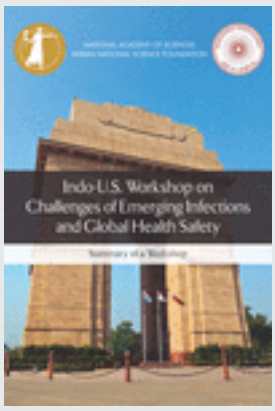

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety: Summary of a Workshop

DETAILS

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Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety

Summary of a Workshop

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Committee on India-United States Cooperation on Challenges of Emerging Infections and Global Health Safety

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PREFACE AND ACKNOWLEDGMENTS

The United States and India, the world's two largest democracies, have pledged to deepen the linkages between their people, their businesses, and their governments "for the mutual benefit of both countries and for the promotion of global peace, stability, economic growth and prosperity."[1] As open societies and leaders in different world communities, India and the United States must both be resilient to domestic and international public health threats. Both nations are now inclined to improve relations and cooperation, but the nations need specific actions that will yield progress and, just as important, build confidence and momentum for further cooperation. Emerging infectious disease is a natural area for partnership.

The Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety, held November 18-20, 2014, on the campus of the Indian National Science Academy (INSA), encouraged scientists from both countries to examine global issues to share experience and approaches, and to identify opportunities for cooperation to improve practice and research in these areas. The workshop was the culmination of a multi-year joint effort by INSA and the U.S. National Academy of Sciences (NAS) to enhance partnership among the scientific and technical communities of the two countries on urgent topics in global health and biological safety.

The primary goal of the workshop was for experts from both countries to share challenges and lessons learned regarding biological safety, laboratory management, and the efficient and sustainable conduct of public and animal health research, and clinical laboratories. A second goal was to encourage collaborative partnerships among Indian and American scientists in areas identified by both groups during the workshop keeping in mind the existing bilateral agreements between the two countries.

[1] U.S.-India Strategic Dialogue Joint Statement released at the conclusion of the United States-India Strategic Dialogue, held in Washington, D.C. on June 1-4, 2010. Available at: http://www.state.gov/r/pa/prs/ps/2010/06/142645.htm; accessed April 10, 2016.

Workshop speakers outlined the burden of infectious diseases and the importance of antimicrobial resistance, pathogen identification, infectious disease control (including the global challenges of influenza and Ebola), and provided an overview of laboratory diagnostics for virulent and drug resistant pathogens. They also emphasized that discussion of biotechnology and synthetic biology is essential because the rate of scientific advancement is only increasing, promising both enormous benefits and potential risks to global health safety.

Participants cited the unique roles and capabilities of the science academies of India and the United States to provide guidance to their governments. Participants also noted that the cooperation between INSA and NAS exemplified in this workshop underscored the opportunities for relevant, realistic, long-term, and sustainable partnership between the life-science communities of the two nations.

In preparation for the workshop, NAS and INSA formed a planning committee comprising prominent Indian and U.S. scientists, laboratory managers, biosafety experts, and government officials. The planning committee members worked collaboratively with scientific and technical experts in both countries to develop the agenda for the workshop.

The following summary intentionally includes a large portion of the material discussed during the workshop to provide readers with extensive insights into the views of the Indian and U.S. participants. The challenges they described are faced by both the United States and India, and both nations have much to learn from the exchange of information and experiences to enhance critical biological research, ensure the efficiency of laboratory operations, and improve the safety of employees, location populations, and the environment. As a result, the technical approaches detailed here will be of interest to many readers. For those readers interested in a high-level overview of the workshop discussions, key messages and promising topics for collaboration arising from the presentations and discussions have been highlighted in the Synopsis.

The U.S. Department of State funded the participation of scientists from the United States and contributed to the participation of scientists in India in this workshop, with supplemental funding from the Kumar and Sheila Patel Endowment to the NAS. INSA provided the facilities and administrative and technical support for the workshop. The generous support of all sponsors is greatly appreciated.

This report is a factual summary of the presentations and discussions at the workshop, and does not provide consensus findings or recommendations. The planning committee's role was limited to planning and convening the workshop. The key issues and selected thoughts on goals and opportunities for collaboration noted in the Synopsis at the beginning of the report are some of those raised by individual workshop participants. Those statements, and any other views presented in the report, are those of individual workshop participants and do not necessarily represent the views of all workshop participants, the planning committee, INSA, or the U.S. National Academy of Sciences.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Academies of Sciences, Engineering, and Medicine's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for quality and objectivity. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We wish to thank the following individuals for their review of this report: Pradip Kumar Chakraborti, Institute of Microbial Technology, India; Bhudev Chandra Das, University of Delhi; Aysen Gargili, Marmara University; James LeDuc, The University of Texas Medical Branch at Galveston; Alemka Markotic, University Hospital for Infectious Diseases, Croatia; Indira Nath, The National Academy of Sciences, India; and David Swayne, United States Department of Agriculture.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the content of the report, nor did they see the final draft before its release. The review of this report was overseen by John Ahearne, Sigma Xi, The Scientific Research Society (Retired). Appointed by the Academies, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs and the institution.

As was demonstrated during the workshop, experts in both India and the United States seek opportunities to work together on issues related to biosafety, high-containment laboratory safety and security, and the benefits to the global population from continued biological and related research. While the task of addressing such a broad range of issues is vast, so too is the experience and expertise available in our two countries to meet this challenge. Joint efforts such as this workshop provide the basis for India and the United States to continue to learn from each other, to exchange ideas for collaborative efforts, and to increase the confidence and support necessary to take their cooperation further as they work to enhance global health safety in their respective countries and around the world.

Rita S. Guenther and Micah D. Lowenthal
Rapporteurs

CONTENTS

Synopsis

The Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety, held November 18-20, 2014 on the campus of the Indian National Science Academy (INSA), encouraged scientists from both countries to examine global issues, to share experience and approaches, and to identify opportunities for cooperation to improve practice and research in these areas. The workshop was convened by INSA and the U.S. National Academy of Sciences (NAS) to enhance partnership among the scientific and technical communities of the two countries on urgent and relevant areas of global health and biological safety. The plan for the workshop is described succinctly in the statement of task in Box S-1.

GOALS AND OBJECTIVES FOR JOINT WORKSHOP

The primary goal of the workshop was for experts from both countries to share challenges and lessons learned regarding biological safety, laboratory management, and the general efficient and sustainable operation of laboratories for public and animal health research, and clinical applications for improving global health safety. A second goal was to encourage collaborative partnerships between Indian and American scientists in areas identified by both groups during the workshop, keeping in mind the existing multilateral agreements between the two countries. The workshop was not intended to provide a particular plan of action or specific concrete next steps for this collaboration. Rather, it was intended to identify a variety of areas in which experts from the two countries can proceed with cooperative efforts pursuing mutual goals and priorities.

Box S-1 Statement of Task

An ad hoc planning committee, under the auspices of the U.S. National Academy of Sciences (NAS) in collaboration with the Indian National Science Academy in New Delhi, India, will convene bioscience experts from Indian academia, industry, and government research laboratories and similar U.S. experts for a workshop to address a suite of issues under the heading of biosafety, biosecurity, and biorisk management. The workshop will feature invited presentations and discussions.

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. The workshop will include topics such as the following: responsible practices in pursuit of the benefits of life science research; matching precautions to risks; facility risk assessment; laboratory certification; mechanisms for reporting laboratory-associated infections; right sizing the regulatory environment; regional transport of samples and specimens; and special challenges and opportunities associated with biosafety level 3 (BSL3) and BSL4 laboratories that were identified in an international workshop held in 2011. This workshop is also intended to inform future discussions of broader topics related to next steps for promotion of biosafety and security in India.

Workshop speakers outlined the burden of infectious diseases and the importance of antimicrobial resistance, pathogen identification, infectious disease control (including the global challenges of influenza and Ebola), and provided an overview of laboratory diagnostics for virulent and drug resistant pathogens. Discussion of biotechnology and modern biology, such as synthetic biology, was also raised as absolutely essential to discuss since the rate of scientific advancement is rapid and is only increasing, posing both potential benefits and hazards to global health safety.

BUILDING ON THE SUCCESS OF THE WORKSHOP

Technical experts in a variety of fields associated with global health security provided presentations and engaged in frank discussions. These

experts were chosen by the workshop organizers from among the countries' leading infectious disease researchers, laboratory managers, biosafety managers of high-containment laboratories from academia and relevant government agencies and organizations. Over the course of the three-day workshop, they provided their perspectives, knowledge, and experience and shared ideas for possible future joint collaborations between India and the United States.

Several speakers from the government of India emphasized the urgent need for advice regarding biosafety guidelines for laboratories, effective training for researchers and clinicians dealing with infectious and zoonotic diseases, and enhanced public engagement and outreach on the importance of safe and secure laboratories.

Beyond India and the United States, multiple speakers and participants discussed the needs of the broader South Asian region for more robust laboratory capacity to address diagnostics, response and research regarding public health challenges. Given India's existing and planned laboratory capacity, capabilities in global health research, and expanding international partnerships, if high standards of safety and security are maintained, the country is well situated to become a regional and global leader in human and animal health safety research.

KEY ISSUES FROM WORKSHOP

The key issues noted here are some of those raised by individual workshop participants during workshop breakout sessions and do not indicate a consensus of workshop participants overall.

- **Strengthening management practices to support biosafety in laboratories**
    - Good management is necessary for good decision making prior to establishing biological safety level 3 and 4 (BSL3 and BSL4) laboratories, during laboratory operation, and in sustaining laboratories over the long term.
    - Safety is dependent on responsible leadership. It is critical that laboratory leadership supports biological safety culture. Culture trumps rules because strong culture results in responsible practices. Good biosafety cultures are created by good leadership or destroyed by poor leadership.

  - Regular assessment of good laboratory management practices can identify best practices and provide options for improvement.
  - Good laboratory management assessments could be included as part of the laboratory accreditation process, conducted by an independent third party.
  - Accreditation, repeated on a regular basis, is necessary but not sufficient. Accredited labs can hide poor culture.
  - Biosafety training in undergraduate and post-graduate course curricula could enhance the culture of laboratory safety by introducing these concepts to researchers early-on in their careers.
- **Levels of Biocontainment Facilities: Answering research questions at economically viable containment levels or with alternative methods**
  - Good quality training and manuals are essential to the safe, effective operation of any laboratory, and video training may be an efficient supplement to other forms of training.
  - Recategorization of biological agents based on the specific research being conducted rather than just on the pathogen itself may allow for more cost-effective and lower-risk research. Submission of protocols to institutional review boards regarding specific research can improve risk assessments and an overall understanding of biosafety needs.
  - Certification, inspection, third-party assessment and re-assessment are essential to credible evaluation of laboratory safety.
- **Establishing and sustaining low-cost and safe BSL-3 facilities**
  - A country could determine the number of biocontainment facilities it will have based on the country's needs, which may vary with time.
  - Biocontainment labs may be specialized for diagnosis of specific agents and specific diseases of national, regional, or global importance.
  - Appointment of maintenance engineers and technicians to contribute at the beginning of the laboratory construction process itself very frequently improves biosafety at the facility.

  - Continuous monitoring of the construction process by trained engineers helps to ensure that they are familiar with the details of the facility's infrastructure, and improves their ability to harmonize design and biosafety measures or practices into the building from the outset.
  - Annual certification and validation of the facility by a certified third party should help to ensure the continuity of biosafety and biosecurity.
  - Biocontainment facilities function properly when managed by well-trained and certified scientists and technicians. This is a prerequisite for the effective surveillance and monitoring of public and animal health.
  - Sustaining safe and secure biocontainment facilities can be aided by allocating dedicated funds for such purposes into all grants for research to be conducted at the facility, and by the development of a group of researchers who can use the facility on a cost-sharing basis.

- **Research of concern on new pathogens: Regulations and codes of ethics**
  - Research on new organisms would benefit from the study of those organisms before they are classified at high levels of biosafety to avoid over-classification.
  - Focusing on naturally-occurring diseases over laboratory-created pathogens may better align research resources with public health needs.
  - All organisms need to be studied, not only a select few; if little or nothing is known about a particular organism, then greater oversight is needed when researching that organism.
  - There is currently no consensus within the global research community on how to address the continuation and/or the publication of research of potential concern.
- **Laboratory-Acquired Infections (LAIs)**
  - The primary causes of LAIs include:
    - Cross-contamination
    - Faulty procedures (causing the majority of LAIs) and facilities/equipment (causing the minority of LAIs)
    - Inadequate inactivation procedures, and
    - Underreporting of laboratory incidents that may lead to LAIs.

