

MANAGEMENT OF NATURAL AND BIOTERRORISM INDUCED PANDEMICS

MICHAEL G. TYSHENKO

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ABSTRACT

A recent approach for bioterrorism risk management calls for stricter regulations over biotechnology as a way to control subversion of technology that may be used to create a man-made pandemic. This approach is largely unworkable given the increasing pervasiveness of molecular techniques and tools throughout society. Emerging technology has provided the tools to design much deadlier pathogens but concomitantly the ability to respond to emerging pandemics to reduce mortality has also improved significantly in recent decades. In its historical context determining just how 'risky' biological weapons is an important consideration for decision making and resource allocation. Management should attempt to increase capacity, share resources, provide accurate infectious disease reporting, deliver information transparency and improve communications to help mitigate the magnitude of future pandemics.

THE CONTEXT OF INFECTIOUS DISEASE

Throughout history humans have been at the mercy of pathogens with disease outbreaks that have emerged and killed indiscriminately. Living prior to the 20th century was a very risky proposition not only from established infectious diseases but also from new emerging contagions. The risk of disease and its effects are reflected in average expected life spans. During the Middle Ages men and women lived about 30 years; mortality from childhood infectious diseases was very high and surviving the first decade of life was an achievement in itself. In North America, at the beginning of the 20th century, the average lifespan had improved to 49 years and by the beginning of the 21st century life expectancy has increased to 77.2 years. The dramatic changes

in life expectancy were largely due to medical advances, improved public healthcare and improved nutrition. The greatest advances have been made in the richest parts of the world, but the same effects are now spreading to less developed parts of the world as their economies, management and infrastructure continue to improve over time.¹

Virulent pandemics have been devastating to many different societies and the three largest pandemics with the greatest impact on human history include the Plague, Smallpox, and Spanish Influenza. The Plague or 'Black Death' of the 14th century was estimated to have killed close to 50 million people. Repeated Smallpox outbreaks and epidemics have

¹ E. Arias. United States Life Tables, 2001. *National Vital Statistics Report* 2004; 52(14): 1–39.

Address for correspondence: Michael G. Tyshenko, PhD, MPA, McLaughlin Center for Population Health Risk Assessment, 1 Stewart St., rm 316, University of Ottawa, Ottawa, ON CANADA, K1N 6N5, Phone: (613)-562-5800 (ext. 2311), Fax: (613)-562-5380. Email: mtyshenk@uottawa.ca

been recorded many times until the 1800s killing tens of millions of people. The Spanish flu pandemic of 1918–1919 emerged killing an estimated 50 million people. Humans are still being assailed by infectious disease threats. In the past five years alone, several pathogens were seen in North America for the first time – West Nile virus, monkeypox virus, low pathogenic avian flu in commercial bird farms, mad cow disease and Severe Acute Respiratory Syndrome (SARS). Another extremely disquieting category of threat emerged in the United States in 2001 with the deliberate release of anthrax, an infectious but non-transmissible biological agent signaling the use of weaponized bacteria and viruses as weapons of mass destruction by inducing a pandemic.²

With increasing awareness of bioterrorism threats and the next pandemic predicted by experts,³ several researchers have called for stricter controls over biotechnology experimentation that provide dual-use information and technologies, dissemination of bioinformatics data and regulation of researchers as a way to manage infectious disease risks.⁴ Such a front-end approach for risk management is largely unworkable for a number of reasons: the number of public and private laboratories, medical institutions and research facilities that use various biochemical and molecular tools globally; the availability of scientific literature available in print; the availability and ease of dissemination of scientific data using the Internet; and the pervasiveness of medical equipment and techniques. Risk issue management of natural or induced pandemics requires a different approach.

MANAGING THE RISKS OF INFECTIOUS DISEASE

In the 17th century several areas of natural science were developing rapidly. There were attempts to understand the connection and interplay between

² D.M. Morens, G.K. Folkers & A.S. Fauci. The Challenge of Emerging and Re-emerging Infectious Diseases. *Nature* 2004; 430(6996): 242–249.

³ R.G. Webster. Predictions for Future Human Influenza Pandemics. *J Infect Dis* 1997; 176(Suppl 1): S14–S19.

