

Overview: International Conference on Biosafety and Biorisks

Information fuels and directs the response to an epidemic. Public health professionals, clinicians, scientists, politicians, journalists, and members of the public make critical decisions based upon what is known about a disease as an outbreak unfolds. However, getting information that is accurate and timely to those who need it takes advance planning and training. An effective response to a disease outbreak will require an interdisciplinary network of public health workers, laboratories able to process clinical samples, researchers available to identify pathogens and/or develop therapeutics, and national and international health officers, all working together in concert with political leadership. This is true whether a disease outbreak is of natural origin, the result of a laboratory accident, or the result of bioterrorism.

To support the requisite planning process and facilitate essential interdisciplinary communication and collaboration, the Center for Biosecurity convened the International Conference on Biosafety and Biorisks in collaboration with the World Health Organization (WHO) Communicable Disease Surveillance and Response office. This multidisciplinary forum in which participants addressed key vulnerabilities in the global epidemic response, lessons learned from past outbreaks, and the safety and biosecurity considerations inherent in pathogen research, set the stage for a promising future of international collaboration.

More than 150 scientists and public health practitioners from 25 countries gathered to hear speakers from the WHO, the European Commission, scientific journals, and public health networks—many of the institutions and individuals who will respond to the next epidemic. Experts discussed organizational and behavioral approaches to epidemic management and biosafety, and the importance of education and training before a crisis. Through discussion of the biosafety and biosecurity challenges presented by past epidemics such as SARS and influenza, participants also recognized that any effort to stop a global epidemic will require new partnerships, shared planning, and a shared response.

For the future, effective public health management of natural and/or manmade pathogens will require harmonization of biosafety, biosecurity, research, and communication standards among nations and across professional disciplines. This conference brought forth strong arguments in support of such a framework, which is the first step toward its establishment. - *Gigi Kwik Grönvall, Ph.D.*

Introduction and Welcome

Presenters: Tara O'Toole, M.D., M.P.H. and Guénaél R. Rodier, M.D.

Dr. Tara O'Toole and Dr. Guenael Rodier, representing the two organizations sponsoring the conference, the Center for Biosecurity of the University of Pittsburgh Medical Center and the Office of Communicable Disease Response

and Surveillance of the WHO, respectively, welcomed the presenters and participants. Dr. O'Toole noted that 25 countries were represented by participants in the conference, which was inspired by the superb job done by WHO in response to SARS. She commented that the degree of global coordination and cooperation that marked the response to SARS was unprecedented, but upon reflection after SARS, it is clear that much more needs to be done to promote this type of response in the future.

Dr. Rodier went on to explain that WHO is concerned with public health considerations in naturally occurring and intentional biological threats and that it is up to others to be focused primarily on security issues; however, WHO guidelines in 1994 and the actions of the WHO assembly in 2002 have addressed the public health issues presented by natural, accidental, or intentional release of threatening biological agents. The WHO is concerned about “public health security” but has no mandate to be involved in criminal investigation. The WHO has moved beyond the traditional vertical programs focused on single diseases with the development of its effort on emerging infections across the entire microbial world. The pillars of this new strategy are: 1. Deal with known risks, i.e. avian influenza; 2. be able to respond to the unexpected; and 3. improve preparedness at the country level. Dr. Rodier concluded by noting that: 1. All countries should have a response system; 2) despite advances we are collectively not prepared; 3. we need more involvement in public health by the business community and other sectors of society; and 4. the WHO is a small organization but has developed a unique and extensive global public health network for epidemic intelligence and risk assessment. - *Summary by Richard Waldhorn, M.D.*

Keynote: International Cooperation to Confront New and Old Diseases

Presenter: D. A. Henderson, M.D., M.P.H.

Dr. Henderson reviewed the history of the successes and challenges in confronting infectious diseases and global public health in the last 50 years, with particular attention given to the watershed events in the emergence of new infections and the threat of bioterrorism.

After the eradication of smallpox in the mid-1980s and the cessation of smallpox vaccination, people wondered what should be eradicated next, and there was a great deal of optimism about the future. Dramatic changes post-1950—the development of vaccines and antibiotics and improvements in nutrition, housing, and sanitation—did lead to the decline or elimination of many diseases such as smallpox, diphtheria, whooping cough, tetanus, polio, and measles, but a cloud soon appeared on the horizon. In June 1981 the first case of AIDS was diagnosed, and HIV as the etiologic agent was identified in April 1984. While it was predicted that science would triumph quickly by producing a vaccine within two years, 24 years later, there is a global pandemic in progress, HIV/AIDS is

now the fourth leading cause of death worldwide, and there is no vaccine or curative drug available.

At the 1989 Conference on Emerging Infections, many wondered if there would be any other surprises like HIV? Since then, SARS, monkey pox, Transmissible Spongiform Encephalitis, a deliberate release of anthrax from an unknown source, and now H5N1 influenza, have emerged, and this is only a partial inventory of the more than 30 new infectious agents that have emerged in the past 25 years. Natural mutation of microbes (i.e., SARS), emergence of microbes from remote areas (monkey pox), laboratory produced microbes (plague, anthrax), and the deliberate release of infectious agents (anthrax) are among the sources of new challenges. These threats can arise in any country and threaten nations across the world.

Why are these infections emerging now? Among the causes cited for the emergence of infections at this time are the growth in urban populations and international travel; the growth of hospitals in endemic areas; creating sites for disease distribution; blood borne infection and antibiotic resistance; and the internationalization of the food supply, industrialized feed lots, and processing with variable amounts of control and regulation. Most people did not think the threat of intentional release of bioagents was significant until 1995, because they believed that organisms were too difficult to grow, technologically difficult to disseminate, or that moral barriers would prevent their use. All of these assumptions have been proven wrong. Advances in biotechnology including the ability to manipulate organisms, an increase in the number of laboratories and trained microbiologists, internet access to information, advances in the science of aerosolization, and the growth of independent terrorist groups have changed the situation today.

