectivity in vitro and in vivo.

Given the antigen complexity of Vaccinia virus a polyclonal antibody would likely be superior to mAb in mediating protection in a natural out-bred population. Thus, we propose that a recombinant polyclonal Vaccinia virus-specific antibody for treatment of vaccine-associated adverse reactions would facilitate general and safe mass vaccination programs.

Importantly, such a Vaccinia virus-specific recombinant polyclonal antibody might also be effective as pre- or post-exposure prophylaxis against smallpox.

Current VIG manufacturing is based on blood sampling from individuals exhibiting a high Vaccinia virus titer, and purification of the immunoglobulin fraction. This product is in short supply, very expensive to produce, of low titer, associated with inherent risks of transmission of human donor-derived pathogens, and problems with batch-to-batch variability.

Symphogen is developing a second generation recombinant VIG based on the Company proprietary antibody discovery and polyclonal antibody manufacturing platforms. Biological proof of concept is expected in 2005.

The project is performed in collaboration with Health Protection Agency (HPA) who is responsible for delivering blood samples from recently vaccinated donors and conducting the preclinical proof of concept studies. The aim is to replace existing anti-Vaccinia virus hyperimmune immunoglobulins (VIG) for treatment of adverse effects in connection with Vaccinia virus vaccination against smallpox and as a biodefense agent for post-exposure prophylactic or therapeutic use against smallpox virus. The project is fully funded by Symphogen and the Company retains all commercial rights to the results from the collaboration. The Company intends to apply for US and EU government research funding for manufacturing and clinical development.

Immunological biodefense agents

The only countermeasure which is active against most human viral infections or bacterial toxins is the human immune system. This is the basis for the victorious entry of vaccines in the history of human medicine. Thus, vaccines act to induce novel or boost preexisting immunity resulting in a subsequent increased state of immunity against the corresponding pathogen in the form of circulating, pathogen-specific polyclonal antibodies (pAb).

The appearance in the body of such circulating pathogen-specific antibodies can obviously also be brought about by direct administration of therapeutic antibody compositions, either therapeutically or prophylactically. The major advantage of this approach is the immediate efficacy of the procedure, since antibodies are active immediately after injection. Vaccines on the other hand have a lag period of over a week before the appearance of protective levels of antibodies. Also, vaccines are less efficient in immune compromised individuals such as elderly people and vaccines may be associated with adverse reactions, such as it has been observed with Vaccinia virus vaccination against smallpox.

Biodefense agents for use against biological weapons of mass destruction such as viruses, bacteria or bacterial toxins needs to be fast-acting and broadly reactive, which is a key characteristic of antigen-specific polyclonal antibodies. Human polyclonal antibodies has a serum half-life of approximately 25 days upon administration, thus offering an opportunity for the prophylactic use of neutralizing pathogen-specific pAb in high-risk groups such as military personnel and healthcare workers during an imminent threat of exposure or as post-exposure prophylaxis. Due to the immediate immunopharmacological efficacy, pathogen-specific pAb may also be applicable for use in post-exposure therapy. Pathogen-specific polyclonal antibodies can also be administered in combination with vaccines to combine immediate protection with long term immunity, as it has been described for rabies and hepatitis B virus. In addition, polyclonal antibodies can be used in combination with antibiotics to afford broad-spectrum microbial neutralization following exposure to hard-to-treat pathogens. Collectively, their pharmacology and the spectrum of potential prophylactic and therapeutic uses make pathogen-specific polyclonal antibodies attractive remedies in both military and civilian defense against biowarfare agents.

Many existing hyperimmune immuno-globulin -based antibody products are relatively low titered and therefore have to be administered by slow intravenous infusion. This is clearly not compatible with efficient mass prophylaxis after pathogen exposure. For this purpose, high titered polyclonal antibodies formulated for small-volume parenteral (intramuscular) injection and even single-use self-administration systems may be warranted. However, the combination of recombinant polyclonal antibody technology and modern mammalian expression technologies may be able to offer such high titered therapeutics. Also, this approach might potentially eliminate the problem with limited supplies of existing plasma-based polyclonal antibody products.