⁴ J. Steinbruner & S. Okutani. The Protective Oversight of Biotechnology. *Bio Secur Bioterror* 2004; 2(4): 273–80; J.L. Fox. US to Safeguard ‘Dual-Use’ Biology Research. *Nat Biotechnol* 2004; 22(4): 369; M. Enserink. Research Oversight. Panel Seeks to Balance Science and Security. *Science* 2003; 302(5643): 206.

man, nature and science, as expressed in the ideas of thinkers like Francis Bacon, René Descartes, and Isaac Newton. New knowledge of chemistry, biology and the emergence of formalized healthcare replaced the prevailing dogma that all human diseases resulted from an imbalance of four different body fluids or humors;⁵ this was a new paradigm of thinking about man’s ability to use science, technology and medicine to overcome the natural world. Today we continue on this trajectory trying to maximize the spread between benefit and loss as well as trying to minimize the downside risk of new introduced technologies.⁶ This paradigm includes management of virulent, emerging diseases as we try to protect ourselves from the possible worst-case consequences, namely a catastrophic pandemic. Industrialized countries have now reached a level of technical sophistication in molecular biology, science, communications and infectious disease control to be able to manage, in real time, biological contagions.⁷ The result is that no longer are humans at the mercy of pandemic diseases. Emerging diseases can be controlled but doing so requires significant funding and a coordinated effort. Implementation of strategies such as modern ‘ring containment’ where infectious disease was cordoned off by vaccinating individuals in a circle surrounding outbreak areas, and hospital quarantine under controlled conditions eradicated smallpox from the planet. Such action shows that coordinated global approaches for infectious disease can be successful.⁸ The 20th century has produced a plethora of discoveries and advances applied to medical care that has changed the natural order, greatly increasing life spans and reducing disease risks.

A DEADLIER THREAT – GENETICALLY ENGINEERED BIOLOGICAL AGENTS

Along with the benefits of increased biological knowledge has emerged a new threat, which is the

⁵ V. Nutton. The Fatal Embrace: Galen and the History of Ancient Medicine. *Sci Context* 2005; 18(1): 111–121.

⁶ W. Leiss W & D. Powell, eds. 2005. *Mad Cows and Mother’s Milk*. second edition. Kingston: McGill-Queen’s Press.

⁷ J. Oeppen & J.W. Vaupel. Broken Limits to Life Expectancy. *Science* 2002; 296(5570): 1029–1031.

⁸ R. Preston. 2002. *The Demon in the Freezer*. New York: Fawcett Publishing.

use of these tools to intentionally design biological weapons to induce a pandemic. Genetically engineered viruses changed to be as deadly as possible serve the purpose of their creators to induce terror and mortality not the constraints of evolution; bioweapons would be designed to be as virulent as possible targeted to densely-populated urban centers in order to achieve the highest lethality possible. Genetic engineering is defined as the process of manipulating the pattern of proteins in an organism by altering its existing genes. Since the genetic code is similar in all species, genes taken from one organism can function in another, allowing traits to be altered or introduced. Either new genes are added, or existing genes are changed so that they are produced by the recombinant. Even the gene expression (timing or amounts) can be changed by this technology.

There are a number of ways in which bioweapons could be genetically engineered to make them much more potent and they include: antibiotic resistance gene stacking in pathogens;⁹ inserting new genes in pathogens to disrupt normal human immune response functions (including interference RNA techniques);¹⁰ creating new synthetic pathogens with minimal genomes;¹¹ creating hybrid bacteria and viruses (man-made viral antigenic shifts);¹² designing viruses to attack plants or animals for widespread social and economic disruption of agriculture; and bioagents designed to target specific ethnic populations.¹³

MANAGING THE RISK OF GENETICALLY ENGINEERED BIOWEAPONS AND INTERNATIONAL PANDEMICS

It would be careless to believe that new deadly bioweapons could not be engineered in the future by smaller terrorist groups or an individual with enough knowledge and funding. The Japanese religious group Aum Shinrikyo recruited university educated members and conducted several acts of biological terrorism before its infamous use of the chemical agent (sarin) in Tokyo subways in March 1995. At the time the cult was a group of well-coordinated and well-funded individuals with religious chapters in many other countries, and each sect could potentially have developed or deployed biological weapons to fulfill their cult's end of the world prophecy.¹⁴