Watershed developments in our assessment of the risk of bioterrorism were the 1995 Aum Shinrikyo release of sarin gas, anthrax, and botulinum in Japan; the 1995 revelations about the Iraqi bioweapons program; and the 1980 Soviet bioweapons program. The Shinrikyo release of anthrax on 8 other occasions probably failed only because they had and released a non-lethal strain. Ken Alibek testified that smallpox was included in the Soviet biological weapons program. The threat of biological weapons is clearly there. What is the agenda for the future? Dr. Henderson's conclusion was that we need a greatly strengthened network of international cooperation and communication for epidemiology and laboratory diagnosis, research and development of vaccines and antimicrobials, and a far more generously supported WHO effort to orchestrate the many national initiatives. - *Summary by Richard Waldhorn, M.D.*

The Global Response to Emerging Epidemics

Presenter: David Heymann, M.D.

Dr. Heymann reviewed the history of international health regulations and the role of the WHO in global disease surveillance and control, including detailed discussion of the events surrounding the global response to SARS and the lessons learned from that experience.

Since as early as the 14th Century, when ships were kept offshore in the Venice harbor to prevent the spread of plague, quarantine and international health regulations have provided a framework for global disease surveillance and response. The first International Health Regulations (IHR), which were drafted in 1969, are a nonenforceable framework to prevent the international spread of infectious diseases, rely upon passive reporting systems, and resulted in late detection and response. Global outbreaks now require early detection and early response.

In preparing for a revision of the IHR, WHO has linked more than 120 institutions through country offices in a partnership for global alert and response to infectious diseases, and most of the WHO's information no longer comes from countries. Now, NGOs, information networks like ProMED, the GPHIN, FluNet, and other informal networks and systems provide 77% of the reports to the WHO. If a reported public health risk is determined to be of urgent international importance then, in addition to national containment, collaborative risk-based public health measures are identified and recommended by the WHO.

Heymann reviewed how this system worked during the the SARS epidemic of November 2002 through May 2003. Information initially collected about respiratory infections among healthcare workers in China, the recognition of a syndrome of atypical pneumonia and respiratory failure in a 48-year old businessman with history of previous travel to China and Hong Kong, and subsequent reports of outbreaks in Viet Nam and Hong Kong, led to the first global alert for SARS in March 2003. This reporting was facilitated by the heightened surveillance already underway through FluNet, a network of laboratory partners, because of concern about avian influenza.

By March 15, 2003 it was clear that there was an outbreak of atypical pneumonia with rapid progression to respiratory failure from which no one had yet recovered, that health care workers appeared to be at greatest risk, and that the cause was likely an infectious agent, but it had not been identified. Antibiotics and antivirals did not appear to be effective, no vaccine existed, and the disease was spreading internationally within Asia and to Europe and North America. A decision was made to issue a second global alert and institute a containment program. A case definition and clinical description of cases, X-ray findings, and geographic links were provided. The disease was named severe acute respiratory syndrome (SARS) and international travelers were informed to notify

a health worker if they returned from one of the areas where an outbreak was occurring and developed symptoms compatible with the case definition. Strategies to increase the power of epidemic control included the use of telephone and video conferencing and other real time electronic communications among members of the Global Outbreak Alert and Response Network (GOARN), which included 115 experts from 26 institutions and 17 countries. On March 27, it was recommended that airlines in areas with local transmission of SARS actively screen departing passengers using two questions: 1. Did a traveler have a history of contact with a person with SARS? 2. Did a traveler have a persistent fever, cough, or other signs and symptoms compatible with SARS?

In Hong Kong, health declarations, temperature checking, medical posts on site, and “stop lists” at immigration control points were instituted. SARS continued to spread internationally by air travel in infected passengers. Some cases could not be traced to known contacts despite intensive contact tracing and environmental transmission was suspected in the Amoy Gardens apartment complex in Hong Kong. Additional recommendations were issued, requesting that international travelers postpone non-essential travel to certain areas with outbreaks of more than 60 active cases and 5 new cases reported each day. By this time the clinical features of SARS, its natural history and descriptive epidemiology were well characterized. Within a month, the SARS corona virus was identified, fully sequenced, and described. SARS was clearly a point epidemic with an index case from Guangdong China with international amplification and transmission by guests at Hotel M, Hong Kong between February 21 and March 26, 2003. The outbreak was rapidly brought under control with cases tailing off worldwide by June 2003.

Important lessons were learned from the SARS experience:

- Health care workers and/or primary responders are at greatest risk of emerging infections.
- Collective action can stop international spread of an emerging infection.
- Airport screening measures are of uncertain effectiveness, but were useful in restoring confidence in business and other international travelers.
- International travelers accept travel recommendations.
- Collaboration between health and other government sectors, such as when public health and law enforcement systems work together, is synergistic.
- Proven epidemiological strategies should be trusted.
- Emerging infections are costly to economies.
- Global alert and response with multiple partners is required to detect and contain internationally spreading outbreaks.
- Internationally spreading outbreaks can overwhelm health systems because of the effect on health care workers and the insufficient infrastructure and surge capacity.

- Electronic, telephone, video conferencing can facilitate the work of scientists and public health experts.
- An element of good luck is required.

In 2005, case identification through surveillance in areas at risk for SARS, collaborative studies in Guangdong Province to identify animal reservoirs and risk factors for transmission to humans, and research and development for diagnostics, vaccines, and antivirals continue. Global surveillance for influenza and other emerging infectious diseases is underway to identify the next major emergence of a new influenza strain or other infection of international importance. Recent avian influenza outbreaks have successfully breached the species barrier, and there is concern that non-immunized humans will serve as the intermediate host.

Dr. Heymann concluded from his experience with SARS that the best investment today is in preparation for and response to naturally occurring infectious diseases as this knowledge and experience will help in the event of a deliberately spread infection. - *Summary by Richard Waldhorn, M.D.*

Scientific Collaboration in a Time of SARS

Presenter: Prof. Dr. Rolf Hilgenfeld

Prof. Hilgenfeld addressed the role of scientific journals, peer review, the internet, and patent issues to explore the issue of whether existing systems for publishing scientific results are relevant in the midst of an ongoing epidemic.