Design of antibodies for use in biodefense

To offer broad protection against biowarfare agents such as viruses or bacteria in a large population, pathogen-specific polyclonal antibodies ideally should encompass a broad range of reactivities against the given pathogen, in order to counter that the microorganism may escape neutralizing antibodies through mutations in the epitopes recognized, as has been described for a number of viruses after antibody treatment. The therapeutic implication is that pAb reacting with several epitopes on the same viral protein should be superior to a mAb which inherently only reacts with a single viral epitope. Thus, it is much less likely that individual viral particles should fortuitously accumulate sufficient mutations to simultaneously escape neutralization of all the antibody specificities in a polyclonal antibody composition targeting multiple epitopes. Also, several viruses exist naturally in a range of strain subtypes, with obvious implications for the need of a carefully designed, broadly reactive reagent.

Similar considerations hold true for bacterial pathogens; a diverse antibody response should lead to more efficacious eradication of a bacterial pathogen. In addition, several bacterial toxins and superantigens exist in multiple variant forms and antibody mixtures have been shown to be more efficient than mAb's in mediating botulinum toxin neutralization.

In addition, microbial mutations could be intentionally induced, by genetic manipulation for example, in order to make pathogens more lethal for biowarfare use. Such mutations may make the pathogen less sensitive to known mAb therapeutics, but might not be able to afford escape of recognition by polyclonal antibodies.

Pathogen-specific Recombinant Polyclonal Antibodies

Currently existing therapeutic antibodies can be grouped into two different generations of antibodies, each displaying one of the two unique features of the immune system, diversity and specificity.

Antibodies derived from human plasma, so-called immunoglobulin, represent the first generation of therapeutic antibodies, and carry the natural diversity of human antibody responses as an inborn strength. Such products have been on the market for decades, and represent a market of USD 3-4 billion today. The second generation of therapeutic antibodies is manufactured as recombinant monoclonal antibodies (mAb) and is characterized by high specificity towards a single, well-described antigen. The introduction of new technologies which make it possible to humanize animal-derived antibodies has made monoclonal antibodies the most important drug class in the pharmaceutical industry with estimated total sales around USD 20 billion by 2010.

Symphogen provides a totally new class of therapeutic antibodies which capture both aspects of the immune system, namely the natural diversity and the specificity. Thus, through its proprietary technologies, the Company aims to produce target-specific recombinant human polyclonal antibody preparations. Such recombinant polyclonal antibodies (rpAb) will prove superior to existing antibody preparations against complex antigens such as infectious disease agents, toxins, and bacteria since they mirror the natural antibody-response produced by humans. The so-called SympressTM manufacturing technology eliminates any cellular growth biases in the polyclonal manufacturing cell bank, thereby producing a technology for robust industrial manufacturing of recombinant polyclonal antibodies.

The first project of the Company is currently undergoing cGMP manufacturing with a contract manufacturer and the first drug development program (a replacement of donor blood-derived rhesus D-specific hyperimmune immunoglobulin used to prevent hemolytic disease of the newborn) is expected to move into the clinic in 2006.

Symphogen's technology is also useful for the generation of novel biodefense agents. Thus, for most of the biowarfare agents listed by NIH as category A biowarfare pathogens, antibodies are a strong immune correlate of survival.

The use of passive immunotherapy against anthrax, hemorrhagic viruses, botulinum neurotoxins, plaque, tularemia, smallpox virus has shown promises in animal models or in humans. Symphogen proposes to develop high-titered recombinant antibody products, which are efficient both in preventing and treating several of these pathogens.

Advantages over immunoglobulin-derived products of rpAb include the ability to produce rpAb in unlimited supply against any target of choice, while eliminating the dependency on unstable blood donor supply and the complicated logistics of blood collection. Also, the composition can be manipulated beyond what is possible with immunoglobulins, including the ability to ensure coverage against several microbial serotypes, and the elimination of unwanted reactivities through negative selection. Finally, there is no risk of transmission of donor-derived pathogens, minimized lot-to-lot variability, and absence of irrelevant, non-specific antibodies, leading to high specific activity and an expected manufacturing cost which is comparable to mAb.

Advantages of rpAb over mAb include the ability to deliver a product which maintains heterogeneity in the reactivity towards the target (broad-spectrum reactivity) as well as heterogeneity in isotype and effector functions, if desired. Thus, activity is maintained against complex antigens including microorganisms of multiple serovariants. In addition, immune escape is less likely, thus making these drugs potentially more efficient in the face of natural microbial variation, or against microbial variation induced by terrorists.