The technology for gene manipulation is already well refined with many universities and biotechnology companies who have genetically altered animals and food crops creating transgenics raising ethical concerns.¹⁵ Scientist Steven Block stated the obvious concerning converging technologies: With 30,000 human gene targets, available biotechnologies, and scientific creativity just about any gene can be turned into a bioweapon target.¹⁶ The problem then becomes one of risk issue management as we try, as a society, to mitigate the risks of subverted uses of biotechnology. In the context of bioterrorism we must ask two important risk management questions: 1) What is the probability that genetic engineering will be used to create new virulent pathogens? and 2) While the potential for creating bioweapons exists should we worry about this risk?

⁹ R. Preston. Annals of Warfare, the Bioweaponers. *The New Yorker* 1998; March 9: 52–65.

¹⁰ O. Voinnet. Induction and Suppression of RNA Silencing: Insights from Viral Infections. *Nat Rev Genet* 2005; 6(3): 206–220.

¹¹ D. Ferber. Synthetic Biology: Microbes Made to Order. *Science* 2004; 303(5655): 158–161.

¹² W.P. Stemmer. Rapid Evolution of a Protein *in vitro* by DNA Shuffling. *Nature* 1994; 370(6488): 389–391; W.P. Stemmer. DNA Shuffling by Random Fragmentation and Reassembly: *in vitro* Recombination for Molecular Evolution. *Proc Natl Acad Sci USA* 1994; 91(22): 10747–10751.

¹³ S. Katiyar et al. p53 Gene Mutation and Human Papillomavirus (HPV) Infection in Esophageal Carcinoma from Three Different Endemic Geographic Regions of India. *Cancer Lett* 2005; 218(1): 69–79; C. Dennis. The Bugs of War. *Nature* 2001; 411: 232–235.

¹⁴ K.B. Olson. Aum Shinrikyo: Once and Future Threat? *Emerg Infect Dis* 1999; 5(4): 513–516.

¹⁵ A.E. Schnieke et al. Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts. *Science* 1997; 278(5346): 2130–2133; T.B. Mepham. Transgenesis in Farm Animals: Ethical Implications for Public Policy. *Politics Life Sciences* 1994; 13(2): 195–203; H. Daniell. Genetically Modified Food Crops: Current Concerns and Solutions for Next Generation Crops. *Biotechnol Genet Eng Rev* 2000; 17: 327–352.

¹⁶ S.M. Block. The Growing Threat of Biological Weapons. *Am Sci* 2001; 89: 28–37.

1) What is the probability that genetic engineering will be used for designer bioweapons?

Any group with sufficient knowledge of biology, microbiology and genetics can begin designing more deadly bioweapon agents. It is this convergence of knowledge from life science technology, genome sequencing projects and biological deconstruction that provides the entire sequences of many organisms, including humans, animals, plants, bacteria and viruses. Most industry and university laboratories have the capability to mutate and move genes between species quite easily. Undergraduates in biology and biochemistry university labs learn how to manipulate genetic material (cutting, joining, copying, mutating); shuttle new DNA into bacteria, yeast, plants, worms and flies; isolate genetic material; and learn how to select antibiotic resistant 'positives'.¹⁷

Not only is there concern that tools to manipulate life are more widely available, there is a concern with ongoing basic research that has resulted in accidental creation of highly pathogenic viruses. Australian researchers when designing a contraceptive for mice for use in pest control accidentally created a genetically engineered mousepox virus with 100% lethality.¹⁸ It was believed that the same lethal results would occur if such manipulations were performed with poxviruses that infect human cells.¹⁹

Whether created through research by a laboratory accident or designed intentionally by those for political or ideological purposes, contagious biological weapons mimic the emergence of a new zoonotic disease that has 'jumped' from animals to humans; the end result is the same, a pandemic that is highly communicable and deadly. The threat of biological weapons remains a reality worldwide but experts consider its use a low probability event

requiring a sufficient knowledge base and funding, but it could have potentially catastrophic results.²⁰ Since the ongoing deconstruction of biological systems continues unabated with the tools and knowledge base that are becoming increasingly pervasive, we should seek to manage this low probability risk event proactively by employing coordinated pandemic responses, improved infectious disease surveillance and transparent reporting.²¹

2) Should we worry about biological weapons as a low probability risk issue?