  - Cultures of trust in which people are made more comfortable with reporting LAIs are more effective than blaming individuals for laboratory accidents.
    Self-reporting policies that do not focus on attribution are effective models for increasing biosafety.
  - Decision-based management is effective, but requires leadership training for managers and other laboratory leaders.
  - Focusing on procedures over policies may substantially reduce the number of LAIs because if the procedures are safer, they can strengthen safety in the lab on a day-to-day basis.
  - Proper inactivation of organisms is critical to reducing LAIs, therefore standard operating procedures, training, knowledge of kill curve, verification, and validation are essential for researchers.
- **Diagnostic and field testing**
  - Low-cost and indigenous sample containers could improve the safety and security of samples collected in the field and in emergency situations.
  - There is a need for responsible courier companies within countries to transport biological samples to laboratories.
  - Procedures for the collection, storage, and dispatch of particularly infectious diseases can be most beneficial when the procedures are widely known and followed.
  - Training and retraining programs for medical, veterinary, paramedical, and paraveterinary staff ensure that threats to public and animal health are addressed quickly and effectively in all situations.

SELECTED THOUGHTS ON GOALS AND OPPORTUNITIES FOR COOPERATION

Following are some of the questions raised by individual workshop participants during focused breakout groups that might be addressed through collaboration. They do not represent consensus views of workshop participants overall.

- **Risk assessment**
    - At the country level: What is necessary for effective laboratory risk assessments? What is the need for research on especially dangerous pathogens? How should risk levels be assigned for specific pathogens, particularly endemic infections?
    - At the regional level: How can labs be consolidated for the greatest efficiency, effectiveness, and sustainability of research? How can collaboration be fostered to share best practices and experiences regarding risk assessments related to right-sized research?
    - At the institutional level: How can and should the effectiveness, efficiency, and sustainability of separate labs best be evaluated? How can risk assessments best be incorporated into these evaluations?
    - At the laboratory level: How can risk assessments and risk-management practices be factored into laboratory designs before new labs are built and existing labs are (re)evaluated?
    - At the procedural level: Are procedures that require higher levels of containment really necessary to answer scientific questions? How can these assessments be made based on evidence in the interests of both science and biosafety and biosecurity?
- **Establishing and sustaining safe and secure biocontainment facilities**
    - How should the needs of a country, a region, and the world be assessed to inform the establishment of high containment labs?
    - Once established, should high containment labs specialize to avoid redundant research?
    - What makes an organization competent and independent to act as third parties to provide certification and validation of facilities to ensure the continuity of biosafety and biosecurity?
    - What are the best practices associated with training and certifying scientists and technicians?
    - How can sufficient and sustained funds be obtained to ensure the safe and secure functioning of biocontainment facilities?

- **Research of concern**
    - What are the views and concerns of Indian and U.S. scientists regarding research guidelines for working with pathogens of concern?
    - Is there a core set of "Do's" and "Don'ts" in both India and the United States as a starting point for understanding each other's guidelines?
    - How should research on new organisms be prioritized and classified to maintain the focus on public and animal health as well as biosafety and biosecurity?
    - What are the best means of oversight for research in new areas or on new pathogens?
    - How should the issues surrounding research and publication on pathogens of concern be addressed to balance the needs for continued scientific research and biosafety and biosecurity?
- **Laboratory-acquired infections (LAIs)**
    - How can cultures of trust be developed to encourage reporting of LAIs?
    - What are the best practices for leadership training that can improve the culture of laboratories?
    - What are the means by which procedures can be effectively developed, revised, taught, and followed to reduce the number of LAIs?
    - What are specific examples of self-reporting models that have been proven effective in reducing LAIs?
- **Diagnostic and field testing**
    - How can equipment currently available for diagnostics and field testing be assessed, and how can improvements be introduced in a low-cost manner?
    - How can the transportation of infectious pathogens be expedited safely in public health emergencies? What agreements and procedures need to be in place within countries, regionally, and internationally prior to a public health emergency? How can India and the United States work to develop the infrastructure necessary to cooperate in a public health emergency?

  - What lessons can be gained from experience with recent outbreaks to inform the training of medical, veterinary, paramedical, and paraveterinary staff as well as scientists?
  - What are the needs nationally and internationally for diagnostic testing for pathogens?

- **Strengthening management practices to support biosafety in laboratories**
  - How can cooperation and coordination between the regulatory authorities of both countries be improved to synchronize biosafety guidance?
  - How can we ensure that leaders and managers have the skills to do their jobs properly to create an organizational environment of safety and security?
  - Given that biological safety training is most effective when tailored to the level of the student, and that training for leaders and managers will most likely be different, are there effective training models to follow? How can they be specified for the needs of a particular manager and/or laboratory?
  - How should management be included prior to establishing laboratories, during laboratory operation, and while sustaining laboratories over the long term? What training and/or input are needed at which stages?
  - How can laboratory managers lead by example to support a biological safety culture among all laboratory staff?
  - How can regular assessment of good laboratory management practices identify best practices and provide options for improvement where relevant? Is mentoring an option? Within a country? Between the United States and India? Informally? Formally?

The workshop concluded with a spirit of optimism and a desire to follow the bilateral effort by drawing in experts from countries in South and Southeast Asia into similar conversations.

INTRODUCTION

President of the Indian National Science Academy (INSA), **R. Gadagkar**, opened the joint Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety by stating that the topic of the meeting could hardly be more important or more timely. Infectious diseases respect no national borders; hence, the focus on global health safety. The joint effort between INSA and the National Academy of Sciences (NAS) provides an opportunity to lead our nations to establish state-of-the-art life sciences research infrastructure and to meet the multiple and complex human and animal challenges ahead.

Krishnan Lal, immediate past president of INSA, added that the unexpected emergence of infectious diseases like Ebola and the recurrence of influenza attract the attention not only of the scientific community, but also of the academies and the governments of India and the United States. Another persistent issue, which remains unsolved and deserves attention according to Lal, is that of drug resistance such as drug-resistant tuberculosis. **V. M. Katoch**, director general of the Indian Council of Medical Research and secretary of the Indian Department of Health Research, noted that scientific cooperation among experts in India and the United States has deep roots extending back decades, and has resulted in formal agreements with the Centers for Disease Control (CDC), the National Institutes of Health, and other agencies. Immense contributions to addressing emergent and persistent health challenges have been made by experts from both countries. Together they are mapping outbreaks of many infections and identifying which are emerging and reemerging, and are trying to solve real problems of disease.

Animal and human influenza in particular motivated a great deal of cooperation. The H1N1 outbreak of 2009 led to the development in India of a plan to create a network of research and diagnostic laboratories.

Thus far, 15 laboratories have been established that have enhanced the speed and capability of diagnostics. Some laboratories are investigating approximately 800 viruses simultaneously representing a wide coverage of the potential disease burden, and have mapped all viral diseases in a specific geographic area. This has resulted in some initial metrics of emerging diseases in some parts of the country.

Through cooperation with the CDC, novel technologies have been incorporated into a network of 10 regional laboratories, which will be part of the Indian federal laboratory network slated to be completed by 2016. In addition, there are 30 state-level laboratories in medical colleges. These colleges have a strong record of publishing both on viral diseases and on bacterial illnesses, such as outbreaks of anthrax, plague, tuberculosis, and other infections. In addition, there are 120 government medical schools, called college-level laboratories.

Katoch highlighted the support provided by U.S. colleagues on the development of the laboratory network, and the need to continue cooperation on growing challenges such as that of drug resistance. In addition, persistent problems remain, such as the potential for outbreaks of anthrax and plague. Due to the potential threats posed by these and other diseases, high-containment laboratories are being used by researchers seeking to address these human and animal health concerns. Regulatory bodies in India are empowered by law to oversee the research and diagnostics in these labs.

The Indo-U.S. partnership has greatly accelerated, and it is truly a unique opportunity to combine the various strengths and the long-term relationships between Indian and U.S. scientists and governments and to harness them for the particularly urgent issues confronting the world. Katoch expressed his hope that the United States would continue to both empower and fund its agencies that work on the ground in India, including CDC, the National Institutes of Health, the Food and Drug Administration, the U.S. Agency for International Development, and the State Department. The cooperation has enjoyed high-level support: When President Obama and Prime Minister Modi met in the United States in September 2014, both specifically highlighted cooperation on health and the desire to strengthen assistance for these efforts.[2] Katoch said that the voices of scientists are necessary to speak truth to power and

[2] U.S.-India Joint Statement. September 30, 2014. Available at: https://www.whitehouse.gov/the-press-office/2014/09/30/us-india-joint-statement; accessed April 10, 2016.

he asked participants to continue to hold their government leaders to their commitments; these efforts on public health security are incredibly important and that importance will not diminish. Katoch then noted recent positive trends. Many countries are starting to reevaluate the implementation of the International Health Regulations (IHR) based on the results of new research and such reevaluations often point to the need of further research. Further implementation of the regulations can only happen if scientists are both producing good work and maintaining strong collaborations with their public health and policy colleagues so that science is translated into strong public health programming.

Amy DuBois, Health Attaché to the U.S. Embassy in India, stated that the joint workshop could not be more timely: The issues of global health safety and emerging infections are in everyone's consciousness. The World Health Organization declared the 2014 Ebola outbreak in West Africa a public health emergency of international concern. The participants who came together for the workshop, and all of the work the event represents, reflect the global community's commitment to start addressing these issues. We must, she said, mitigate the resulting humanitarian crisis and dedicate ourselves to the science necessary to increase the likelihood of preventing future outbreaks. When outbreaks cannot be prevented, we must be able to respond with better management and better tools.

DuBois hoped that the results of the workshop would include innovative ideas and new areas for collaboration, new proposals, and new opportunities and that participants would communicate those to the world and translate them into reality.

DuBois emphasized that participants should take the discussions from the workshop beyond the conference hall to people who are not as aware of what needs to be done and are likely to forget the urgency of these issues as soon as the immediate crisis has been addressed. These discussions should be shared with the people upon whom we depend to ensure that there is funding, sustained engagement and political commitment, and that there will be an effort to put the science that is created—the science that is analyzed, packaged, and published—into strong public health policy.

B.M. Gandhi, who is responsible for biosafety-related issues at the Department of Biotechnology (DBT), then noted that ensuring universal research safety is challenging in India because there are so many universities and so many institutions and private industries. As a result, it is not clear whether the necessary biosafety precautions are being taken

by everyone engaged in these activities, and if not then biosecurity issues could arise. At a meeting in Hyderabad, an expert discussion was held on these issues, and the participants felt it necessary to have a dedicated body in India to address biosecurity and biosafety, because experience indicates that until recently there was little attention given to biosecurity. A further challenge is that many hospitals use potentially hazardous materials, and they are often discarded in open containers. Some precautions have been taken, but participants therefore suggested that these issues should be examined very seriously and ways to mitigate these problems should be developed. Due to the magnitude of the challenges, India would definitely gain from the experience of the United States, Gandhi said. He suggested that it would be useful for workshop participants to outline collaborative programs that can be initiated by the government agencies of the United States and India.

Indira Nath added that she also believes that there are not enough people working on biosafety and biosecurity in India. Experts at the biosafety lab in Bhopal have been doing a great deal, but they concentrate on animal health, and a similar human equivalent is needed, perhaps through an association or society. This does not seem to exist currently in India.

Diane Griffin, NAS vice president, stated that the academies of sciences across the world, but certainly those in the United States and India, are extraordinarily important in providing independent advice to governments on many issues, including those related to infectious diseases. The ability to bring that kind of independent advice to speak truth to power is informed by having strong interactions with other countries.

She continued by saying that we live in a global world, and that is very obvious when we talk about infectious diseases, which do not respect national borders. But being able to learn from each other and having strong interactions with other academies also makes the advice that the individual academies can provide to their governments much stronger and much better informed. This kind of workshop is important to reflect the long-term, long-standing interactions between the Indian and U.S. governments, and also among Indian and U.S. scientists.

Griffin noted that there are many Indian experts who have been elected as foreign associates of NAS, including some of the workshop participants, as well as of the U.S. National Academy of Engineering, and the Institute of Medicine. This provides another mechanism by

which scientists can interact and inform each other and eventually their respective governments.