Involvement of the biopharmaceutical industry

The business model of the biopharmaceutical industry and especially of the smaller, innovative biotech industry in development of novel biodefense agents hinges upon clarifying the potential product market. Thus, for investor-backed companies to choose to enter into research and development of biodefense agents, for which there is commonly no conventional market for the product, alternative business opportunities must be made clearly available by governments and governmental organizations. One way to ensure this is to issue calls for tender in the form of e.g. EU Commission proposals which define clear characteristics to be met by the development of novel products. If such characteristics can be met then the issued contract should guarantee procurement of a certain amount of that product from the biotech drug development company. Such a novel funding structure through public tender for acquisition of specific biodefense products would allow companies to assess the potential market directly from the call and thus eliminate the commercial risk attached to the project portfolio decisions stemming from the unknown market size.

Particularities of Acquisition in Medical Research: Pharmaceutical Product for NBC Medical Protection as Orphan Products

Dr. Florin Paul
MD, PhD, MPH, Deputy Surgeon General,
Romanian Ministry of National Defence Medical Directorate

Introduction

Recent worldwide terrorist acts and hoaxes have heightened awareness that incidents involving weapons of mass destruction (WMD) may occur everywhere. This fact requires the development of preparedness programs to train and equip emergency services and emergency department personnel in the management of large numbers of casualties exposed to nuclear, biological, or chemical (NBC) agents. Hospital pharmacies and national pharmaceutical stockpiles will be required to provide antidotes, antibiotics, antitoxins, and other pharmaceuticals, in large amount and have the capability for prompt procurement. There is no doubts that both physicians and pharmacists should became knowledgeable in drug therapy of NBC threats with respect to nerve agents, cyanides, pulmonary irritants, radionucleotides, biological agents as antrax or botulism, and other possible WMD.

Protection against nuclear, bacteriological and chemical hazards and emergency treatment of induced toxic effects is based

on antidotes and special pharmaceutical products, other than current drugs. These pharmaceutical products should be included in the "orphan drugs" group that includes also the medicines used in more than 3000 rare and very rare diseases. Antidotes and other pharmaceutical products as vaccines or antitoxins are called "orphan drugs", in the sense that, following their sporadic use in normal times, their production is not profitable for pharmaceutical companies.

The development of drugs for these diseases, intended for a limited number of patients, often require considerable research, and subsequently, cost. A particular approach of ethical, political and economical problems relevant for development and disposal of orphan drugs is also required.

The registration of this special means encounters high difficulties in almost all countries, following their inclusion in the category of usual drugs. A lot of requirements concerning a very wide, preclinical and clinical investigation, which practically hinders registration of antidotes and makes no sense in case of these special pharmaceutical products.

Complying with such requirements can lead to drastic reduction of the availability and to long delays in obtaining the approval for registration and industrial production.

Mass casualty in NBC disasters, require immediate availability of antidotes and special pharmaceutical products that can save the live of affected population.

In respect to this issue in USA and European Union special legal provisions were released to facilitate the production and use of orphan drugs.

These stipulations would provide to society a tool for imposing on pharmaceutical companies to support an important part of these expenses for production of "less profitable" orphan drugs, especially that are for NBC medical protection of the population.

Particularities of NBC orphan drug research and production

The lack of financial profit of the production of orphan drug production is the main obstacle in achievement of the protection task. NBC orphan drugs (NBC-OD) are necessary in large amount, only in "critical situations" (war, natural or technological disaster, terrorist attack etc.). Practically all NBC-OD, with very few exceptions, like anthrax vaccine, have no "civil" use, as drugs. Another serious difficulty arises from the assimilation of NBC-OD with common drugs.

Almost all NBC-OD do not fulfill the requirements for registration as drugs; their registration must be leaded by other rules.

The technical difficulties in research, production and use of NBC-OD are less known. These difficulties come first from special requirements imposed to NBC-OD.

The requirements for treatment of chemical and antitoxin NBC-OD are:

- increased stability;
- self-administration;
- universal action;
- high efficiency;
- instantaneous onset of action.

Preventive antidotes, protectors and decorporators must have:

- lack of incapacitating effects;
- oral or percutaneous administration;
- lack of adverse effects after long term and many administrations;
- longer biological half-life after administration.

The requirements for vaccines, immune treatment prophylaxis products and antibiotic are:

- rapid efficacy and high immunogenesis effects;
- availability and long shelve time;
- stability of microbial strain used in vaccine;
- covering the entire antigenic profile of the targeted pathogen;
- wide spectrum for antibiotics and no special condition for preservation;
- appropriate conditions for storage, transportation and usage for large areas;
- quality control for immune serum in order to avoid transmission of other diseases, as hepatitis B and C, HIV infection etc.