According to the psychometric theory, low probability risk issues can be perceived as more hazardous by individuals if they display a number of specific risk characteristics. Contagions demonstrate a number of these risk factors including: the lack of personal control, high degree of uncertainty, dread, catastrophic widespread outcomes, unfamiliarity, fatal consequences (death), and two kinds of unequal distribution of risk (children and elderly are vulnerable groups; and developing countries will be impacted to a greater degree).²² In addition, Alexander identified additional factors as pathogens are generally not readily identified through the senses (undetectable), have delayed effects in time and have the power to generate social disruption through mass panic.²³ Deployment of biological weapons is also intended to demonstrate that governments and other organizations are unable to protect their citizens. The impact of these factors can be greatly reduced by public trust in government health officials, effective risk communication and health care systems with a demonstrated capacity to safeguard the public.²⁴ The public must be able to trust institutions and believe that virulent outbreaks can be quickly contained or managed well as demonstrated

¹⁷ W. Gardner. Can Human Genetic Enhancement be Prohibited? *J Med Philos* 1995; 20: 65–84.

¹⁸ R.J. Jackson et al. Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox. *J Virol* 2001; 75(3): 1205–1210.

¹⁹ E.M. Wall et al. A Novel Poxvirus Gene and its Human Homolog are Similar to an *E. coli* Lysophospholipase. *Virus Res* 1997; 52(2): 157–167; J. Schriewer, R.M. Buller & G. Owens. Mouse Models for Studying Orthopoxvirus Respiratory Infections. *Methods Mol Biol* 2004; 269: 289–308.

²⁰ M. Karwa, B. Currie & V. Kvetan. Bioterrorism: Preparing for the Impossible or the Improbable. *Crit Care Med* 2005; 33(1 Suppl): S75–S95; S.C. Clarke. Bacteria as Potential Tools in Bioterrorism, with an Emphasis on Bacterial Toxins. *Br J Biomed Sci* 2005; 62(1): 40–46.

²¹ L. Szinicz. History of Chemical and Biological Warfare Agents. *Toxicology* 2005; 214(3): 167–181.

²² P. Slovic. Perception of Risk. *Science* 1987; 236(4799): 280–285.

²³ D.A. Alexander. Bioterrorism: Preparing for the Unthinkable. *J R Army Med Corps* 2003; 149(2): 125–130.

²⁴ R.G. Peters, V.T. Covello & D.B. McCallum. The Determinants of Trust and Credibility in Environmental Risk Communication: An Empirical Study. *Risk Anal* 1997; 17(1): 43–54.

by sufficient infectious disease capacity, trained personnel, robust emergency plans and infrastructure in place to withstand such an attack to reduce levels of panic and uncertainty.²⁵

Our current response capacity and ability to mobilize people to combat contagions is impressive and continues to improve. During the recent global outbreak of SARS in 2003 scientists around the world pooled their expertise and resources to better understand the disease. The effort was well coordinated at the international level by the World Health Organization (WHO) with many laboratories working quickly to help put into the public domain the information that was necessary to learn about this disease; this was done faster for SARS than any other previously encountered pandemic pathogen. Within two weeks of the disease's spread to several countries it was determined to be a novel strain of coronavirus. In less than two weeks after isolating the causative virus, the entire genetic sequence and structure had been determined. It took just over a month to solve the mystery of SARS.²⁶ In contrast to this rapid pace of scientific understanding of SARS, it took two years, in the 1980s, to identify HIV as the cause of AIDS.²⁷ This is a testament to the power of modern science and its increasing ability to deconstruct biology.

The ability to share information about infectious disease risks has also improved our preparedness capacity over time. The Internet as a new communications tool allows for the sharing of information in real time with details, accessible diagnostic guidelines and public health recommendations to contain the spread of the virus. Modern communication systems (telephone, teleconference, videoconference and Internet) allow scientists in disparate regions of the globe to communicate instantaneously, sharing information and results.²⁸

Given the ability, number and amount of expertise available to draw upon from the global medical research community the public should be reassured that any attempts by bioterrorists to induce a man-made pandemic would, in all likelihood, be ineffective to destabilize society. The window between identification of the agent and use of infectious disease control practices (surveillance, tracking, quarantine, containment, identification and medical treatment) has been improving consistently over time. The large number of scientists and well-funded laboratories able to focus and work on infectious diseases should give us comfort that whatever contagion bioterrorists unleash would be rapidly deconstructed.