Dinakar Salunke, vice president of INSA, underscored the fact that in addition to epidemics faced over the last decade, new diseases continue to emerge. The two democracies and their independent science academies are in a unique position to discuss emerging challenges and global health safety. He believes there is no other combination of academies that could do this better. The workshop discussions raised important policy-related issues, and considering that the Indian health research secretary and the biotechnology secretary have addressed workshop participants, it is obvious that the government of India is listening. Given the interest and commitment of the two governments, as Lal said, scientists at the workshop and beyond should develop ideas that will be useful to our governments.

1

Framing the Issues

James LeDuc, workshop co-chair, explained the origins of the workshop: It was based on a similar workshop that convened experts from 32 nations in Istanbul, Turkey, in 2011.[1] At the end of that workshop, attendees visited a BSL-3 laboratory that was under construction in the outskirts of Istanbul. At the workshop, LeDuc met a bright young veterinarian with a Ph.D. in virology who had a special interest in tickborne diseases. Subsequently, she went to the University of Texas Medical Branch (UTMB) for a fellowship to conduct research and to work on biosafety and biosecurity at LeDuc's laboratory. During the year-long fellowship, she went through the entire training program, along with mentorship, to learn how the laboratory is managed and how to ensure that it is working efficiently. At the end of the fellowship, she had full and complete independent access to the lab.

When she returned to Turkey, having conducted transmission studies on Crimean-Congo hemorrhagic fever and published her research, she observed a tremendous demand, not only for good science, but also for hands-on training in biosafety and biosecurity. She then offered a class on biosafety and biosecurity to participants in Turkey, based on materials provided by UTMB. This is a success story, both in a scientific sense and in terms of capacity building—the ultimate in the train-the-trainer concept. LeDuc expressed hope that New Delhi workshop participants would identify similar kinds of opportunities where people can have honest exchanges and true partnerships.

LeDuc continued by framing the issues related to the overall workshop goals. Ebola is clearly a global issue that deserves significant attention. LeDuc recalled that his home state of Texas received an

[1] National Research Council. 2012. *Biosecurity Challenges of the Global Expansion of High-Containment Biological Laboratories. Summary of a Workshop*. Washington, D.C.: The National Academies Press.

imported case.[2] This provided real, firsthand experience of what happens when someone arrives at a hospital with Ebola. No country is immune from the possibility of disease importation. What would happen if a case were imported to Asia? The U.S. response and prevention strategy focused on points of entry for people coming from West Africa, but that strategy would have to change if Ebola or another disease were to come from many points around the world.

There has been a proliferation of new biocontainment laboratories around the world, including in India. As more laboratories are built, there are more people involved in the handling of pathogens. This requires us to seek to maximize the benefits from laboratory research while minimizing or managing the risks that they can pose. Biocontainment training is one element of addressing those risks, but even in the best programs, the most conservative environments, accidents still occur. In the United States, three recent incidents have garnered a great deal of attention: the release of potentially infectious anthrax; the transport, unknowingly, of highly pathogenic avian influenza; and the discovery of 60-year-old smallpox virus stored away in the corner of a laboratory at the National Institutes of Health.[3] Any one of these incidents alone would have been a significant issue. The U.S. government described the incidents as unacceptable and decided to take action. The White House has encouraged all U.S. research organizations to suspend research with dangerous pathogens and to review their current biosafety and biosecurity protocols. These organizations are also being directed to conduct an inventory to make certain that there are no additional smallpox caches and to increase awareness about biosafety and biosecurity more generally.

In addition, there is ongoing discussion of the great benefits and potential risks arising from the tremendous advances being made in biotechnology, including the dual uses of research of concern. Gain-of-function studies, in particular studies enhancing transmission of influenza viruses, have been among the most contentious issues. The United States recently instituted what is called a "pause" on gain-of-

[2] For more information, see the Centers for Disease Control: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html; accessed April 10, 2016.

[3] Julie Steenhuysen. "White House Issues Report on Improving Biosafety at Federal Labs," Reuters. October 29, 2015. See: http://www.reuters.com/article/usa-whitehouse-biosafety-idUSL1N12T4EV20151029; accessed April 10, 2016.

function research while the community reexamines these issues.[4] Different countries have different perspectives on these issues and there is no single "right" answer. Nonetheless, LeDuc said, problems encountered in this type of research should be examined in the context of a global, interconnected environment: An outbreak anywhere is a threat everywhere. Ebola is a prime example. Another critical set of issues surround the topic currently called One Health: The lines between animal health and human health continue to blur, with many diseases originating at the intersection of animals and humans. Addressing all of these issues well requires the sharing of experiences and lessons learned from both sides.

LeDuc said that as research and laboratory capacity are developed, it is clear that both strong technical competence and responsible leadership are needed. The Turkish veterinarian who trained at UTMB returned to Turkey not only with technical skills, but also leadership skills on how to run a laboratory safely and securely; experience that is scarce and valuable. Grooming leaders going forward is an essential area that deserves discussion and suggestions.

DETERMINING AND DEVELOPING THE RIGHT ELEMENTS FOR SAFE AND SECURE RESEARCH

David Franz opened his remarks by recalling his early experiences as a researcher and as the director of a high-containment laboratory prior to the September 11, 2001 attacks on the United States (9/11). At that time, he would have led a command briefing by stating that his three top priorities were biosafety, biosafety, and biosafety. Also, when he took over as commander, he changed the organizational diagram so that the safety officer reported directly to the commander instead of lower down in the chain of command. Franz stated that he took those actions not because he was particularly smart or wise, but because he was afraid and did not want anything to go wrong on his watch. He realized that if a researcher in a BSL-4 lab sticks a needle through a glove or if a bone fragment of a laboratory animal punctured a glove while a researcher

[4] For more information, see: White House, "Doing Diligence to Assess the Risks and Benefits of Life Sciences Gain-of-Function Research," October 17, 2014. Available at: https://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research; accessed April 10, 2016.

was conducting a postmortem, it could mean certain death for that person. This realization was a strong motivator.

With that context, Franz described a conversation he had at a biosafety and biosecurity meeting in Casablanca in May 2013. Participants were discussing how to make biosafety and biosecurity part of the scientific and research culture. In other words, how do we move beyond just a certificate on the wall and a checkbox in some book that says someone has been trained? Although nearly all participants at the meeting in Casablanca were biologists, one Tunisian engineer and a former government minister were also involved, and the engineer said, "It has got to be in the soup. It has got to be in the soup." He explained that biosafety and biosecurity have to be part of the culture of laboratory research, along with scientific knowledge, experience, and many other factors. Each factor acts as an ingredient in soup, essential to both taste and nutritional value.

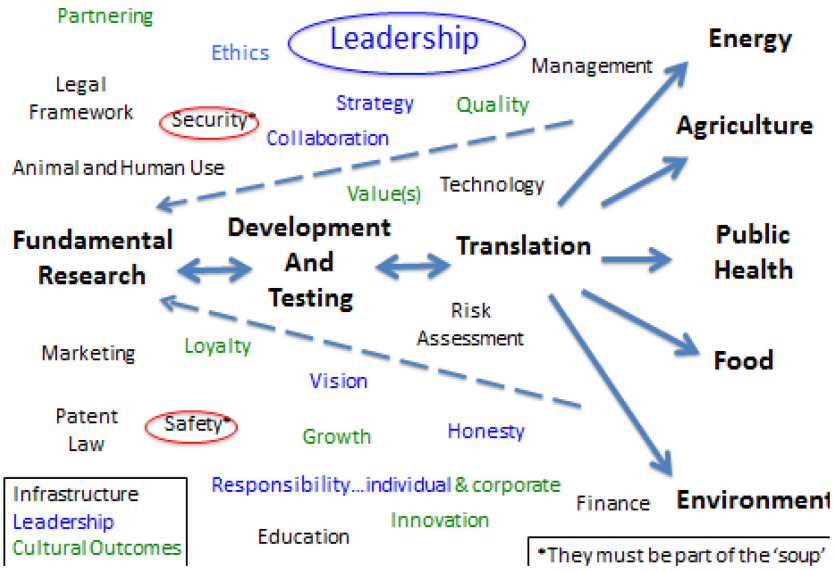

FIGURE 1-1: Sustainable biological safety and biological security programs. SOURCE: David Franz, presentation at the workshop.

One category of ingredients required in the "soup" is infrastructure, which might include a legal framework, animal and human use, marketing, patent law, risk assessment, management, and/or technology. A second category is leadership, which is also absolutely necessary. Leadership might provide strategy, it might encourage collaboration, it might provide a personal, and subsequently a corporate, set of ethics or a sense of corporate responsibility, honesty, vision, and integrity. A third category is culture, which Franz calls a healthy enterprise culture or a healthy laboratory culture. That culture includes outcomes such as innovation, growth, loyalty, quality, values, and so on. The entire system has to work together, including safety and security, to differing degrees in different types of organizations or facilities. In these research endeavors, we are all working toward something of societal value. However, there is no market for safety: Security does not feed hungry children, and fences around labs do not make vaccines available to animals or humans.

As the United States, particularly the government, has been in a hurry to make the world a safe and secure place, American experts have traveled around the world and trained many people. However, a training certificate alone is not enough; biosafety and biosecurity have to be part of the culture of a healthy research enterprise, a healthy laboratory culture.

Franz recognized that there are many different circumstances around the world. When he was in Sierra Leone in May 2012, he talked to a health ministry official and naively asked about their life sciences research. The official replied that research occurs where the basic needs have already been met, but Sierra Leone's basic needs have not been met, so they essentially do not conduct research. In that situation, for many people the most important enterprise is finding food, or firewood to cook food for the next day, and so on.

In nations with more means, Franz continued, researchers have the luxury of working to develop agriculture, public health, and food. In still others, such as in India and the United States, experts have the greater luxury of working on all of these areas to provide all of these products for the citizens of our countries. In those enterprises, each of us needs safety and security of some kind to differing degrees. However, there are challenges resulting from differing government visions; differences within governments and between governments. For example, right after 9/11 and the anthrax letters, it seemed that all of the emphasis in the United States was on security. Over time, the emphasis has drifted

increasingly toward safety. During the Cold War, U.S. researchers working in biocontainment laboratories focused on threat agents: anthrax, plague, tularemia, and Q fever. Since then we have moved much more toward naturally emerging diseases, which Franz believes is the right approach.

There are also resource imbalances around the world and even within countries. There are always political barriers and there will always be some hurdles to overcome in that regard. However, there are many opportunities as well. There are many common views among individuals, and many similar needs, such as public health, security, and energy. We are fortunate to live with enormous technological capabilities and improvements that have occurred over the past 15 to 25 years. Yet without collaboration those technological tools are not enough to address the needs of our societies. That is why Franz thinks collaboration is so critical, within our organizations, between our organizations, and between our countries.

Returning to the soup, Franz underscored that biosafety and biosecurity act as metaphorical immune-enhancing vegetables, which is important. However, biosafety and biosecurity are necessary but not sufficient. Over the last 10 years, the United States has engaged with scientists around the world to consolidate pathogens into central laboratories. U.S. programs have tried to improve the security of select agents, trained and certified people on biosafety and biosecurity, and helped to start biosafety associations around the world. Yet the long-term positive effect of these efforts, that is their sustainability, is still unknown. If these elements are embedded in a healthy research laboratory culture, they will be sustainable.

Where do we go from here? There are many ongoing global efforts on risk assessment, infectious disease detection and reporting, collaborative life-sciences research, and so on. In recent months, the International Health Regulations, which have existed for many years have received more attention.[5] These new efforts have been more "bottom up," arising from interactions among practitioners. The new Global Health Security Initiative is more of a "top down" approach to

[5] For more information, see: World Health Organization, International Health Regulations. Available at: http://www.who.int/topics/international_health_regulations/en/; accessed April 10, 2016.

engagement, with the goals and framework provided by governments.[6] It is important that at the laboratory leadership level or at the ministry level, people are involved in understanding the value of safety and security in our organizations. Leaders who value these programs must support them and ensure that the communities with in these organizations know that this is critically important.

The question is, How can we move beyond the status quo? Franz then shared an example about the large aluminum company Alcoa. When Paul O'Neill became the new chair of this corporation in 1987, he gave a briefing for the shareholders. He started by discussing worker safety. There had been many problems in the company, and many accidents. When O'Neill began speaking about worker safety, some of the shareholders actually ran for the door and called their brokers to sell Alcoa stock, because they thought he was crazy.