A new corona virus was identified as the infectious agent causing SARS on March 22-25, 2003 by three laboratories working collaboratively in a WHO Network of Laboratories. Three weeks later the first complete genome sequence of SARS-CoV was published on the internet, and on May 1, 2003 the paper was e-published in *Science Xpress*. SARS-CoV is most closely related to group 2 coronaviruses. Previous work which determined the crystal structure of Coronaviurs 229E main protease dimer enabled construction of a homology model of the SARS-CoV enzyme on April 13, 2003, and suggested that a compound being developed for use in the common cold, AG7088, could be a good starting point for the design of anti-SARS drugs.

The scientific review process for this paper was relatively fast, but one of three suggested referees was difficult to contact for judgment after minor modifications in the paper, thus delaying publication until May 13, 2003. Patent application was made quickly on a weekend and did not delay publication.

Hilgenfeld drew the following conclusions:

- The research community has responded extremely quickly to the new threat of SARS.
- Scientific journals managed to keep the scientific standard high through rigorous peer review.
- Pre-publication on the internet is essential for quickly making scientific results available in an ongoing emergency situation.
- Peer review is absolutely essential, but is also the weak link when a single reviewer can delay publication.
- Patent applications can be filed without much delay and in parallel to the ongoing scientific review process.

On the topic of international scientific collaboration during and after an epidemic outbreak, Hilgenfeld explained that during the SARS outbreak, Chinese science opened for international collaboration, which created attractive opportunities for researchers outside of China and increased access to samples. Sharing samples was a problem in several cases, but not among the crystallographers. Funding opportunities for collaborative projects on SARS were announced during and shortly after the epidemic, but the funds often became available up to one year later. Ethical issues on the quality of informed consent of the patients donating blood samples were addressed, and procedures were adopted to ensure confidentiality of samples and health information for SARS patients. - *Summary by Richard Waldhorn, M.D.*

Emerging Infections: How Can Laboratories Prepare?

Presenter: Dr. Wilina Lim

In 1997 Hong Kong experienced the first human outbreak of H5N1, and in 2003 it was hit with SARS. These outbreaks imposed considerable strain on Hong Kong's public health laboratories. Dr. Lim, a consulting medical microbiologist from Hong Kong's Department of Health, recounted her experience and the lessons learned.

Both outbreaks posed the same major challenges—not enough manpower and a high volume of samples to be processed. In each instance, workload increased four-fold, and highly trained and specialized personnel were required to work long hours for prolonged periods. To help with the load, they borrowed staff from other labs and employed junior technicians and workmen to assist with simple lab work. Safety was also an issue, since prior to these events Hong Kong had no BSL3 lab. Other challenges included lack of space, lack of equipment, difficulty in transferring specimens, and communication. As a result, a new lab with new equipment was built, staff training was improved, and safety and security practices were enhanced.

Lim also discussed findings related to SARS-CoV in a laboratory setting, noting that the highest concentration of virus shedding they found was in stool, and that

it was relatively lower in nasopharyngeal secretions and serum. SARS-CoV at high concentration was stable in the environment and was more stable on non-absorbent surfaces such as disposable gowns.

She offered the following as lessons learned from these experiences:

- SARS-CoV was easily inactivated by disinfectants and detergents.
- A preparedness plan was needed.
- Continuous personnel training was needed.
- Laboratory quality assurance was essential.
- Lab safety and security needed to be enhanced.
- An enhanced information system was needed.
- There must be a consensus between labs on testing protocols.
- Labs assessed to have the capacity must be recruited.
- One must network with local and international partners.

- *Summary by Eric Toner, M.D.*

Influenza: A Developing Crisis

Presenter: Robert G. Webster, Ph.D.

Dr. Webster came to Lyon directly from Vietnam, a trip that took less time than the incubation period of H5N1, meaning that, theoretically, he could have been carrying the seed of a new pandemic—a sobering thought he shared with the group. The 1918 pandemic which, he stated, killed 100 million people, resulted from an avian influenza virus that had evolved to a form capable of efficient human-to-human transmission and that had a much lower human mortality rate than the current H5N1 strain. Influenza A viruses can evolve by exchanging genes (reassortment) or without reassortment by virtue of the constant mutation that occurs with each replication of an influenza virus. The 1918 virus evolved without reassortment. The other pandemics of the 20th century (1957 and 1968), he noted, were due to reassortment between avian viruses and circulating human influenza viruses, and Webster explained that there is significant evidence that the 1977 H1N1 pandemic was due to an accidental lab release, as it was genetically identical to a strain that circulated naturally decades before.

Whether the current H5N1 strain reassorts with a human adapted influenza strain or simply evolves efficient human to human transmission through mutation, the risk of a pandemic from this virus is very real, Webster said. He traced the evolution of H5N1 over the last 8 years, highlighting the chain of multiple episodes of reassortment resulting in the current dominant “Z” genotype. This virus readily infects pigs but, at least at the moment, cannot be transmitted by them. He pointed out the expanding host range of this strain, including tigers and domestic cats, and the rapid evolution of the virus in ducks.

Reverse genetic techniques are being used to develop vaccines and to understand the molecular basis of disease caused by influenza viruses. This technique employs plasmids to insert genetic material from one virus into another. In so doing, a new virus is created that expresses some, but not all, of the characteristics of the original virus. Thus, a benign virus can be created that carries the surface antigens of the pathogenic virus. A vaccine developed using this technology is currently being tested. While this vaccine may or may not be a perfect match for whatever H5N1 strain develops in the near future, the hope is that it will impart sufficient immunity to prevent death, if not infection, should a human epidemic occur. While much has been learned about the H5N1 virus, key information, —such as the determinants of transmissibility—have yet to be elucidated.

The only antiviral treatment for the current strain is oseltamivir. Since 1997, H5N1 has developed resistance to amantidine due to its use in chicken feed. In order to reduce the risk of resistance to oseltamivir, Dr Webster advocates limitation of its use for routine influenza. He also advocates the large scale stockpiling of oseltamivir. - *Summary by Eric Toner, M.D.*

Avian Influenza: The Indonesian Experience

Presenter: Amin Soebandrio, M.D.

Dr. Soebandrio reviewed the H5N1 Highly Pathogenic Avian Influenza (AI) outbreak which started in Indonesia in August 2003 and outlined how it was controlled. Originally discovered in 2 areas of Java, it spread quickly, so that by September it was in 98 areas of 15 provinces. As a result, between August 2003 and November 2004, 8,894,124 birds were reportedly killed. Of 829 persons with a history of contact with infected birds, none contracted the disease.