All these requirements are difficult to be achieved, some of them being rather contradictory.

Particularities in acquisition of antidotes – registration, delivery and usage

Antidotes are listed and classified in accordance with their effectiveness and availability (Table 1). Antidotes reduce the overall burden of health service in managing of poisoning cases.

In developing countries that lack adequate facilities for intensive therapy of poisoned people, antidotes may be more essential in the prevention and treatment of poisoning. But availability of antidotes is different from one country to another. In developing countries, physicians reported difficulties in obtaining even common antidotes. Even in industrialized countries, could be noticed administrative difficulties and the lack of suitable drugs (pharmaceutical formulation, concentration etc.).

A very important issue is that pharmaceutical companies may hinder the access to certain antidotes from different reasons.

Difficulties in obtaining of adequate availability arose from three interrelated areas: scientific and economical, regulatory and administrative requirements, and managing distribution in crisis.

Governments and chemical industries are responsible for ensuring comprehensive scientific studies for regulatory authorities to accept registration of effective antidotes.

In the same time pharmaceutical companies involved in production of antidotes must be encouraged to register their products in their own countries.

In this respect, is very helpful that administrative procedures of registration and disposal of an antidote, for example, to comply with international rules regarding the orphan drugs.

Pharmaceutical companies will manufacture and supply antidotes only if they are encouraged by adequate economic refunds for their investment and by simple registration procedures.

Particular aspect regards common drugs (active substance) used in therapy that could be used successfully as antidotes, but in different formula or concentration. In that condition additional authorization is required. Important is that procedure for authorization to be simplified. Authorities need to accept similar criteria for registration of a new antidote (less comprehensive that than for normal drug) as, for example, for anticancer or anti AIDS agents because of the special conditions of their use.

Particularities of acquisition of vaccines

The development of vaccine against rare emergent infectious diseases is hampered by many disincentives.

Vaccine development involves a substantial investment in time, effort, and resources. Any public or private research and producing facility should allocate huge financial and human rescues when development of vaccine is decided. The cost from research to licensure, the risks inherent in vaccine development (e.g. technological constraints, regulatory approval) and short- or long-term evaluations of scientific and financial results may constrain this activity. In the developing world, price has been a major impediment to the introduction of new vaccines.

Reliable information on the epidemiology, disease severity, and effect on public health is essential to sustain the need for a vaccine. The authorities must develop the policy to prevent infectious diseases and in the same time countermeasures against effects of biological weapons attack.

Development of orphan vaccines is guided by the limited need for or markets potential of the product, with the accompanying regulations, as well as the specific characteristics of the vaccine and those who need it. After September 11th, 2001, the threats of biological attack open perspectives for acquisition of new vaccines and immune-prophylaxis products.

However, research for new effective products needs long time, and the development of any orphan vaccine should be broadly supported by measures to increase the awareness of immunization benefits at three levels – the decision-makers, the care-givers, and the patients.

Developments in biotechnology have created the promise of prevention for many more infectious diseases and chronic diseases and build the confidence in acquiring new effective measures against biological warfare agents.

Particularities in stockpiling and delivering of pharmaceutical products

The availability of an NBC-OD is highly dependent on its manufacturing, delivery procedures, and economic power of society.

The costs of procurement of NBC-OD is a sensitive issue, looking to developing countries that can not afford high expenditures even in crisis situation.

By the other hand it is practically impossible that all countries to develop production facilities for the whole range of NBC-OD.

In circumstances of increasing the threat of international terrorism, and attack with WMD, the regional and international cooperation become mandatory. A part of this cooperation is the availability of NBC-OD for affected population. In same cases, like biological attack, the affected area could be larger, pathogens crossing the political or administrative borders.

If certain NBC-OD are not available from local manufactures and must be imported there are two alternative solutions: to establish a manufacturing facility (or a pharmacy laboratory) supported with government funds or the establishment of a central agency for import and distribution of antidotes, under governmental control. The decision depends on the economical and technological capabilities.

Storage facilities for NBC-OD require specific conditions:

- distance from medical facilities and transportation facilities (airport,roads);
- inside temperature and humidity;
- communications;
- building safety in case of WMD attack, natural or technological disaster;
- capacity of storage;
- real time of intervention.