He persuaded them to stay by saying that if the company moves forward and becomes more prosperous, it will be because individual workers at this company have agreed to become part of something important; they will have devoted themselves to creating a habit of excellence. Safety became an indicator of progress in changing habits across the entire institution. O'Neill assumed his position in 1987 and retired in 2000. Over that time, the company's market value increased from $3 billion in 1986 to $27 billion in 2000, while net income increased from $200 million to $1.4 billion. Even though O'Neill is now long retired, safety is still a high priority for the company. He left a legacy that changed the culture of the company. Franz believes it is possible to have this type of impact in laboratories as well.

Franz shared his thoughts about how leaders can influence the culture of a laboratory. If we all lead with science, and emphasize quality, safety, vision, education, responsibility, accountability, honesty, transparency, and ethics, then a culture of trust will result. We could also lead with regulatory oversight and security, guns, gates, guards, background checks, psychological evaluations, lists, and pathogen controls. We experienced this in U.S. laboratories post-9/11 and after the anthrax letters. A culture of trust, Franz believes, is more effective than the alternative.

[6] For more information, see: Global Health Security Initiative. Available at: http://www.ghsi.ca/english/index.asp; accessed April 10, 2016.

In his book, *The Speed of Trust*,[7] Stephen M.R. Covey describes the characteristics of high-trust and low-trust organizations. Leaders like Alcoa's Paul O'Neill, and like any of us, can establish high trust organizations with that kind of culture, Franz said. We have the power as leaders to do that if we have the will to do so. In a healthy laboratory culture, safety, security, and also scientific productivity are all present.

Discussion

The discussion following Franz's presentation focused on ethics; incorporating ethics, biosafety, and biosecurity formally into education and training curricula; the need for guidelines; the roles of practitioners and leaders in improving biosafety and biosecurity; and other topics.

Ethics

A participant asked whether ethics is part of Franz's conception of essential ingredients in the research endeavor he calls "the soup." Franz replied affirmatively, saying that scientists should be aware of relevant treaties, norms, and codes. As the discussion continued, ethics, biosafety, and biosecurity were sometimes referred to with blurry definitional boundaries or as a common category.

A participant from the National Institute of Immunology in New Delhi stated that the institute has a robust human ethics committee of seven members: a lawyer, a layperson, two practicing clinicians, two medical researchers, and a basic scientist. Each research project is evaluated on the basis of how human material is going to be used ethically. The institute also has an equally robust system regarding animal biotechnology. This is a slightly tricky and sensitive issue because there is an attempt by the animal biotechnology committee to reduce the number of animals used in research, which creates a problem when trying to obtain statistically significant findings.

Another participant from India refined this point, saying that the ethics being taught in India do not address biosafety as discussed to that point in this workshop. What is taught addresses the procedures used to determine the number of animals needed for an experiment, whether the animals will experience pain, and whether they will be sacrificed during

[7] Covey, S.M.R. and Merrill, R.R. *The Speed of Trust: The One Thing that Changes Everything.* Free Press, New York: 2008.

the experiment. However, laboratory procedures by which workers should be safe and secure is not addressed by the ethics committee.

Franz noted that over the course of his career, similar programs have been developed, such as those required under the Animal Welfare Act.[8] Scientists may initially ask why they need to reduce the number of mice. It is important to have someone who can articulate this goal and help implement those measures at the scientist level. It is also helpful if the director of the institute emphasizes the need to fulfill the spirit and the letter of the Animal Welfare Act, or the Human Ethics Act.

Another participant said that the All India Institute of Medical Sciences has a biosafety committee, which also looks into the safety of work on recombinant DNA.[9] It is now mandatory in India that every institution have such a committee to examine biosafety issues as well as the safety of projects involving recombinant DNA. The participant serves as a member of the institute's ethics committee and has served as a member of the biosafety committee. The biosafety policy states that if a question is referred to the human ethics committee and it has issues related to biosafety, then the matter is referred to the biosafety committee, and the researcher must acquire clearance from both the ethics and biosafety committees before proceeding with the experiment.

Another participant noted that biosafety committees in India address primarily recombinant DNA issues and to a lesser extent chemical hazards. They do not address more difficult issues of biosafety and biocontamination; that is still not mandatory. Another participant noted that there are also separate safety committees for stem cell research. In some cases, researchers follow the guidelines for the biosafety committee, the bioethics committee, and the stem cell committee. Currently, the Department of Biotechnology (DBT) and the Indian Council of Medical Research (ICMR) insist that every project submitted have bioethics clearance or human ethical committee clearance. Biosafety clearance is not required, which according to the participant is why it is not frequently addressed. The regulations exist on paper, but frequently they are not followed; these guidelines are also not very clear.

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[8] For more information on the Animal Welfare Act, see the U.S. Department of Agriculture at: https://awic.nal.usda.gov/government-and-professional-resources/federal-laws/animal-welfare-act; accessed April 10, 2016.

[9] For more information on the All India Institute of Medical Sciences, see: http://www.aiims.edu/en.html; accessed April 10, 2016.

B. M. Gandhi noted that ethics is related to the attitude of the scientists. ICMR already has a code of conduct—an ethics code—which clearly spells out how researchers should proceed, which direction should be taken, and so forth. This is the same with the 2000 guidelines, which has a code of ethics for researchers. There is another guideline from DBT from 2002 for preclinical testing.

Gandhi agreed that with regard to biosafety, researchers do not always follow the code of ethics. He added that if they follow this code properly, they automatically address biosafety as well. Nath, however, was not certain about that. Another participant stated that, as of the time of the workshop, there was no guideline written on biosafety, as being discussed in this context. Nath agreed with this impression. Biosafety and biosecurity, she said, are still not sufficiently taken into consideration by India's leaders.

Indira Nath noted that a bill slated to go before parliament is about ethics (see Chapter 5), and she asked Franz to share his thoughts about the separation of ethics issues from biosafety issues, and about biosafety issues not falling under the ethics committee. Nath expressed concern that if there are too many committees from which an institution and a researcher must obtain research approval, a disincentive for creativity and for conducting scientific work will be created. Should these two elements be combined? Franz replied that his experience is perhaps outdated. He believes in establishing a culture of personal responsibility and corporate responsibility. Then, if these exist, it becomes a matter of just knowing what is right and wrong, and doing what is right. That, however, does not necessarily scale well. Some ethics training includes topics like dual-use research of concern. Traditionally, ethics committees in the United States addressed issues such as plagiarism, and now some of the other issues raised in this discussion have been brought together in certain settings. One committee may not be able to cover it all. The technical needs for the human use committee and the animal use committee are going to be different. Nath noted that ICMR and DBT jointly released a code of conduct especially for dual-use researchers. For the past 2 years, however, it has not functioned.

Nath also noted that still other issues fall under the Environmental Protection Act such as guidelines addressing risk management, detection, and other topics. These issues are not part of the training, so there is a disconnect. This new code of conduct, which is on the ICMR website, addresses dual-use research, researchers' responsibilities, institutions' responsibilities, and issues of compliance. There is a need to discuss

biosafety and biosecurity further, because there are people who do not understand these issues, she said.

A U.S. participant, who serves on a committee on genetic manipulation, noted that most organizations have three separate committees: One for animal ethics (the Institutional Animal Care and Use Committee or IACUC),[10] one for human ethics, and one for institutional biosafety. If a researcher is conducting research on recombinant DNA and a high-risk pathogen, approval is also required from the institutional biosafety committee (IBC). If an animal experiment is involved, the researcher has to gain approval from the IACUC, and if samples are being taken from humans or if experiments are being conducted on humans, then the human ethics committee approval is required. In the IACUC, the animal ethics approval form has a question at the end of a column which asks the researcher about the use of a recombinant organism or a high-risk category organism. If the answer is yes, then the IBC must also grant approval.

Incorporating Ethics, Biosafety, and Biosecurity Formally into Education and Training Curricula

Gopal Pande noted that a workshop on biosafety and biosecurity was held at Punjab University, and he found the overall response from students to be striking: The student community really sought greater understanding about general research methods regarding safety and security pertaining to microbiology and wanted it incorporated into the curriculum. He asked how much biosecurity and biosafety are part of the curriculum in the United States and whether they could be discussed in a joint meeting. Another participant from India stated that biosafety and biosecurity should be incorporated into the curriculum of all the sciences that deal with organisms from the fields of human health, veterinary health, and homeopathy.

Franz replied that there are some centers in the United States that teach ethics, safety, and security (see Chapter 6). **Joseph Kanabrocki** stated that the University of Chicago has developed methods to try to impress upon faculty, staff, and students at all levels the importance of improving the culture of safety and security. There are lessons learned through experience, but he agreed that education has to begin early in a

[10] The IACUC addresses ethics issues as well as the daily care of animal, training, compliance, etc.

person's career. At the University of Chicago, the concepts have been incorporated into basic microbiology courses. He has been asked to lecture in medical microbiology programs, in undergraduate microbiology courses, and in ethics training courses at the university.

A participant stated that India has training programs on biosafety and biosecurity for those working in biocontainment facilities. Similarly, they have been conducting training programs on the code of ethics for human and animal use and safety. There are very few training programs integrating these two components—codes of ethics and security issues—together because often researchers do not understand the need for one or the other component. The participant said that there ought to be training programs combining these two so that there is a total awareness of the entire set of issues. Problems arise because people are not clear about how the issues are related.

A participant stated that scientists need to understand that biosafety and biosecurity can be beneficial for them. The amount of training required on these issues is astounding. However, many scientists think that most of the training is for liability purposes, for the institution, and not at all for them. It is becoming very cumbersome for a scientist to be required to take even more training such as human trafficking training, for example, because it has nothing to do with scientific work in any way. He said that the most challenging question is how to consolidate these issues for the benefit of both the institution and the individual.

The time has come, agreed another participant, to combine education about laboratory procedures with biosafety and biosecurity training so that people are aware of these issues in totality, especially at the university level. However, it is currently not possible to introduce core ethics training into the curriculum at universities or in medical schools, the participant said. Biosafety is even further away.

Another participant added that laboratories should also be concerned about dual-use research. This may be discussed at some labs where basic research is conducted, but comprehensive information is lacking and more training needs to be developed. These kinds of courses already exist in many U.S. universities, and the participant suggested that these courses should be examined and such a program should be developed in India, especially at the undergraduate and graduate levels. Other participants also stated that such courses are currently nonexistent in India and are urgently needed.

A participant from India asked other participants from India who have more experience with regulations and guidelines about whether

such an integrated curriculum would be advisable. There may already be too much information being added to the curriculum to be effective, since undergraduates are also trying to learn the science itself. One participant replied that this integrated approach will become part of the system as they learn the content matter; they ought to learn the safety issues simultaneously because it cannot be disaggregated, and it is more difficult to add this information after the fact. If this material is incorporated from the beginning, it is not an additional burden and students learn from the beginning that this is necessary.

The Need for Guidelines

Another participant sought clarification regarding whether national guidelines for biosafety exist in India. A participant replied that they do not and added that such guidelines must be developed within a framework that follows from national policy.

A participant noted that regardless of national-level initiatives, individual institutions and individual scientists are the ones closest to the research. The institution has ultimate responsibility, but the researcher assumes the obligation to conduct research appropriately, according to the framework of the guidelines that have been provided by the national authority and by the institution. To leave these issues to a committee that has no national guidelines, for instance, is not something that would work well.

Umesh Datta Gupta added that there are biosafety guidelines for institutions in India. However, there is a great deal of emphasis on genetically modified organisms, and there is a great deal of plant research involved. In a way, the guidelines are there, but they are also not there because they do not cover the topics that were being discussed at this workshop. As a member of the Institutional Biological Safety Committee, and as a DBT representative, Gupta said that the full extent of the questions currently asked is the following: Will you use a vector? If so, will it be a bacterial vector or a viral vector? If a researcher uses a viral X-vector for a protein expression, the researcher is to follow biosafety measures. But if the researcher uses plasmids, there are no questions. These types of inconsistencies exist in the current guidelines, and they need to be addressed.