Soebandrio reviewed Indonesia's control strategy, detailing the following:

1. Improve biosecurity: Prevent susceptible birds from having contact with the AI virus and stop replication of AI virus in infected birds by controlling bird traffic (birds, bird-products, farm workers, and vehicles), cleaning and decontaminating coops and cages, isolating infected flocks, burning and burying dead birds.
2. Vaccinate poultry populations: Although larger farms, particularly breeding and commercial layer farms, vaccinated their flocks, only 30% of commercial broiler farms complied. Seven different vaccines from different countries were used.
3. Depopulate poultry flocks: The depopulation procedure, which entailed large scale destruction of poultry flocks, was complicated and had to be followed by careful disposal to prevent the carcasses from becoming a source of infection. Small farmers were compensated for their loss.
4. Conduct surveillance and tracing of new outbreaks.

5. Restock farms: After infected flocks were destroyed, farms were restocked with new poultry, but farmers had to wait until 30 days after disposal of dead birds and had to disinfect equipment and/or utilities.
6. Stamp-out new outbreaks: When a new outbreak occurred, infected birds and all birds within a 1 km radius were destroyed.
7. Increase public awareness: A multi-media approach to educate the public and to increase awareness of threat of AI was adopted.
8. Monitor and evaluate: Regional meetings and coordination between agencies was employed to monitor AI outbreaks and response.

Finally, Soebandrio compared the effects of the avian influenza outbreak to other challenges faced by Indonesia recently, noting that AI has resulted in the destruction of 8 million birds, with no human deaths; dengue fever infected 60,000 people in 2004, killing 800; and the recent tsunami, a national tragedy that killed 166,000 people and left 100,000 missing. - *Summary by Eric Toner, M.D.*

WHO Activities for Management of Biorisks

Presenter: Brad Kay, M.S., M.P.H., Dr.PH.

Our world is changing—we have changed the way we live, microbes have evolved, new threats have emerged, and new solutions for dealing with those threats are needed. With this introduction Dr. Kay outlined the workings of the World Health Organization's Department of Communicable Disease Surveillance and Response (CSR), which is charged with strengthening national capacities to prevent and control disease epidemics. He pointed out that deliberately caused epidemics fundamentally transform the context in which the public health response must be delivered, and that biological research with a legitimate scientific purpose may be misused to pose a biological threat to public health and/or national security. Kay distinguished between biosafety (working safely) and biosecurity (keeping the work safe) and noted that developing countries have few resources for either biosafety or biosecurity. In order to be sustainable, biosecurity measures must be linked to clear advantages.

From a public health standpoint, bioscience facilities are potential sources of harmful biological agents, but the bioscience community is not accustomed to security issues, global standards for professional conduct of science do not exist, nor do global regulatory mechanisms for biological materials.

From an international standpoint, many nations do not have biosecurity legislation, and uncoordinated national standards could lead to inconsistent regulations or weak implementation. Furthermore, uniform standards on which states can base national legislation for biosecurity are nonexistent.

Kay also highlighted problems associated with control of biological agents, including the fact that microbes are naturally occurring and ubiquitous, traditional

security measures can be ineffective, minute amounts are significant, travel and trade promote ease and speed of spread, there is no global means to control or monitor distribution, and the origin of an agent can be difficult to trace.

He concluded by asserting that harmonized, comprehensive global norms and standards for laboratory biosafety and biosecurity with biological materials are needed but missing. Furthermore, the development of norms and standards must be broadly inclusive. International organizations can play a significant facilitating role for global cooperation, he said, and the WHO and its technical partners must work together to produce needed guidance on laboratory biosafety/biosecurity issues. Lastly, he pointed out that resources are needed to address fundamental needs and to assist WHO Member States. - *Summary by Eric Toner, M.D.*

Building Robust Response Systems for Epidemics: An Organizational Approach

Presenter: Jean-Marc Choukroun, Ph.D.

"Systems thinking" is a management tool that has evolved over the last 30 years, but its roots can be traced to biological principles. As an analytical tool, systems thinking represents a shift from traditional analysis which tends to break down an organization or a network into smaller, seemingly more manageable elements, to one which evaluates the system as a whole. This approach is based on the belief that the performance of a system depends more on how its parts interact than on how they act independently of each other. Therefore, using a systems approach to optimizing the efficiency of a system, one cannot simply improve the efficiency of each of the parts separately. Rather, all of the subsystems must be optimized in relation to each other. In this manner, no one subsystem takes responsibility for the failure of the larger system; rather, responsibility is shared among all.

Before a system can be optimized, the entire organization and its subparts must be defined and their interdependencies understood. Doing so, however, requires the understanding that solutions to inefficiencies in the system may give rise to additional problems which will require additional solutions. Therefore, the organization's definitions and the interdependencies must be constantly reevaluated.

In the context of large systems such as public health networks, a systems approach suggests that:

- Problems and their solutions are socially defined.
- Stakeholders (representing subsets of the larger system) may have multiple, often conflicting, perspectives.
- There may be different priorities and senses of urgency for each of the subsets
- Crises often require acting before learning; therefore, models for "learning in action" are needed.

Using this analytical tool could help a public health system understand its interdependencies and identify critical weaknesses that potentially stand in the way of a robust response to crises. - *Summary by Jennifer Nuzzo, M.S.*

Biosafety: What are the different levels and what is the continuum?

Presenter: Jonathan Richmond, Ph.D.

Mr. Richmond, a former Director of CDC's Office of Health and Safety, outlined the key objectives, elements and, in some cases, challenges of building a comprehensive laboratory biosafety program, the importance of which has increased as the number of high-hazard, high-containment laboratories and their attendant accidental releases and laboratory accidents have multiplied globally. He first distinguished between biosafety and biosecurity, describing them as two related but different goals. Biosafety is directed at "reducing or eliminating accidental exposure to or release of potentially hazardous agents" in the laboratory, while biosecurity is focused on "protecting against theft or diversion of select agents" from a laboratory for "nefarious" uses. While he defined a "Responsible Scientist" as an individual who should be held responsible for day-to-day conformance of their laboratory to established biosafety norms, Richmond pointed out that accountability itself may be viewed differently in different cultures.