The amount and the type of NBC-OD reserve depend on:

- size and geographical profile of the exposed area to WMD attack;
- nature of potential NBC hazard;
- number and density of population in the affected area;
- distances to medical care facilities from theater, communications etc.

Conclusions

- international and regional consensus in fighting against WMD threats and elaboration of common strategy of intervention in crisis situation;
- governmental support for developing the facilities for production, import and storage of NBC-OD;
- simplifying the methodology of registration and approval for NBC-OD, and special legal provisions in this respect is mandatory;
- development of international and regional programs for scientific research, production and distribution of NBC-OD appear as an urgent requirement in fighting the NBC threats and international terrorism.

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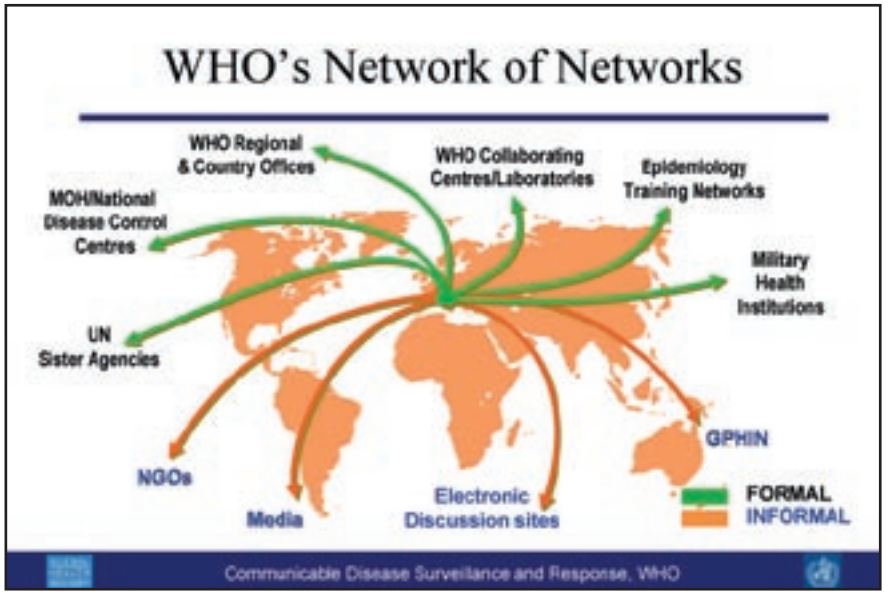
WHO Presentation

Dr. Randall Hyer

Dr. Randall Hyer

Medical Officer, Civil Military Liaison Activity and Alert and Response Operations, World Health Organisation (WHO)

The following slides are part of an introductory presentation given by Dr. Hyer at the 18 October meeting.



Simplified Containment
smallpox eradication, 1967–1978

Multipuncture vaccination by bifurcated needle

Communicable Disease Surveillance and Response, WHO

Lessons Learned: smallpox eradication

- Disease eradication saves lives and decreases human suffering and cannot be completed without strong international partnership
- Interaction of previously unrecognized infectious diseases may interfere with safe use of previous interventions
- Vaccine stockpiles must be maintained post-eradication, but the risk associated with routine immunization may be greater than the known risk of the disease itself
- Research and development of safer vaccines and anti-viral or bacterial drugs must be continued post-eradication/countries must be prepared
- Systems must be in place for continued surveillance, investigation and containment post-eradication

Communicable Disease Surveillance and Response, WHO

Smallpox Eradication
public health optimism

- **In 1967**
  - cost in lives — over 1.5 million
  - cost to the world — US$ 1,400 million
  - cost for vaccination in USA alone — US$ 92.8 million
- **1967–1979**
  - cost of eradication: — US$ 300 million

USA saves equivalent of its investment in WHO smallpox eradication campaign every 26 days

Communicable Disease Surveillance and Response, WHO

Reports to WHO of smallpox-like disease, 1 January 2000–15 July 2002

- 8 reports of **smallpox** from 5 different WHO Regions:
  - 1 accidental exposure to *Vaccinia virus* (8 children hospitalized)
  - 2 varicella outbreaks
  - 1 measles outbreak
  - 4 single cases, not clinically smallpox but aetiology unproven
- 25 outbreaks of suspected **human monkeypox** (all but one in the Democratic Republic of the Congo)
  - 11 were laboratory-confirmed as monkeypox
  - 4 were varicella
  - 8 laboratory results are pending/being re-confirmed
  - 2 laboratory investigations were not possible