A participant noted that there is a need for guidelines to be published in advance because when each new epidemic emerged, like HIV, there was such initial fear that few doctors were willing to treat patients. HIV patients were admitted to hospitals only after procedures clearly stated

how to control the spread of the virus. The same thing happened with Ebola as with any new infection. Similarly, there was a time when almost no one was willing to go to a tuberculosis hospital, although the statistics indicated that the incidence of tuberculosis among hospital workers with close contact with the patients was far lower than that in the general population. Yet until these statistics were released, it was difficult to find medical people who were willing to work in such a hospital. This indicates the importance of the type of guidelines being discussed and the need for recommendations to be formulated regarding research and treatment procedures.

The degree to which guidelines about the movement of people from countries experiencing an epidemic to other countries should be implemented was raised by another workshop participant. Under which circumstances should movement be restricted? Are there some guidelines available? If not, should they be prepared? Franz replied that this is exactly what the United States was going through with respect to Ebola at the time of the workshop. Different countries and regions of the world set different standards for acceptance of travelers into and out of their countries. The World Health Organization provides guidelines, which are sometimes followed.

Nath added that the problem really emerges at the nascent stage of an epidemic, when knowledge is still not sufficiently developed. Guidelines can be developed after an epidemic has occurred, such as with Ebola. Likewise, the early stage of research is still very vulnerable because it is a very creative stage. Franz agreed that the most valuable resource we have at that stage is smart subject-matter experts around the world who have worked on a variety of outbreaks in many geographic areas, who know each other, and who know whom to call. It is more important than having a drug or vaccine because we are always dealing with the unknown, and we cannot predict outbreaks very effectively.

Leadership

Franz added that workshop participants, as leaders, have to live the values of ethical, safe, and secure research so that the people working for them can see that they believe and know the importance of those values. All of these essential components need to be integrated into the culture as a whole package.

Another participant added that biosafety classes are an excellent way, especially for the bench scientist, the microbiologist, and the student, to begin to strengthen the culture of safety and security. There

has been success in twinning or mentoring where people do not just go to classes and lectures to absorb the material. Rather, people who are in leadership positions, usually in biosafety leadership, go to the labs and spend months with the scientists to see how operations are conducted. Part of the success comes from knowing and understanding the intricacy of how all these issues fit together. It is not just the physical building or the safety equipment, but also the people and how they work and operate, their procedures and policies, that are all critical to establishing and maintaining a biosafety culture.

A participant from the United States who works on HIV relayed that at least once a month a member of a committee visits the lab and ensures that procedures are followed, for example, that items are not put in the corridor and that items are being discarded in a way that does not result in aerosolization. There may be a way for institutional committees in India to similarly visit labs once a month.

Another issue of leadership is linking compliance to funding. A participant noted that this approach gives credibility to the biosafety program; it is an initial foot in the door, so to speak. Following from this, a participant proposed the idea that labs and institutions could be accredited. This would cover all critical aspects of research oversight.

Encouraging the Participation of Scientists

A participant from the United States pointed out that the "soup" is fantastic, but following the metaphor, there needs to be an incentive to eat it. Although it is not a popular thing to say, most people who work in science have certain self-interests, such as seeing their work published, improving their standing in the scientific community, and so on. These interests may take priority over biosafety issues. One of the easiest incentives to encourage researchers to fully embrace biosafety, norms, ethics, biosecurity, and so on, is international collaboration. It is incredibly difficult to collaborate with scientists from other countries and to publish the results if the standards are not the same in the different laboratories. By establishing common guidelines, young scientists could more easily be convinced to absorb these norms as part of the culture if they know that they will be able to publish.

Nath contributed an idea regarding publication. Scientific journals can be very powerful by establishing requirements for publication. For example, ethics really improved after ethical clearance was required by publications. They have a great deal of power, which they are not using to advance these issues. Since they require ethics committee approval,

they could also ask for biosafety committee approval from authors as a prerequisite to publishing.

Further, a participant pointed out that it has been challenging to publish with international collaborators because many of the journals require authors to provide the numbers of the institutional biosafety committees' (IBC) discussions and the numbers for grants and so on. These numbers do not exist in all countries. Although the laboratory where the experiments are being conducted adheres to U.S. specifications and committees evaluate their work, official evidence of this is difficult to acquire in many countries, so they cannot send their results to any journals. This is a double-edged sword: On the one hand, people want these institutions to be established, which is very good. At the same time, many people cannot become visible as researchers because journals are asking for several requirements that are difficult for individual scientists to obtain.

Balanced Regulations

A workshop participant discussed the need for balance between creativity and regulation. The consequences of an imbalance are faced at the laboratory level when a regulation becomes too strict and constrains scientific creativity. Franz agreed that this balance needs to be addressed, and he provided an example from his own experience. At one very good laboratory, he met with eight principle investigators. Three or four of them said that if they had to do it again, they were not sure that they would become infectious disease researchers because it was becoming so difficult to conduct research, and there is little research funding available. Franz said that if we do not make conditions better for scientists, they will go into different fields.

Infectious Diseases Kill

Another participant and Franz noted that while there is some awareness in the general population that weapons used in war can kill many people, very few people realize that pathogens, what the participant called "agents of mass destruction," kill many more people than any weapon of mass destruction. What mostly kills people is not weapons, it is drug resistant tuberculosis, HIV, hepatitis, soil parasites, and so forth. They kill approximately 15 million people a year globally.

2

Human Health

INFLUENZA AS A GLOBAL CHALLENGE FOR HUMAN HEALTH RESEARCH

Todd Davis opened his remarks by emphasizing to participants that the influenza virus is very complex: There are multiple types of influenza, A and B being the most common genotypes. Among these types are many, many different subtypes of influenza. To date, as many as 18 different hemagglutinin (HA) genes have been detected. The influenza A viruses have potentially 11 neuraminidase (NA) genes. Two influenza A viruses have been detected in bats recently. These are, to date at least, viruses that have not been replicated in any in vitro or in vivo systems. Aquatic birds are believed to be the reservoir for these viruses, because all of these HA and NA subtypes, with the exception of the bat influenza viruses, have been found in aquatic birds. These viruses have crossed over to mammalian hosts and avian hosts, primarily terrestrial poultry, as well as to humans. This is just a very cursory overview of all the animals that have been infected by these viruses, there is a growing number of hosts susceptible to influenza viruses.

Davis displayed a diagram showing the timeline of influenza A viruses that have been detected over the years in humans (see Figure 2-1).

Other novel influenza A subtypes have recently been detected in humans, namely H10 and H6, found in parts of China and Taiwan. More and more examples of these influenza A viruses and subtypes can be found in humans with the potential to cause pandemic disease.

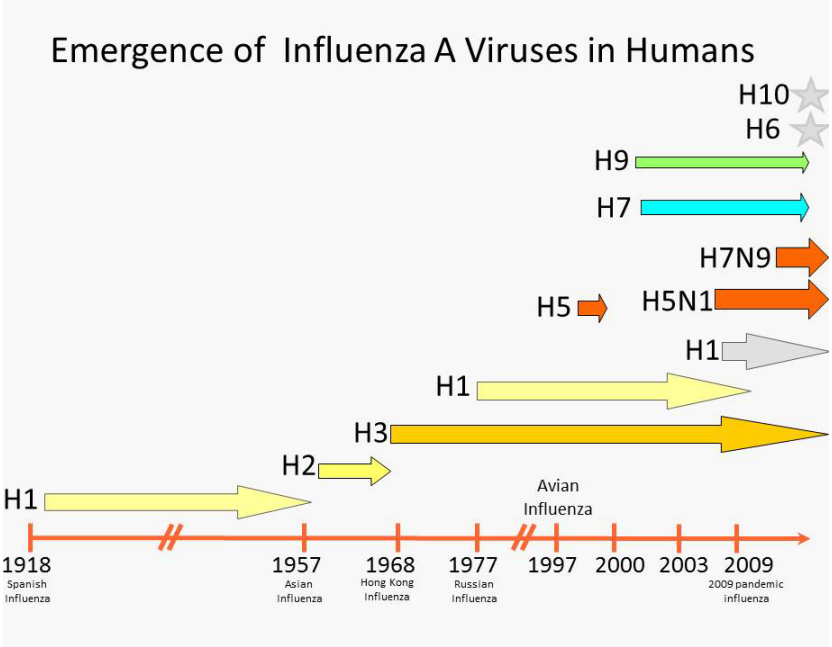


FIGURE 2-1 The long arrows in the diagram represent the seasonal viruses that caused pandemics and then remained in the human host population and circulated as seasonal viruses. Toward the end of the scale there are some zoonotic viruses, such as the H5 viruses, in particular H5N1; H7 viruses, particularly H7N9 circulating in China since 2013; and H9N2 viruses that cause sporadic human infections.
SOURCE: Todd Davis, presentation at the workshop.

As a segmented RNA virus, influenza is capable of evolving very rapidly, and does so via mechanisms such as mutation, recombination, and reassortment. Mutations occur through misincorporation of nucleotides in the absence of a proof-reading mechanism. Recombination is a rarer event, but does occasionally occur and can also lead to the development of highly pathogenic strains. The recent highly pathogenic virus that circulated in Mexico in 2014 is a good example of how recombination of a low-pathogenic virus can result in the circulation of a highly pathogenic virus. Reassortment involves two distinct viruses infecting a single cell, with the resulting progeny having swapped gene segments. Unfortunately, this is a common occurrence in influenza viruses and something that contributes to the pathway of transmissibility from animals to humans.

Influenza viruses are characterized by their surface receptors which are noted as alpha-2,3 sialic acid-linked (α-2,3) receptors and alpha-2,6 sialic acid-linked (α-2,6) receptors. Several key differences are important to recognize, mainly the α-2,3 linked receptors bind well to the avian host cells, and are thus avian-like viruses, versus the *α*-2,6 linked receptors which bind better to human host cells and are considered human-like viruses. Pigs function as a so-called mixing vessel. They are susceptible to being infected by both the avian and the human-like viruses, which experts believe has resulted in genetic reassortment, resulting in swine-like flu and leading to at least three previous pandemics, including the H1N1 pandemic of 2009. A great deal of the work Davis's group conducts with U.S. Department of Agriculture focuses on understanding what is occuring in the animal host and understanding the evolutionary mechanisms that drive the adaptation of these animal viruses to circulate in human hosts and potentially lead to pandemic disease.[1]

This becomes important to human health because over the years there has been an increase in the number of human infections with the so-called variant swine viruses. For many years there were sporadic cases on the order of one or two cases per year. In 2012, there were more than 200 cases of an H3N2 swine variant virus, which resulted in many human infections, primarily in young children that were visiting agricultural fairs who came into close contact with pigs. Subsequently, due to public health messaging, the number of human cases of swine influenza has declined in the past 2 years. In 2013, there were only approximately a dozen cases, and as of November 2014, there were only three cases. Experts do not fully understand why this spike occurred and then declined in human cases, but it is of significant concern, considering the ability of these viruses to transmit easily to humans.

Prior to the 2009 pandemic, it was clear that there was a large number of reassortments in genotypes circulating in swine populations.

[1] There is a great deal that is still unknown about the avian influenza virus. The Centers for Disease Control and Prevention has received a few of the H7N9 viruses from China, Hong Kong, and Taiwan and has been able to characterize some of those viruses and use them for vaccine development.

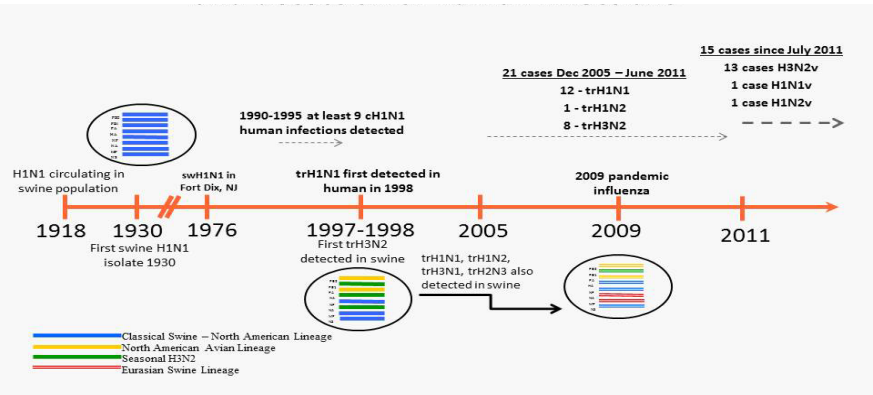


FIGURE 2-2. Historical overview of swine influenza virus circulation in pigs and detection of human infections.
SOURCE: Todd Davis, presentation at the workshop.