The concept of four biosafety levels (BSL-1 to BSL-4), which was introduced in the mid-1970's, is a framework adopted by the CDC in the late 1970s and by the WHO in the early 1980s. Each level provides for correspondingly higher safety expectations for the experience and responsibilities of a "responsible scientist," for program requirements and staff training, and at the highest levels, for employee health surveillance and self-assessment, along with rigorous safety engineering. A designated level of needed safety protection is based on a risk assessment, which must be science-based and conducted by the most knowledgeable individual on a team (e.g., the principal investigator). While a number of challenges exist for establishing a sound biosafety program (e.g., risk assessment, facility design, personnel hiring), the most fundamental one is creating a suitable "biosafety culture" that reflects responsible behavior at all levels of an organization. Richmond emphasized that establishing that shared value requires the support of top management. Government failure to adapt standardized biosafety guidelines that would better steer the efforts of the scientific community has created another challenge.

Consistency requires uniform guidelines and program self-assessments; to this end, Richmond has developed self-assessment criteria based on the guidelines that can be applied to laboratory operations. He concluded by discussing the role and functions of the Biological Safety Officer and Safety Committee, and how risk assessment, supported by these functions, is ultimately directed at breaking the

“chain of infection” in a laboratory environment. - *Summary by Joseph Fitzgerald, M.H.S., M.P.H.*

BioSafety Challenges for BioRisk Management

Presenter: Dr. Nicoletta Previsani

Dr. Previsani prefaced her presentation by citing the prevailing challenge of “how to get people to accept and implement biosafety principles and practices” and then offered a “reality check” by showing photographs of various laboratory environments, both good and bad, in developing and developed countries. Her point was that poor practices are as much responsible for unsafe conditions as are old equipment and dilapidated facilities.

The recent SARS laboratory-acquired infection in Taiwan, in her view, illustrated her point: A researcher inappropriately used alcohol as a disinfectant and purposefully breached a glovebox to shortcut the disinfectant process.

Dr. Previsani then outlined the WHO biosafety program—promoting the use of safe practices in the laboratory, transportation, field investigations, manufacturing facilities, and health care facilities. She noted the precedent of WHO biosafety review teams routinely visiting the BSL-4 smallpox laboratory repositories at CDC in Atlanta and at VECTOR in Russia. The provisions of the program and the status of current efforts in each of these environments were described, with emphasis on the importance of creating a strong biosafety culture and the need for uniform guidelines. To this end, WHO has been active in publishing guidelines (e.g., WHO Laboratory Biosafety Manual, 2004, and its biosecurity guidance) and best practices, as well as holding meetings to promote information exchange and collaboration among member nations.

For instance, the WHO held a conference in Lyon on “Biorisk Management in Laboratory Environments” on February 3-4, 2005, to address the key question, “How do we get to a needed biosafety culture?” One approach is to make the inculcation of a sound biosafety culture integral to national pursuit of BSL-3 and 4 laboratories. The WHO's vision for strengthening biorisk management includes increasing awareness of biosafety, clarifying training strategies, enhancing capacities for biosafety, and securing commitments and accountability from key institutions. This will be promoted through WHO's five regional collaboration centers, which will need to be expanded further, and though its linkages with other NGOs such as the American Biological Safety Association (ABSA) and the European Biological Safety Association (EBSA).

Dr. Previsani also underscored the importance of distinguishing between wishful thinking and reality when it comes to what can be accomplished globally given current resources and behavioral barriers. Constraints include lack of awareness at the highest levels of national governments, inadequate resources and infrastructure, lack of sufficient technical expertise, and inadequate emphasis in

training courses. The WHO strategy is to pursue “integrated biorisk management,” which is directed at ensuring workers' safety and keeping laboratory work secure. This will be accomplished by promoting awareness of biosafety and biosecurity as the principal means to bring about culture change in the laboratory, with targeted training, increasing capacities, and securing worker commitments as other means to this end. - *Summary by Joseph Fitzgerald, M.H.S., M.P.H.*

Leading with Safety: Shaping Culture and Behaviors

Presenter: James Grant

Mr. Grant is the Global Accounts Manager of Behavioral Science Technology, Inc., longstanding specialists in safety management strategies and programs. His firm specializes in addressing the human behavior components of strong workplace safety programs. This issue is particularly pertinent to laboratory safety, given the need to change prevailing practices and attitudes so they correspond with the heightened hazards and challenges of handling increasingly more hazardous bioagents.

Grant pointed out that a sound safety program relies on strong leadership supported by both “safety enabling systems” and “organizational sustaining systems.” The former consists of traditional safety mechanisms such as hazard recognition skills and training, while the latter consists of systems to promote performance management, employee engagement, and sound organizational structure. Along with the prevailing organizational culture, these systems have a direct influence on the safety effectiveness of workers, procedures, equipment and facility design. Within this safety management framework, safety leadership is critical and draws its strength from the personality, values, and emotional commitment of the leader.

Grant explained that many leaders do not naturally have all of the personality attributes necessary to manage safety effectively; however, he asserted that the key is to manage one's personality to enhance the safety culture of the institution for which one is responsible. For example, while some managers may not seek out regular interaction with employees, this is an important leadership attribute in promoting worker engagement in safety and in demonstrating management support. Grant then outlined five key elements of a behavior-based performance improvement program:

- Develop outcome measures
- Identify critical behaviors (“in a positive manner”)
- Gather data (“best individual to do so is a peer in the organization”)
- Provide two-way feedback
- Use data to remove barriers (“collect data and use it”).

He concluded by discussing the “ABC” framework for describing “what controls behavior,” using the use or neglect of safety glasses to illustrate. In this framework, A = Antecedents or “anything which precedes and sets the stage for behavior.” B = Behavior or “an observable act.” C = Consequences or “anything that directly follows from the behavior.” In the context of the safety glasses example, A = factors influencing worker use of safety glasses (e.g., timing, discomfort, ready access, etc.), while B = recognizing need to wear glasses, and C = reprimand, eye injury, etc. A corresponding framework exists for managers, as well. By changing or influencing the factors in A and B, one can change the outcomes in C. Key factors are timing (sooner vs. later), consistency (certain vs. uncertain), and significance (positive vs. negative). Grant concluded by pointing out that “consequences control behavior” and that “antecedents influence behavior only to the extent that they predict consequences.” - *Summary by Joseph Fitzgerald, M.H.S., M.P.H.*

Training for Crisis Management Dilemmas in Europe

Presenter: Jesper Grönvall, M.S.