Communicable Disease Surveillance and Response, WHO

Improving Preparedness

preparedness for deliberate epidemics

http://www.who.int/csr/delibepidemics/en/

deliberate@who.int to answer questions on WHO's activities on BCW

WHO Smallpox Vaccine Bank

- Long incubation period, highly contagious, no effective drug therapy
- 1979 – 200 million doses, two sites
  - Reduced to ~2.5 million doses in 1980s
- 500 million doses estimated need

Smallpox Today

- Ad hoc advisory group on orthopox infections continues same recommendations for vaccine use
- Reports of virus outside two WHO repositories
- Between 90-100 million doses of smallpox vaccine remain in the world but stockpile is increasing
- Insignificant amounts of vaccinia immune globulin available
- No effective antiviral cure
- Intensified research on new vaccines, antivirals and diagnostics in US and Russia/virus retention
- Industry scaling up vaccinia vaccine production
- Countries stockpiling vaccine

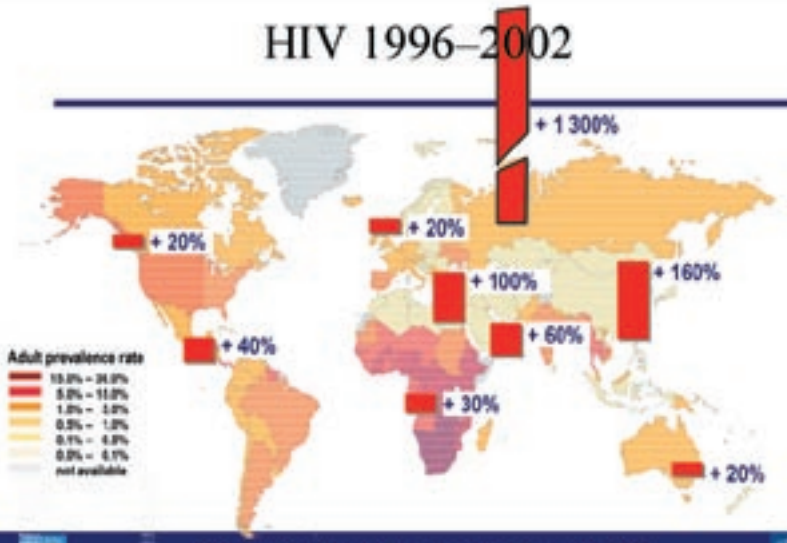
500 Million Doses?

- Possibility of simultaneous, deliberate releases, multiple locations, different routes
- Lack of clinical familiarity
- Inadequate national capacity to detect and confirm
- Increased global population level, density, mobility, international travel
- Decrease in people immune
- Seven month lag for mass production of vaccine

Considerations

- Pledged vacccine stocks become WHO property once released during emergencies
  - Independent of any bilateral arrangements
- Disclaimer absolving WHO and original owner of all liability arising from use
- Use of vaccine in absence of real exposure risk is not warranted
- Proven approach of search and containment procedures in conjunction with ring vaccination