However, after 2009, and perhaps from reintroduction of the 2009 H1N1 back into the pig population, there has been a very comprehensive and confusing reassortment of the pandemic H1N1 genes into the already reasserted H3N2 virus backbone. Figure 2-2 shows the current understanding of influenza A viruses in pigs. Further understanding becomes increasingly difficult as more and more of these viruses continue to reassort.

With this background, Davis turned to the primary focus of his presentation, the H5N1 viruses in the context of biosafety and biosecurity. Currently, more than 60 countries have experienced H5N1 either in bird outbreaks or in human infections. Cambodia, China, Egypt, Indonesia, and Vietnam continue to struggle with the containment of the virus in poultry. Consequently, a large number of human infections have occurred in these countries. The genetic diversity within the H5N1 viruses creates a very complicated story. The term *clade* is used to describe the set of viruses that evolved from a common ancestor virus. In the early days of the H5N1 outbreaks that were primarily restricted to China and South East Asia, there was limited genetic diversity. As this virus has continued to spread and evolve over time, more clades have developed. A very large number of these clades have not yet been classified, which makes diagnostics, vaccine development, and the clinical picture difficult to address.

Human and animal virus surveillance, virus isolation, and genetic sequence generation feeds into sequence databases. Bioinformatics and

phylogenetics are used to understand the evolution of these viruses. As more is learned about the molecular features of these viruses, this information is fed into gain-of-function research where reverse genetic studies or other types of methods are used to actually pinpoint mutations, which are important to a specific phenotype of that virus. This information then feeds back into the molecular-based risk assessment, which then contributes to public health countermeasures. Such measures include diagnostics, candidate vaccine virus development, antiviral drug development, and ultimately biosafety considerations as well. Centers for Disease Control and Prevention (CDC) depends a great deal on molecular-based surveillance to inform decision-making, and in some cases even policy.

Davis then turned specifically to a recent example in Cambodia. In 2013, there was an unusual anomaly of 26 human cases of the H5N1 virus in comparison to only 21 human cases detected in Cambodia for the previous 7-year period.[2] In the context of the increase of human cases, there were also genetic mutations identified in the hemagglutinin gene of these viruses, two of which were associated with increased transmissibility in a ferret model. These two particular mutations have been described by both Ron Fouchier's lab and Yoshi Kawaoka's lab as being important for the aerosol transmissibility of influenza viruses in a ferret model.[3] Having seen these two mutations appear in the Global Initiative on Sharing All Influenza Data (GISAID) database, Davis and his group reached out to colleagues at the Pasteur Institute in Cambodia.

They started an epidemiological investigation to determine whether other viruses that had been isolated from humans in Cambodia might have also had these two mutations. The concern was that there may be some increased transmissibility that may have led to the increase of human cases. The possible reasons for this were not clear, although there is speculation that there was increased circulation of the virus in poultry or the environment. Potentially, there was increased testing in humans, and there was certainly improved clinical awareness about H5N1 in the country. They were dealing with a novel genotype: a virus that had

[2] For more information, see: https://www.cambodiadaily.com/archives/new-mutation-in-bird-flu-virus-in-cambodia-54896/; accessed April 10, 2016.

[3] For a brief overview of this research, see: http://www.nature.com/news/the-risks-and-benefits-of-publishing-mutant-flu-studies-1.10138; accessed April 10, 2016.

acquired internal genes from a different H5N1 virus and had some unique properties.

Davis spent several weeks in Cambodia to try to understand the scope of this potential problem and then to conduct risk assessments, both in Cambodia and in Atlanta. They started by looking at the specific mutations in the hemagglutinin genes of H5N1 viruses that were detected in Cambodia.

The mutations shown in Figure 2-3 are noted in red, along the phylogenetic tree. Some of the mutations were conserved in all of the H5N1 viruses circulating in Cambodia in 2013, and some were found only in unique viruses.

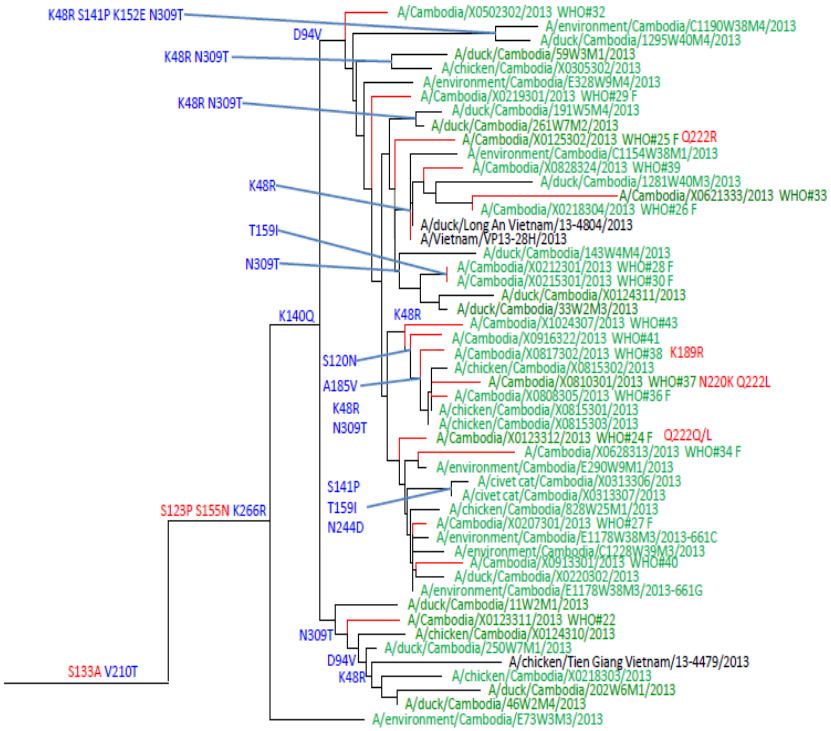


FIGURE 2-3 Clade 1.1.2 HA tree with mutations.
SOURCE: Todd Davis, presentation at the workshop.

Figure 2-4, depicts WHO Case Number 37, which was a human infection obtained through aerosol transmission. Gain-of-function research detected two markers for mammalian adaptation that had been conducted, as well as other mutations that had previously been described in gain of function studies to enhance α-2,6 receptor binding specificity.

Eleven of the 26 specimens from Cambodia were sent to Atlanta, where Davis's group attempted isolation from those 11 specimens. Nine viruses were isolated for additional characterization. They were particularly interested in knowing if any of the mutations had been detected in poultry or in environmental samples that had been collected in 2013. It became apparent from the beginning that these mutations were restricted only to human infections of H5N1. Follow-up investigations by the Cambodian Ministry of Agriculture, in response to the human cases, provided viruses that were also isolated. Even samples from the same flocks that may have been implicated in cases of human exposure did not have these mutations. That was very good news.

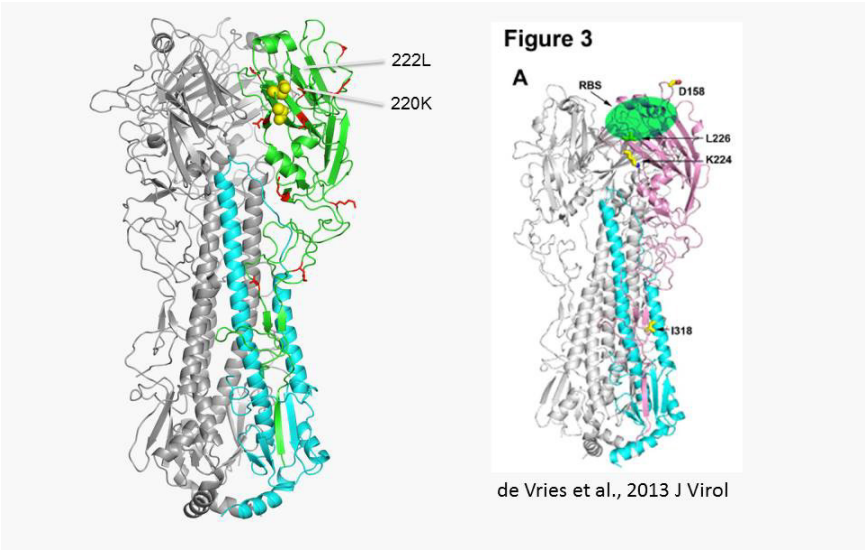


FIGURE 2-4 Clade 1.1.2. with Imai et al. RBS mutations vs. A/Vietnam/1203/04. Reprinted with permission of the American Society for Microbiology.
SOURCE: Todd Davis, presentation at the workshop.

Davis's group wanted to try to understand, using more specific assays, whether these viruses might have a shift in receptor-binding specificity that could have been predicted based on the mutations. They used analogs of the sialic acid glycan receptors in a glycan array model to understand how these viruses behave, at least in an *in vitro* detection system. Davis found that many of the viruses in the isolates they made existed as quasispecies, or mixed-based populations, in the viruses. Using traditional plaque assays and plaque purification, they isolated viruses with a glutamine in position 222 versus an arginine at position 222 and viruses with the serine at 155 versus an asparagine at 155. Both positions, again, have been implicated in the adaptive feature of some viruses to replicate and transmit in mammalian models. Surprisingly, the glycan array data showed that all of these viruses, regardless of the single mutations, had specificity that was very similar to a typical avian H5N1 virus. They used the Vietnam/1203 virus as a control, and even with the mutations that were found, these viruses still displayed an avian-like receptor-binding specificity.

One of the disappointing findings from this study was that the virus happened to have the two mutations associated with the aerosol transmission as identified by Imai et al. in their ferret transmission studies. Unfortunately, the position 222 from a glutamine to a leucine was lost after egg isolation. Therefore, Davis's group was never able to replicate that virus due to the loss of that marker after passage in the avian egg host. They used much of this molecular data to inform additional studies and additional characterization of influenza viruses as a means of understanding how they behave antigenically.

A large part of what Davis's lab does at CDC is to understand how well a vaccine might cover a specific virus. Therefore, they conducted additional studies to determine how this virus with the ferret-transmissible mutations would be protected by ferret antisera generated against a small panel of reference antigens. Using a ferret model, they inoculated the animals with these viruses and produced antibody against the specific viruses. Then they looked at the antigenicity of the profiles of test antigens relative to some of these strains.

When they compared these strains to the Vietnam/1203 vaccine candidate, several of these viruses had at least a fourfold, and in some cases an eightfold, reduction in viral load. Whereas using the Cambodian virus detected in 2013, all of the new viruses from 2012 and 2013, the vaccine candidate tended to react equally, as did the vaccine produced against X081301, a reference strain. Using the molecular data and

incorporating the antigenic data, CDC can propose or recommend the selection of certain viruses for vaccine development, either for seasonal virus vaccine development or for prepandemic vaccine development.

This usually leads to production of a small pilot lot. Many of the H5N1 vaccine candidates, as well as H7N9 vaccine candidates (for example, some of the swine influenza vaccine candidates), have been developed as pilot lots. Some have been tested in Phase 1 clinical trials to understand the immunogenicity of these viruses should they be needed in response to pandemic disease caused by these viruses.

Davis then mentioned, in the context of this discussion, that all of this begins in a biosafety level 3 (BSL-3) enhanced laboratory for the highly pathogenic viruses, in particular, but also for any exotic low-pathogenic avian influenza viruses or other exotic animal influenza viruses. All of the initial work, even the extraction of virus RNA, is performed in a BSL-3 enhanced laboratory. After the initial work, further steps (e.g., cloning, sequencing, and screening of constructs), are conducted in a BSL-2 laboratory. Then, due to the features of these viruses, the transfected virus goes back into a BSL-3 enhanced laboratory, where the virus is harvested, passaged in eggs, and stored and titrated.

At that point, they assess biosafety risk and reclassification, which generally involves several different safety assessments. The first safety assessment is performed in chickens at the USDA's Southeast Poultry Research Laboratory, where they determined that the multibasic cleavage site that has been removed in the vaccine no longer causes clinical illness in chickens. The vaccine passes an intravenous pathogenicity index test demonstrating a lack of a highly pathogenic phenotype in this animal model.