The hallmarks of a crisis are a threat to core values, an urgency to resolve the threat, and uncertainty about how to do so. Crises are stressful; there are consequences to be resolved that often include difficult choices, such as those between public good and individual well-being. Yet, crises also present opportunities for organizations to make societal and/or cultural improvements.

The key challenge of effective crisis management is incident characterization, or defining the crisis. When a crisis is framed, limitations are set. An ineffective response is often the result of a limited initial assessment.

Innovative crisis management depends upon team efforts that improve awareness, enhance skills, increase “horizon scanning,” create effective networking, and make use of functional planning tools such as scenario training exercises. Decision-makers must have experience in planning and in exercising plans, because in practice, organizational vulnerabilities will be revealed and capabilities can be improved.

During exercises in the management of a crisis and in situations of “near misses,” it is essential to document the lessons learned, and to both evaluate and share them. In most instances, effective crisis management will require coordination, leadership, and solidarity of cause across multiple organizations.

There are several opportunities for getting onto a productive track:

- **Communication:** A plan for public communication is essential; effective response is both the “correct” decision and the “correct” communication.

- Resources: An accurate assessment of resource limitation and distribution is essential.
- Local level: Identifying the important planning questions tailored to each organization is essential.
- Public's role: There are new constellations for public participation—the “civil/military,” the “public/private” and the “governmental /nongovernmental organizations.”

If done well, effective training and education for crisis management can lead to more functional organizations. - *Summary by Penny Hitchcock, D.V.M., M.S.*

Anthrax-EuroNet:

Challenges of Scientific Research Communication on High Risk Agents

Presenter: Dr. Amanda Ozin

How should scientific research on potentially dangerous agents be conducted and coordinated? How should the results be disseminated to prevent the misuse of information? Dr. Ozin addressed these questions in her discussion of the Anthrax-EuroNet, a network of industry, academia, education, and public health professionals and organizations formed to strengthen networking activities among anthrax researchers and harmonize best research practices.

Currently, it is difficult to compare results of anthrax experiments performed in different laboratories because of the many different existing animal models, strains, and protocols. Through networking and the establishment of standards, Anthrax-EuroNet aims to improve the comparability of data results, minimize waste, and accelerate development of safe vaccines and therapeutics. Anthrax-EuroNet is also hoping to become part of a larger “network of networks” which, in the future, will work to coordinate and set priorities for research into dangerous pathogens.

Anthrax EuroNet is now working to revise questionnaires it designed to identify problems in labs in the U.S. and Europe that may be remedied through coordination among anthrax researchers. Last year's questionnaire was unsuccessful in eliciting much information, as “biosecurity issues” about the exchange of sensitive information prevented many labs from completing the form. Future projects will include developing a handbook for anthrax researchers and convening meetings and symposia on biosecurity issues and regulations.

Dr. Ozin also identified strategies for addressing the dual-use dilemma of research on dangerous pathogens, namely, how to communicate information that can be used for beneficent as well as nefarious purposes. Such strategies include forming international scientific advisory/review boards, developing a self-governance “code of conduct” for researchers, and encouraging open communication among scientists, journals, and the public on how to address potential security threats. - *Summary by Brad Kramer*

Global Digital Awareness of Disease Outbreaks: The Experience of ProMED

Presenter: Marjorie Pollack, M.D.

The ProMED-mail electronic outbreak reporting system (abbreviated ProMED) is a moderated email list-serve used to monitor emerging infectious diseases globally. Dr. Pollack's presentation focused on ProMed's role in global public health as an informal, internet-based early warning system.

ProMED collects information on health threats from official reports, the media, and individual subscribers. It screens the information, and then sends it via email, along with expert commentary, to 33,000 subscribers in more than 150 countries. The system monitors human disease and exposure to toxins, as well as plant and animal diseases. Electronic communication enables ProMED to provide up-to-date and reliable news about health threats around the world so that action can be taken to prevent epidemics and save lives. In 2003, ProMED played an integral role in drawing attention to the outbreak of atypical pneumonia in China that marked the beginning of the worldwide SARS crisis (see slide 14). Drawing from ProMED's experience with the SARS and avian influenza crises, Pollack asserted that because we live in a "global village," no single institution has the capacity to address disease surveillance completely. Pollack also briefly outlined regional programs being undertaken by ProMED, including communications in Spanish, Portuguese, and Russian; disease surveillance collaboration in the Mekong basin; and an integrated disease surveillance network in east Africa. As this presentation demonstrated, by combining rapid reporting, expert commentary, and a forum for cooperation among diverse groups involved in public health, ProMED augments the world's surveillance and response to global health threats. - *Summary by Brad Kramer*

The Technical Foundation for Public Health Decisions

Presenter: Caroline Ash

Ms. Ash is Senior Editor for *Science Magazine*, a weekly publication devoted to fast dissemination of leading edge and high quality science. Ash discussed the magazine's efforts to respond to and document epidemic crises, noting that during an epidemic, pertinent information must be made widely available to provide an accurate picture of vulnerabilities, an assessment of the immediate response, and accurate data to guide the development of global solutions.

Peer-reviewed publications must manage the tension created by the drive to publish rapidly while also ensuring accuracy. Ms. Ash discussed examples of editions published during epidemics to illustrate how *Science* publishes high quality literature promptly. She noted that in times such as the 2001 epidemic of foot and mouth disease in the U.K. and the 2003 SARS crisis, papers were peer-reviewed, edited, and published online within two weeks of receipt. These time-sensitive papers were posted on *Science Express*, a website designed to publish

articles online that have already been accepted and peer-reviewed but have not yet come out in print. Ash also noted that scientists who hope to publish important data rapidly during an epidemic must balance their desire to make crucial data public as soon as possible to support a swift and effective response with their desire for the personal recognition that comes with publication in a respected journal.