HIV 1996–2002

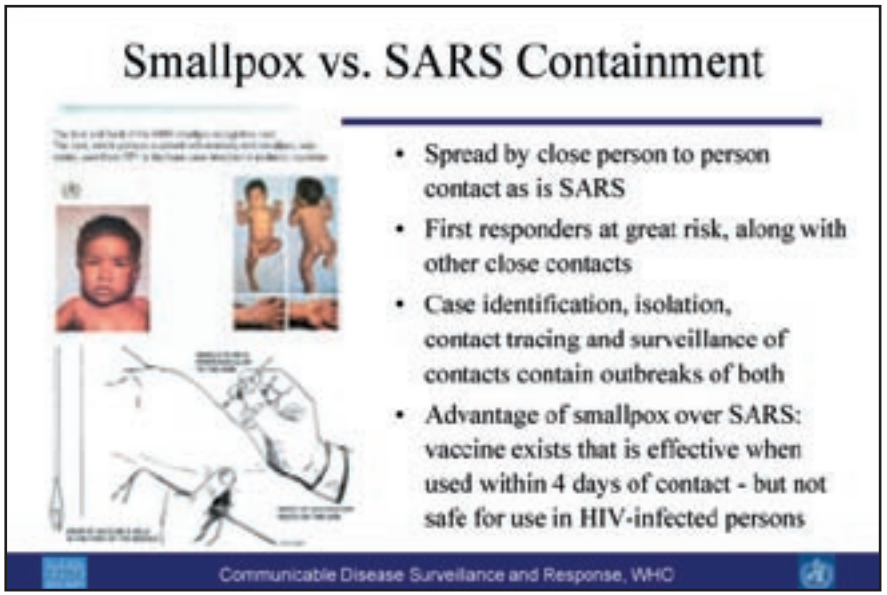


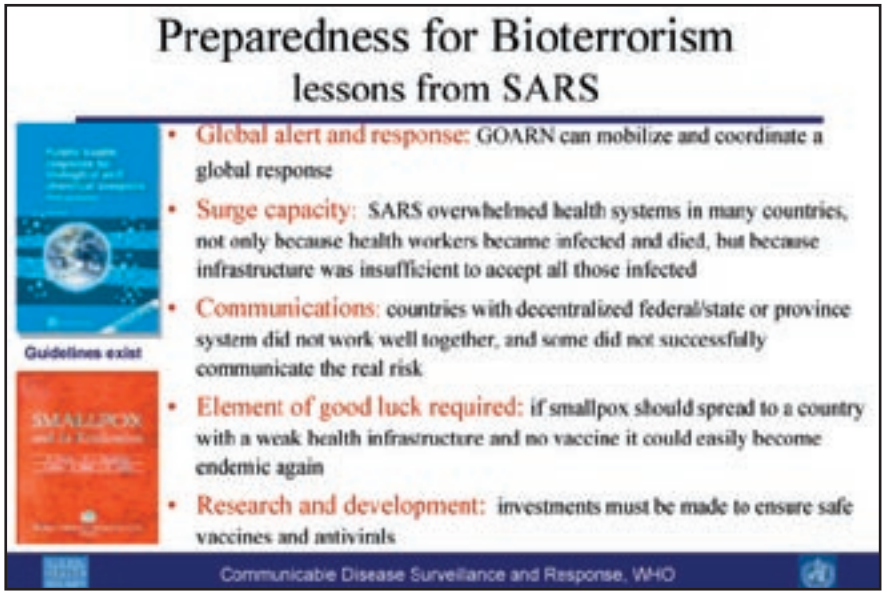
Ad Hoc and IHR Emergency Committees

- Basic descriptive epidemiology
- Country vaccine supplies, capacity to vaccinate
- Population immunity
- Logistics for secure vaccine transport
- Primary responders needing vaccination
- Security
- Lab capacity
- Volume of national and international traffic
- Communications infrastructure

Strategies that Contained SARS

- Case identification (active surveillance)
- Case isolation/hospital infection control
- Contact tracing
- Surveillance/quarantine of contacts
- International travel recommendations based on epidemiological evidence
- Element of good fortune
  - did not spread to countries with weakest health systems





About the New Defence Agenda (NDA)

The New Defence Agenda was launched in 2002 under the Presidency of Eduardo Serra, former Spanish defence minister, and under the co-patronage of Lord Robertson, Javier Solana and Chris Patten. Under this patronage and with the close collaboration of prominent defence experts drawn from a cross-section of government, politics and industry, the NDA quickly established itself as the only regular forum in Brussels devoted to debating the future of defence and security policies.

NDA is also a networking centre of defence-related think-tanks around Europe, and has strong contacts with the Brussels-based press corps – the largest international press corps of the world. The NDA's success is based on the support of a wide-range of institutions, industries, government representations and think tanks. Because of their continued support, the New Defence Agenda brings clarity and new ideas to the rapidly-changing defence policy scene through its monthly roundtables and regular international conferences, press dinners and publications.

Bringing clarity and new ideas to the fast-changing defence policy scene has been the NDA's aim from the start. We see ourselves as a builder of partnerships with nationally-based defence think-tanks whose expertise needs to be more widely shared with other analysts and with European-level decision-takers.

NDA brings together a wide range of actors in the security and defence world and its activities range from monthly roundtables, international conference, press dinners, reports and discussion papers, which attract high-level speakers and industry support.

One of our prime objectives is to raise the profile of defence and security issues among the Brussels-based international press. To encourage more in-depth coverage of defence and security topics holds regular, informal dinners for journalists.