Meanwhile, Davis's CDC group also conducts studies in Atlanta to examine the lack of a trypsin-independent replication. They want to be able to demonstrate that the virus cannot grow unless trypsin is supplemented in the cell culture media, another feature of a highly pathogenic avian influenza virus. They also look for a lack of chicken embryo lethality, again showing that the virus is no longer highly pathogenic. Finally, they conduct a risk assessment using a ferret model. In this assessment, they look for evidence of reduced pathogenicity of the candidate vaccine virus relative to the parental wild-type strain so that they can demonstrate reduction in clinical symptoms, that is, replication in the respiratory tract to a minimal level or no replication before they can then move into the declassification of these viruses and the

deselection of the virus as a select agent according to the USDA'S Animal and Plant Health Inspection Service and CDC regulations. The vaccine then enters a pipeline where the virus has become a BSL-2 level organism and can be handled by manufacturers for pilot lot production and vaccine development.

This is an ongoing activity that the CDC's influenza division is involved in as part of its responsibility as a WHO collaborating center.

Davis stated that each of the steps that he discussed in his presentation involved at least three different biosafety lab levels. When considering the necessity for biocontainment laboratories in a surveillance setting, one begins with sample collection. It is essential to have good personal protective equipment (PPE) in the field, and good shipping guidelines to be able to transport viruses from the field into the BSL-3 enhanced laboratory. The molecular assays conducted in a BSL-2 environment are also very important. Davis's group is trying to use BSL-2 molecular assays to understand more about these viruses before the isolation stage and the additional propagation of BSL-2 and BSL-3 organisms. The Influenza Division of CDC is working to try to improve their advanced molecular detection of viruses from clinical specimens so that they can avoid some of the additional isolation and propagation that occurs in the BSL-3 enhanced laboratory. Finally, vaccine development for zoonotic influenza viruses involves the use of recombinant DNA in research, which is overseen by CDC's Institutional Biosafety Committee, and animal studies may also involve review and approval by the National Institutes of Health's Institutional Animal Care and Use Committee.

There is a great deal of transparency regarding dual-use research now at CDC. Even for studies that are not considered to be dual-use research by definition, any research involving select agent work or exotic animal virus work is still submitted for review to be certain that the dual-use committees are aware of the research being conducted, this is a mechanism to provide as much transparency as possible within CDC.

Discussion

The discussion following Davis's presentation focused on the role of mutations in his study, including those identified in previous studies.

A participant opened the discussion by asking if the reduced transmission, replication, and pathogenicity resulted from dominant mutations or recessive mutations. Davis replied that most of the known mutations are associated with reduced transmissibility and replication.

He thinks most of those are tied to the internal genes of these viruses. The virus that is used as the backbone for candidate vaccine production has known mutations that result in a phenotype that does not replicate well in a mammalian system. In this case, there are many mutations that function together, so it is not possible to say whether one is dominant or recessive; rather, it is a combination of mutations that give these viruses this phenotype.

Davis was asked if his group would have paid as much attention to these two mutations if they had not been previously identified in the ferret model. Davis replied that, no, they would not have paid that much attention to those mutations. **Diane Griffin** noted that in general it is useful to know about mutations because they may be of future benefit.

David Relman had the same question about the role of previous work studying induced enhanced transmissibility in the laboratory on Davis's surveillance effort. The 222 mutation was known prior to 2012. Relman wanted to understand what in particular was learned from the Fouchier experiment on induced enhanced transmissibility. Davis replied that his group's work was initiated because of the combination of the mutations that had not been seen previously in naturally circulating H5N1 viruses. It is absolutely correct that the leucine of position 222 is something that has been known for a long time. It leads to the swing to an α-2,6 receptor binding specificity. The mutation position 220 had not been previously seen in circulating H5 viruses, and it had never been seen in combination with the mutation at 222. This combination of mutations identified in this one virus was the impetus for starting the enhanced surveillance.

Another participant asked if there are patents protecting the sale of viruses based on the reverse genetic method used. Davis replied that these methods are all used within a research environment. If the viruses are distributed to manufacturers, those manufacturers then have to be certain that they understand their legal and financial obligations to the patent holder.

The participant also asked about the disappearance of the mutation. Davis responded that his group did do some next-generation deep sequencing of the virus used for the egg passage. They found that there was actually a low percentage of the avian mutation present in the first passage. Once it went back into eggs, it really shifted and outgrew the more human-like mutation that was identified. It was a quasispecies in the original infection.

CHALLENGES IN DIAGNOSIS OF PATHOGENS AND STATUS OF BIOSAFETY AND BIOSECURITY IN WHO'S SOUTH EAST ASIA REGION

Aparna Singh Shah began her presentation by quoting Dr. Margaret Chan, who said, "Today collaboration to achieve public health goals is no longer simply an asset. It is critical necessity."[4] There are 11 countries in WHO's South East Asia region, which has six percent of the world's land area, 25 percent of the population, and approximately 30 percent of the communicable disease burden. Despite this, there is relatively little laboratory capacity. Labs tend to receive low priority, even though they are the cornerstone for the surveillance and detection of communicable diseases.

What are the prerequisites for the detection, containment, and prevention of emerging infectious diseases? Adequate and trained public health staff are needed, as is coordination with other sectors and partners. Strong information gathering capabilities, reliable public health laboratory capacity, and efficient and swift management of public health measures, including logistics, are also needed. Adequate resources are essential to support each of these elements. WHO advocates for the support of various laboratory functions starting with surveillance and diagnostics, which then supports the treatment of patients. With the help of laboratories, WHO shares information and material with the global WHO network.

In 2003, when there was concern about the resurgence of severe acute respiratory syndrome (SARS), there were at least two cases of laboratory-acquired infections (LAIs) from Singapore and Taipei. These incidents drew international attention to the issue of lab biosafety and potential costs associated with the breakdown of lab safety.

In 2005, the WHO Assembly adopted a resolution on enhancement of laboratory biosafety. During the same assembly, International Health Regulations (IHR) were adopted, which came into effect in 2007. The IHR requires the 94 countries who have adopted them to develop minimum core capacities to prevent, protect against, control, and provide

[4] Margaret Chan, acceptance speech as Director-General of WHO, November 2006.
See: http://www.who.int/mediacentre/news/releases/2006/pr66/en/; accessed April 10, 2016.

a public health response to the international spread of diseases and events of public health risk.

Following the adoption of IHR, this region developed the Asia Pacific Strategy for Emerging Diseases (APSED) to meet the challenges of emerging diseases and to provide a framework for compliance with the core capacity requirements of the IHR. The key aspects of APSED involve quality assured laboratories, safe laboratory environments, and safe practices. The APSED was further expanded to include the Asia Pacific Strategy for Strengthening Health Laboratory Services. The components of the Asia Pacific Strategy include biosafety, biosecurity, occupational health, and safety and waste management.

Shah then listed what she called the 11 M's that are necessary for building laboratory core capacity to detect pathogens safely:

- Manpower
- Machinery (equipment)
- Materials (reagents)
- Methodology (SOPs and protocols)
- Management
- Motivation
- Monitoring and evaluations of techniques and infrastructure
- Maximum containment, safe environment in laboratories
- Matrix or network of laboratories
- Maintenance of expertise (infrastructure)
- Money

Shah continued by pointing out several major issues in health laboratories in the South East Asia region that prevent labs from meeting the 11 criteria. There is limited public health laboratory capacity, which varies from country to country, and not all member states have laboratory policy plans, focal points, or national frameworks for health labs. Not only do many people have limited access to laboratories, but there is also a lack of new technology and an inadequate number of trained staff. There is no continuous supply of reagents, and no systematic assessment of laboratory quality and biosafety. In other words, biosafety and biosecurity awareness and practices are inadequate. In addition, there are few regional and global linkages for technical support and collaborations, as well as inadequate resources. At this time, training is not specifically focused on biosafety and biosecurity: There are few training programs focused on biosafety, and when training is conducted, biosafety is often a

small part of laboratory quality training or it is occasionally combined with training on lab techniques. Designated biosafety officers are also rare, biosafety guidelines are often either not available or poorly implemented, and regular safety inspections and waste management programs are few. Mandatory immunizations for lab personnel are insufficient, and occupational health and medical surveillance programs are rarely mandatory. In addition, safety issues persist, including the following: The processes for biological safety cabinet certifications may need improvement, documentation of safety errors and LAIs are minimal, and often there is an inadequate supply of PPE. Expertise and facilities available to plan and construct BSL-3 and -4 labs exist, but coordination between and among various stakeholders is limited. Likewise, national funds dedicated for biosafety and biosecurity are often limited.

WHO conducts assessments of laboratories under the IHR capacity building program. Self-assessments are vulnerable to being subjective. For example, at times countries have very limited resources, but they report 100 percent biosafety in their facilities. Conversely, some countries have good biosafety measures in place, but they believe that their compliance is closer to 20 percent.

Table 2-1 lists the BSL-3 laboratories in member states. India has BSL-4 laboratories, five member states have BSL-3 laboratories, and almost all countries have BSL-2 laboratories.

Shah also mentioned that WHO has published a popular book providing overall information on biosafety, security, and biorisk management. WHO has conducted many biorisk management trainers' workshops, as well as regional and national level trainings. Following the outbreak of Ebola, WHO conducted specific training, but none of the member states have facilities to perform laboratory testing of Ebola. WHO also developed a shipment project so that countries can ship their suspected specimens to WHO-designated laboratories; all member states were trained on shipping requirements and core team management.

Through WHO efforts, awareness and involvement of national policy-makers has gradually increased. National laboratory policies that include biosafety components are being developed, and in some countries, there are biosafety assessment committees, even in some of the countries that do not have BSL-3 facilities. Biosafety and biosecurity associations are being formed to foster biosafety and biosecurity practices. They hold regular biosafety trainings, which include sections

TABLE 2-1 Biological Safety Labs in South East Asia Region Member States.

Country	BSL-2	BSL-3	BSL-4
Bangladesh	+	+	-
Bhutan	+	-	-
DPR Korea	?	-	-
India	+	+	+
Indonesia	+	+	-
Myanmar	+	-	-
Maldives	+	-	-
Nepal	+	+	-
Sri Lanka	+	-	-
Thailand	+	+	-
Timor Leste	-	-	-

SOURCE: World Health Organization, 2014.

on PPE. Training also includes biological waste management, good laboratory practices, and infection prevention and control guidelines.

WHO plans to improve biosafety and biosecurity in South Asia by advocating for the development of national policies on biosafety and biosecurity. WHO also requests that national governments allocate resources to improve the status of biosafety and biosecurity. It assists the governments in reaching this goal by providing technical support for policy development and implementation. Additionally, it has developed and distributed guidelines, and member states are encouraged to form their own SOPs. WHO also assists member states in linking to global expertise by promoting networks and collaborations.

Discussion

The discussion following Shah's presentation focused on diagnostic capabilities of regional and WHO-designated labs and WHO guidelines for regulatory policy.

A workshop participant asked about diagnostic facilities for Ebola and what capacities exist in the region. Shah replied that WHO

recommends that specimens be tested for Ebola in BSL-3 labs. These exist in Bangladesh, India, Indonesia, Nepal, and Thailand. However, after testing at least 50 specimens determined to be negative for Ebola, and 25 specimens determined to be positive for Ebola, results should be validated in WHO-designated labs. These countries can perform RT-PCR, but again, they need to validate their results by sending their representative specimens to designated laboratories.

Thomas Ksiazek asked how BSL-3 laboratories testing samples for Ebola are obtaining the necessary reagents and whether the tests are being validated. Shah replied that in India, Ebola testing occurred on a regular basis whenever there was a suspected specimen. Indonesia and Thailand have in-house kits for Ebola testing, but WHO and CDC also have provided them with iNtRON kits available for viruses. At times, when a country is not able to procure a reagent, they ask WHO to facilitate procurement. Indonesia is now in the process of sending their specimens for validation to designated labs.

A participant followed up on guidelines developed by the WHO South-East Asia Regional Office (SEARO). How many of WHO SEARO's guidelines pertain to biosafety and biosecurity, and how many of the member states have actually used the WHO guidelines to develop regulatory policy or specific guidelines that require implementation at their own laboratories or medical institutions? Shah replied that WHO does have information about member states' regulations. WHO requested that global experts conduct assessments and assist in implementing guidelines. Such assessments were conducted in Bhutan, Myanmar, and Nepal. As far as she knows, all BSL-3 laboratories have their own SOPs and guidelines, however, implementation of these guidelines in peripheral labs is inconsistent.