Finally, Ms. Ash provided advice for those wishing to submit a manuscript to *Science* for rapid publication:

- Contact the editors early on to assure suitability
- Obtain *Science's* guidelines for manuscript preparation and adhere to them
- Write a comprehensive methods section that allows replication of the work described in the paper.

- Summary by Brad Kramer

Global Public Health Intelligence Network (GPHIN) – Early Warning System for Global Public Health Threats

Presenter: Abia Mawudeku

With globalization, it is becoming increasingly easy for local disease outbreaks to become international epidemics, making critical the timely exchange of information between local and international agencies. However, while it is becoming ever more important that information about threats to the global public's health be relayed rapidly, traditional and existing public health surveillance systems are largely inadequate to the task. Mawudeku presented the Global Public Health Intelligence Network (GPHIN), an informal surveillance system that uses advanced technology to provide an early warning about potential public health threats to the international community.

GPHIN continuously monitors more than 10,000 electronic sources of information worldwide (radio, television, newspapers, newswire alerts, etc.), employing multi-language search criteria to find terms that may indicate news of an outbreak. Alerts are then filtered by GPHIN analysts and disseminated to subscribers around the globe, who can then investigate and verify the existence of any threats to the public's health. Indeed, GPHIN is responsible for the initial reporting of approximately half of all reported events of potential public health concern to the WHO.

GPHIN can be accessed at any time from anywhere in the world through an internet connection. It monitors and disseminates information in Arabic, Chinese, English, French, Russian, and Spanish. Initially designed to monitor news on human health only, GPHIN's scope has been expanded to search for news on animal and plant diseases, chemical and radiological exposures, unsafe

products, and natural disasters. The system is also proving versatile in its usefulness—it can help identify control measures proving effective in an outbreak, or the concerns of the public. Furthermore, GPHIN's infrastructure may be useful for other industries searching for global information. In the future, GPHIN plans on implementing new technologies, including predictive modeling, GIS mapping, and speech recognition. - *Summary by Brad Kramer*

Interpol and Bio-criminalization

Presenter: Ronald K. Noble, J.D.

Biological agents, including bacteria, viruses, protozoa, and biological toxins are the weapons of the new millennium. Incidents of bioterrorism have been documented, and many attempts have been thwarted. Recipes for making biological weapons can be found on the internet, equipment for making and dispersing biological weapons can be purchased on eBay, and the number of people seeking training in microbiology and biochemistry for purposes of ill-intent increases daily.

Law enforcement agencies face many challenges:

- Personnel lack training in biology
- Awareness of the *potential* for bioterrorism acts is “spotty”
- A traditional law enforcement paradigm makes a visible response at a crime scene to gather evidence, but this approach may not be appropriate, especially if there is no “scene”
- Questions driving police investigations currently focus on “what happened?” However, in bioterrorism acts, the antecedent question must be addressed: “How do we know if/when something has happened?”
- The crime scene presents a risk for first responders.

Superimposed on the challenge is the differentiation between naturally occurring and deliberate outbreaks. Although the public health response is common to both, if a crime has been committed, law enforcement has a critical role to play in apprehending the perpetrator, thereby preventing additional attacks, i.e., the re-load phenomenon.

In this time of transition, law enforcement agencies have numerous unmet needs:

- Regulatory systems must be developed to enable law enforcement agencies to intervene and prevent such crimes
- Police officers must be trained in bioterrorism countermeasures
- Channels for law enforcement to access information must be created
- A cadre of experts to act as confidential informants will be necessary
- Methods for establishing functional relationships between law enforcement and public health personnel must be developed.

Noble's discussion raised several key issues, including the need for accurate and timely disclosure to the public; the need to establish, integrate, and exercise law enforcement and public health command and control protocols; and the tension between and need to address the privacy of medical records versus the use of those records as "evidence sources." Mr. Noble acknowledged that all three areas will require considerable effort in order to optimize law enforcement's effectiveness in the age of bioterrorism. - *Summary by Penny Hitchcock, D.V.M., M.S.*

Preparedness for Deliberate Epidemics

Presenter: Dr. Ottorino Cosivi

The World Health Organization (WHO) authored *Health Aspects of Chemical and Biological Weapons* in the Biological and Chemical Weapons Conventions of 1972 and 1993. These documents include provisions for assistance in the event or threat of an attack. Although the United Nations has agencies that are responsible for monitoring and verifying a chemical or nuclear attack, [i.e., the Organisation for the Prohibition of Chemical Weapons (OPCW) and the International Atomic Energy Agency (IAEA)], there is no similar organization to deal with a biological attack.

The WHO's role in such events, however, is constitutionally mandated, delineated in the newest version of the International Health Regulations, and clearly stated by the World Health Assembly. In accordance with that mandate, the WHO is pursuing a three-pronged effort: 1. strengthen global surveillance; 2. provide tools and support to strengthen national health systems; and 3. issue international guidance and technical information.

The overall objective of the WHO's efforts is to prepare member states to recognize, respond to, and manage the consequences of a deliberate epidemic. The WHO utilizes the Global Public Health Intelligence Network (GPHIN) to identify potential outbreaks, verify outbreaks, and assist in a member state's public health response. The recent SARS outbreaks have exercised this infrastructure; however, because they were not deliberate, the coordination and interaction between health and security agencies was not involved in WHO's response.

The WHO has launched a two-phase process. Phase 1, now completed, involved an overview of the risks for public health from deliberate epidemics and established an international network of scientists and institutions. Phase 2 will involve regional planning (through workshops) and exercising the in-country infrastructure, including the outreach to the international network. The WHO Office for National Epidemic Preparedness and Response (Lyon, France) is coordinating this effort. Examples of disease-specific networks and guidance documents, including risk assessment and preparedness assessment tools, can be found in the slide presentation.