In the past, civilizations dealt poorly with plague, smallpox or deadly influenza. The contagions would move through entire populations sometimes with repeated waves of infection unabated. Response to infectious disease like SARS showed that many countries are much better able to confront and deal with infectious diseases, and, unlike previous pandemics, we have demonstrated the ability to contain pathogens, quickly mitigating the threat and the amount of mortality. The public should place the impacts of future pandemic disease in relation to the historical context of infectious disease and have trust in those managing the risks of pandemics. Our current and still improving level of scientific sophistication for dealing with infectious disease (whether naturally occurring, accidental or genetically engineered) will provide the necessary tools to confront the next pandemic.

One important control that has emerged is the development of international coordination for infectious disease. The WHO's International Health Regulations (IHR) was originally applied to only a small number of diseases whose spread was historically associated with trade and travel, for example cholera, plague, and yellow fever. The SARS outbreak in 2003 accelerated the IHR revision process to expand its range with a new mandate to ensure maximum security against the international spread of diseases with minimum interference to world trade and travel.²⁹ The IHR now encompasses

²⁵ P. Slovic. Trust, Emotion, Sex, Politics, and Science: Surveying the Risk-Assessment Battlefield. *Risk Anal* 1999; 19(4): 689–701.

²⁶ D.M. Skowronski et al. Severe Acute Respiratory Syndrome (SARS): A Year in Review. *Annu Rev Med* 2005; 56: 357–381.

²⁷ R.C. Gallo et al. Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS. *Science* 1984; 224(4648): 500–503.

²⁸ T. Tam et al. Fortune Favours the Prepared Mind: A National Perspective on Pandemic Preparedness. *Can J Public Health* 2005; 96(6): 406–408.

²⁹ D.P. Fidler. Germs, governance, and global public health in the wake of SARS. *J Clin Invest* 2004; 113(6): 799–804.

public health risks whatever their origin or source including naturally occurring infectious diseases (whether known or unknown), international non-communicable diseases caused by chemical or radiological agents in products and intentional or accidental releases of biological, chemical, or radiological substances.³⁰

CONCLUSION

Given the increasing prevalence of available tools for genetic manipulation to create bioweapons, the risk management of subverted biotechnology requires strong management, not of the biotechnology sector itself but focused on our capacity to respond quickly and effectively. The response to any new infectious disease threat, whether it emerges, re-emerges, is created by accident, or is deliberately introduced, requires an effective mobilization strategy of different types of public health activities in a coordinated manner. Frontline surveillance and response is critical and depends on rapid detection, clinical diagnosis and containment to be effective. Basic and applied research provides information for risk assessment and evidence based decision making for effective medical countermeasures. Advances in

different fields such as biology and biochemistry (genomics, transcriptomics, proteomics, nanotechnology, protein structural determination, immunology), geography (geographical information systems-GIS), epidemiology, communications and imaging all have contributed to our improving response to contagions with surveillance tools, contact tracing, diagnostic tests, vaccines and therapeutics.³¹ We have reached a point through science and communication technology where we can detect, track and contain most emerging diseases in real time, no longer passive victims from the assault of infectious diseases.

Emerging infectious diseases have caused incalculable suffering and death throughout history and, despite improving our overall response capacity, it is not a panacea as it will continue to impact humanity in unpredictable ways. The global public health and scientific communities, through broad based and well-coordinated prevention strategies, must deal with this reality. Infectious disease surveillance tools, reporting, diagnostics, therapeutics and vaccines must be tested, refined and improved continually over time. Realistically it is impossible to prevent or contain contagions that may emerge in the future but the scope, size and magnitude of pandemics and their impact can be greatly reduced.

³⁰ D.P. Fidler & L.O. Gostin. The new International Health Regulations: an historic development for international law and public health. *J Law Med Ethics* 2006; 34(1): 85–94.

³¹ Morens, *op. cit.* note 2, pp. 242–249.