Its patrons Javier Solana and Chris Patten have backed the initiative from the start along with NDA's president, Eduardo Serra, former Spanish defence minister. The NDA's Advisory Board is made of some 20 prominent defence experts drawn from a cross-section of government, politics and industry.

Recent NDA Events 2004

DOES EUROPE NEED A BLACK SEA SECURITY POLICY?

Roundtable, 20 September 2004

Speakers included

Oksana Antonenko
Programme Director (Russia and Eurasia), International Institute for Strategic Studies (IISS)

Sergei Konoplyov
Director, Harvard Black Sea Security Program

Ovidiu Dranga
Director General, Department for Defence Policy and Euro-Atlantic Integration, Ministry of National Defence, Romania

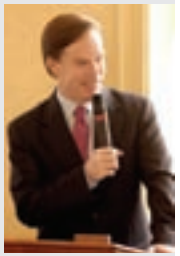
Yannis N. Papanicolaou
Director General, International Center for Black Sea Studies, Greece

Rear Admiral Serdar Dülger
Chief of Plans and Policy Department, Ministry of National Defence, Turkey

VIP Lunch with **Ambassador Turan Morali**, *Director General for International Security, Ministry of Foreign Affairs, Turkey*

ON THE EVE OF ISTANBIL: CAN NATO BECOME A MOTOR FOR REFORM?

Roundtable, 21 June 2004



Speakers included

Julian Lindley-French
ETC Course Director, Geneva Centre for Security Policy (GCSP)

Alessandro Minuto Rizzo
Deputy Secretary General, NATO

Ergin Saygun
Military Representative, Delegation of Turkey to NATO

John Koenig
Deputy Head of Mission, Delegation of the United States of America to NATO

VIP Lunch with **Ambassador Nicholas R. Burns**, *US Ambassador to NATO*

DEFENDING GLOBAL SECURITY: THE NEW POLITICS OF TRANSATLANTIC DEFENCE COOPERATION

Annual Security and Defence Conference, 17 May 2004

Speakers included

Jaap de Hoop Scheffer
NATO Secretary General

Vecdi Gönül
Minister of Defence, Turkey

Paulo Portas
Minister of Defence, Portugal

Cristian George Maior
State Secretary for Defence Policy, Romania

Sir Peter Ricketts
UK Ambassador to NATO

HOPES AND AMBITIONS OF THE NEW EUROPEAN DEFENCE AGENCY

Press Dinner 28 April 2004 with

Nick Witney

Head of the European Defence Agency Establishment Team

Press included

The Guardian	Time Magazine
Reuters	Defense News
Financial Times	Die Zeit
Le Monde	Knack Magazine
Armed Forces Journal	Zweites Deutsches Fernsehen (ZDF)

EDITOR: Giles Merritt

RAPPORTEURS: Brooks Tigner and Jessica Henderson

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Web site: www.symphogen.com

FOLLOWING THE INTEREST GENERATED IN PAST NDA EVENTS AND THE ENCOURAGEMENT OF THEIR PARTICIPANTS, THE NDA DECIDED TO CREATE A VENUE FOR MORE FOCUSED DISCUSSIONS ON THE AREA OF BIOTERRORISM. THE BIOTERRORISM REPORTING GROUP WILL ALLOW THE DISCUSSIONS NOT ONLY TO BE TAILORED TO THE EVOLVING DEVELOPMENTS IN THE BIOLOGICAL FIELD BUT MOST OF ALL, THE RESULTING REPORT WILL ACT AS A CATALYST FOR THE POLITICAL WORLD.

There is no question of the need for policies directly focused against the use of biological agents as weapons. The use of disease as a weapon of mass destruction (WMD) is considered a low probability, high consequence event. However, if such an event were to occur, the consequences would be so severe that preparatory action must be undertaken to prevent it. Although biological weapons are often grouped together as agents of mass destruction, biological weapons vary significantly from chemical and nuclear munitions. Biological weapons and materials have the capacity to silently infect thousands of people, destroy agriculture and infect animal populations.

Of all the classes of WMDs, biological weapons remain the most vulnerable to diversion while also being the most difficult to detect. Unlike the Chemical Weapons Convention and the nuclear Non-Proliferation Treaty, which have full verification regimes, the Biological and Toxin Weapons Convention does not. This leaves the development and potential use of bio-agents entirely unchecked. It is therefore imperative governments begin to address the serious threat biological terrorism poses to the EU and the international community.

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