Note: In the discussion that followed the presentation, Dr. Cosivi stated that there are no designated funds for this effort; it will be financed through grants and extra-budget contributions. - *Summary by Penny Hitchcock, D.V.M., M.S.*

Health Security Cooperation in the European Union

Presenter: Germain Thinus

The responsibility for terrorism surveillance (biological, chemical, and radiological) and early warning among the 25 member states of the European Union (EU) is charged to the Health Threat Unit, located in the Commission's Health and Consumer Protection Directorate. The Health Threat Unit has established seven working groups:

- Preparedness and response planning
- Chemical threats
- Prudent use of antimicrobial agents in human medicine
- Incident investigation and sampling
- Medicinal products
- Co-operation between laboratories
- Risk communication

The EU Rapid Alert System conducts surveillance on communicable diseases and diseases caused by acts of bioterrorism through a complex network of rapid alert systems, including the national surveillance systems of member states, other Commission Directorates, and the WHO. Surveillance data are coordinated and evaluated by the Health Emergency Operations Facility; in turn, this facility initiates alert notifications and conducts follow-up. The criteria for notification include:

- Suspicion of danger
- Internationally relevant events; need for a complex response
- Need for coordination (investigative and control actions)
- Suspicion of deliberate action of a terrorist organization
- Risk of trans-frontier spread of the agent/event
- Need for assistance from other countries

Actionable information and warnings are sent to the member states by the Communication and Crisis Center (BICHAT) and the Security Office in Brussels. BICHAT conducts follow-up management, disseminates and coordinates information, and deploys emergency teams. BICHAT reaction time is one hour. The on-duty officer receives the alert via an SMS notification to his/her mobile phone (pager system) and by a telephone call from the Security Office in Brussels. More information about the activities of the Health Threat Unit and Health Security can be found online at:

http://europa.eu.int/comm/health/ph_threats/threats_en.htm

The Health Threat Unit also has responsibility for other reportable diseases, including:

- Diseases preventable by vaccination
- Sexually transmitted diseases
- Viral hepatitis
- Food- and water-borne diseases and diseases of environmental origin
- Air-borne diseases
- Zoonotic diseases
- Diseases transmitted by non-conventional agents
- Serious imported diseases
- Special Health Issues (nosocomial infections; antimicrobial resistance)

- Summary by Penny Hitchcock, D.V.M., M.S.

The Global Outbreak Alert and Response Network (GOARN)

Presenter: Dr. May C. Chu

In its Communicable Disease Surveillance and Response activities, the WHO seeks to detect global disease outbreaks and to provide a rapid response in order to reduce suffering of infected populations, contain the international spread of disease, and minimize impact on travel and trade that could result from international efforts to control a disease outbreak.

At the WHO, the Assessment and Field Operations Unit (AFO) scans incoming disease outbreak reports from both official and nonofficial sources to detect potential epidemics of global public health significance. Non-official sources of information, such as reports from the Global Public Health Intelligence Network (GPHIN), ProMED, and NGOs play a major role in the detection of disease. During the period from 2000 to 2004, 61% of all events were reported through these nonofficial sources. When the WHO detects a potential disease outbreak, it will work with member countries to verify the event. Once the event has been verified, the WHO may be invited by affected member countries to assist in responding to the epidemic, or if it is not invited, the WHO may advocate for permission from member countries to assist in the response.

Instrumental in responding to global epidemics is the Global Outbreak Alert and Response Network (GOARN), a voluntary technical partnership of more than 120 members coordinated by WHO to provide multi-disciplinary technical support to countries for outbreak response. In this capacity, GOARN serves as the operational arm of the WHO that can be mobilized to assist countries with disease control efforts by providing technical support.

GOARN team members deployed in the field and those that offer professional guidance from their home countries communicate with each other and with the WHO through teleconference. The recently constructed Strategic Health

Operation Center at WHO provides added functionality for this process, but according to Dr. Chu “[it] doesn’t really change what we do.”

In the 2000 to 2004 period, GOARN responded successfully to more than 36 outbreaks worldwide, such as the 2003 SARS outbreak in Asia. Despite these successes, the network is continually challenged by resource limitations. Although most GOARN members self-fund their participation in the network, it can be very costly for the WHO to coordinate the deployed teams. The WHO does not have a budget for GOARN activities and therefore must solicit external funds for coordinating GOARN teams each time they are mobilized. The most recent example of this is the 2005 outbreak of plague (one of the three diseases that are reportable under the current International Health Regulations) in the Democratic Republic of Congo, in which WHO was faced with the challenge of simultaneously planning its response to the outbreak while raising nearly \$400,000 USD to ensure the safety and transportation of the responding GOARN team. These resource limitations raise questions about the WHO's capacity to respond to large disease epidemics that are occurring in multiple locations or that require sustained responses. - *Summary by Jennifer Nuzzo, M.S.*

The New International Health Regulations

Presenter: David Byrne

As Special Envoy to the WHO, David Byrne was charged by the Director General with building political consensus for the revised International Health Regulations (IHR). The revision process was born of a need to establish a “rules based system” for dealing with disease outbreaks not covered by the current IHR. From his observations as Special Envoy, Mr. Byrne is confident that the revised IHR will be adopted at the World Health Assembly in May 2005.

Although they are not yet finalized, the revised IHR essentially differ from the current regulations in that they emphasize disease outbreaks of global public health significance instead of relying on a list of diseases that member countries must report. They also accord greater flexibility in response to disease outbreaks by allowing the WHO to consult nonofficial reports of disease outbreaks and make requests to collaborate in the response to a verified outbreak. In turn, member countries must provide a timely response to a request from the WHO for disease outbreak verification. If a member country does not respond, the new IHR allow the WHO to disclose that information publicly.

Mr. Byrne reflected on key observations he has made during his experience as Special Envoy to the WHO:

- Questions of national sovereignty are difficult to solve; some member states do not regard the WHO Secretariat as a partner for negotiation.
- WHO is considerably under funded.

- The world is simply not ready to respond to some public health threats, such as a potential influenza pandemic.
- Even in developed countries, public health does not get funding commensurate with its importance.

To these observations, he offered the following recommendations:

- Member states should strongly consider the benefits of pooling sovereignty with respect to responding to public health threats.
- The status and influence of the WHO must be upgraded in order to encourage the improvement of public health capacity in all member countries.
- Developing countries will have to pitch in to help build the public health capacity that the new IHR will require.
- It is in every member country's best interest to accord greater emphasis on public health, as citizens of all countries may ultimately penalize governments for failing to protect them from public health threats.

Finally, Mr. Byrne commended the work that the scientific and health community has done in the area of international public health and encouraged the community to continue to speak up on these issues. - *Summary by Jennifer Nuzzo, M.S.*