PERSPECTIVES ON THE WEST AFRICAN EBOLA OUTBREAK

Ksiazek recounted the 6-week trip he took to Sierra Leone at the invitation of CDC in August 2014. He provided some of his personal perspectives on the outbreak in Guinea, Liberia, and Sierra Leone, and described the history of the Ebola outbreak and the filoviruses within Africa (see Figure 2-5).

The first outbreaks of Ebola occurred in 1976, in what was then northern Zaire and southern Sudan. These were actually two different viruses, but that was not known for some time. There were two

simultaneous outbreaks in the same approximate region, bordering the Congo Basin. Since then there have been a number of outbreaks of Ebola in the Democratic Republic of Congo (DRC). The Ebola virus responsible for those outbreaks was the same as that found in the 2014 West Africa outbreak.

There was a fairly large hiatus after the 1976 outbreaks, with the exception of a smaller one that occurred in the area of the initial outbreak in 1979, and a single case in northwest DRC. No other cases were reported until 1995, when the Kikwit outbreak occurred.

The 1995 Kikwit outbreak itself was transformative; previously in the 1976 outbreaks the nature of Ebola and its transmission were not discerned. The people who investigated the original 1976 outbreak arrived very late in the process, so they were unable to observe the initial symptoms and transmission of the disease. In contrast, the 1995 Kikwit outbreak had been ongoing for only a month or so by the time infectious disease experts arrived, so there was an opportunity to observe transmission in the midst of the outbreak. The isolation facility parameters for operating safely with Ebola patients were established during the 1995 Kikwit outbreak; and control measures for health care workers were also established over the course of the outbreak. When outside healthcare workers initially arrived, facilities were largely abandoned. A small number of CDC workers cleaned up a hospital that had essentially been abandoned, including the removal of 23 bodies that had been left behind. They then led the effort to reestablish a treatment facility where infected individuals could be isolated and cared for by people who were appropriately protecting themselves with PPE.

What causes Ebola outbreaks? The virus is the etiologic agent, but that is not really the underlying cause of outbreaks, which are poor infection control practices in countries with poor health care systems. If it were not for a lack of resources to maintain some level of infection control, these outbreaks simply would not occur. In fact, hospitals are often the amplification foci largely responsible for the expansion of outbreaks and for much of the early transmission. This is not because of a lack of will or capability on the part of the individuals that operate these facilities. It is simply due to the lack of basic resources (such as running water) to practice infection control and standard precautions. These conditions create outbreaks in West Africa in general, and they were largely responsible for the early genesis and size of the 2014 outbreak in Sierra Leone in particular.

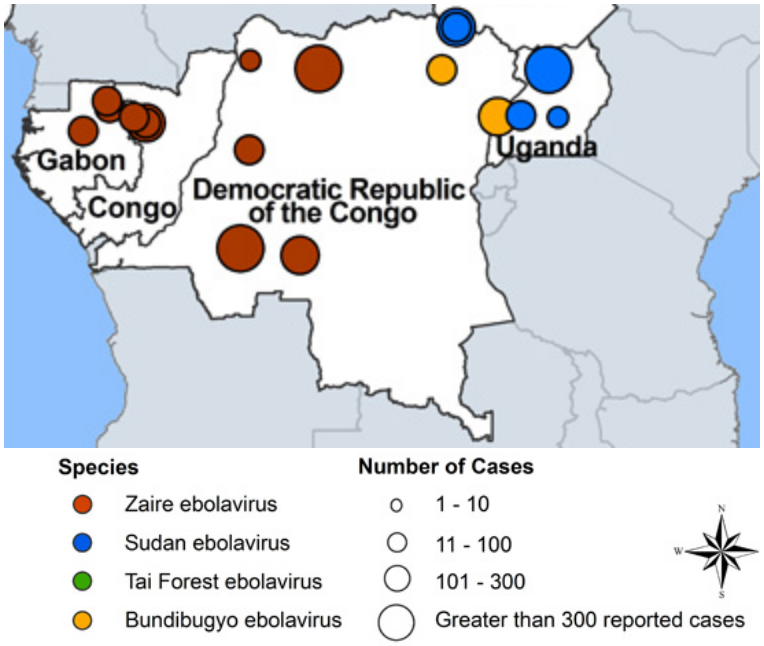


FIGURE 2-5 Map showing Ebola outbreaks over time prior to 2014. SOURCE: Centers for Disease Control and Prevention, E.Ervin CDC/VSPD 2014.

Part of the control efforts that were developed and implemented, which Ksiazek called the 'Ebola play book,' were simple methods: existing cases need to be found and isolated, and their contacts need to be quickly and accurately identified because those people may become sick. The contacts do not need to be isolated or quarantined, but they should be followed carefully. If they become sick, action must be taken to isolate them. If this can happen thoroughly and rigorously, an outbreak can be stopped.

Household quarantine, in contrast, is not an effective means of infection control. Following this method, if a case is found in a household, rather than removing that individual and placing him or her in an isolation facility, the house is merely closed up, leaving the infected person with family members. As a result, in a very short period of time a cluster of cases arises rather than a single case. Transmission does not occur before an individual becomes sick. Therefore, if the infected individual can be identified before he or she becomes seriously ill and develops diarrhea and heavy shedding of the virus, transmission can

probably be avoided. Other issues specific to the cultural practices prevalent in the outbreak area also increased transmission. Burials were a significant contributing factor in the West African outbreak, and are a critical source of infection. Specifically, after patients die they are often buried by their families in a manner that poses high risk for transmission. Therefore, it is important to ensure that burials are conducted safely, for example, through supervision or burial teams. Some cultural practices must be maintained without direct contact with the body, Ksiazek said, such as allowing family members to see the individual being buried.

There are also modes of transmission that have nothing to do with medicine or medical practices. Traditional healers are active in West Africa communities and may play a role in transmission by practicing traditional healing methods like scarification or cutting with razor blades or other sharp objects, or they may give injections of unknown substances rather than known medications.

Figure 2-6 provides a map showing the three countries mainly affected by Ebola in 2014: Guinea, Liberia, and Sierra Leone. Where these countries come together is where the outbreak began, in a town called Gueckedou. The outbreak was not successfully diagnosed until some cases had reached the Guinean capital of Conakry, on the Atlantic coast, and specimens were sent to Europe for diagnosis.

By the time the diagnosis had been made in Guinea, the outbreak had already spread through a number of cities in Guinea itself, and infected patients were suspected of having traveled across the borders of these three countries. Since these borders were open, people regularly moved in tribal groups or social organizations across them from country to country.

CDC was sent to West Africa based on a bilateral arrangement between CDC and the government of Sierra Leone to help with data management and tracking of the outbreak. The primary goal was, therefore, for CDC officers to assist in forming a national surveillance system that would inform outbreak control. Initially, the quality of data available was not very high. Early reports stated that mortality was running at about 30 percent, which did not accurately reflect the true mortality rate. As part of its response to the Ebola outbreak, CDC assisted in data collection by sending officers to the local areas of infection. Data collected in these areas also helped to create a database that allowed CDC to track the progress of the outbreak, or the lack of progress in controlling the outbreak, using a viral hemorrhagic fever

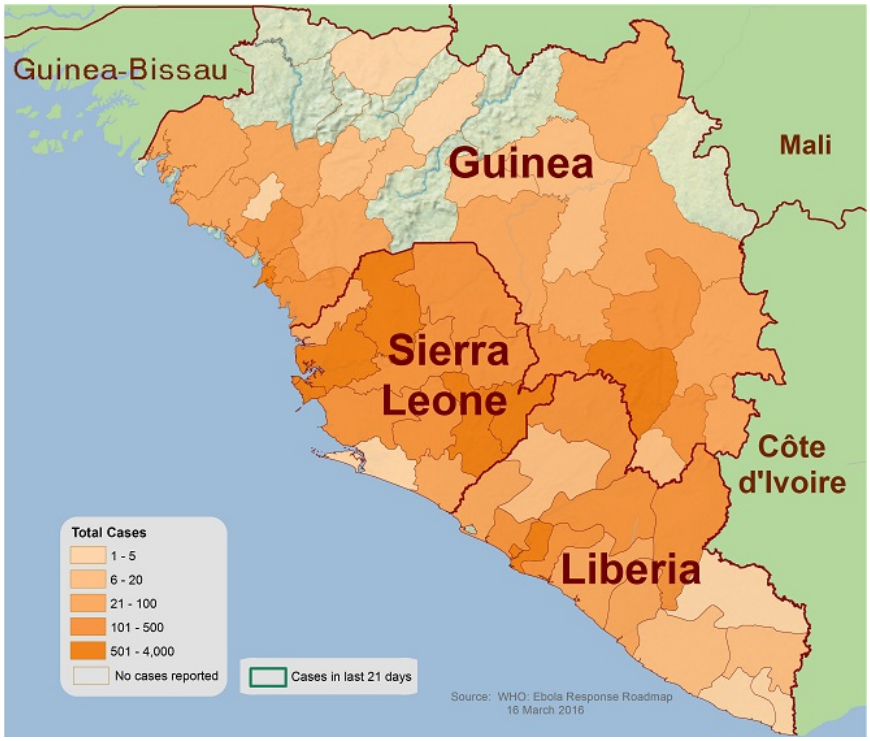


FIGURE 2-6 Countries in West Africa affected by Ebola.
SOURCE: WHO Ebola Response Roadmap.

(VHF) database module in Epi Info, a common program used by epidemiologists that CDC developed in responding to previous outbreaks in Africa. Epi Info was designed primarily to deal with existing outbreaks, which were mostly local and small. This outbreak, however, was already in three countries and larger than the total sum of all the previous cases of Ebola.

The total death toll of the outbreak at the time of the workshop was about 5,000.[5] In contrast, the total number of cases estimated for all previous outbreaks was approximately 1,200. Because existing tracking methods were designed to deal with smaller, more limited outbreaks,

[5] For information on the death toll of the 2014 Ebola outbreak in West Africa, see the U.S. Centers for Disease Control and Prevention: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html; accessed April 10, 2016.

they had to be re-scoped to deal with much larger outbreaks. Several modifications were quickly made with assistance from programmers at CDC. One modification was to convert the program from a single-user application, one that could be used on a single laptop, into a sequel server version outfitted with Wi-Fi routers so that multiple people could enter data from multiple laptops onto a single server version. Another necessary modification was to devise a means by which data from individual regional or local databases could be uploaded into a national database to obtain national statistics. Some changes to the application were easily made, but the data still have to travel from one place to another, and communications networks in West Africa are not always adequate. Even though mobile phones have changed Africa, the bandwidth available with a mobile phone is often insufficient to transmit larger amounts of data.

Ksiazek was part of the first team that was sent by CDC to Sierra Leone in mid-August 2014. By the time he arrived, CDC was already operating at three locations: at the site of the original outbreak, in Kailahun District; in Kenema; and in Bo. Initially, approximately 12 people from CDC had been deployed in Sierra Leone. Subsequently, that number was increased to 37, and then to 70 individuals.

By the time Ksiazek arrived in mid-August 2014, there were already two epicenters in Sierra Leone. The virus was already spreading and was beginning to appear in and near Freetown, a city of over one million people, and in another district near Freetown. Yet the situation in Sierra Leone was better than the outbreak in Liberia, which was nearly out of control. The resources and logistics of bringing control efforts to bear were limited. For instance, finding and moving patients into an isolation facility requires ambulances or some other suitable form of transportation, which frequently were not available. Patients remained in remote villages or even in towns due to a lack of sufficient ambulances or crews. In addition, tracing and transporting contacts and safely removing dead bodies posed challenges. Ksiazek was there during the rainy season, which made it difficult to unload supplies and move them into warehouses immediately. In general, PPE and disinfection supplies were available nationally, but because they required distribution from a single entry point, supplies at the local level were insufficient.

Another challenge Ksiazek faced was case finding. Quarantine is not generally recommended or supported by either the WHO or the CDC in dealing with these outbreaks because they often lead to unhelpful isolation of officials and aid workers. However, because politicians and

other high-level people were frequently involved, quarantine became a regular part of the response. The goal was to stop transmission, but when it was determined that Ebola was occurring in one part of the country, and the decision-makers were in another part, communications were essentially cut off to the affected area. Hence, sufficient efforts to control the outbreak in that part of the country were not forthcoming, and the prevalence of disease kept growing, eventually spilling over and spreading into other areas. Ksiazek stated that more effort at the local level would have been more appropriate than trying to isolate the outbreak from a central point. Poor application of case finding and perhaps a lack of more beneficial distribution of resources more broadly contributed to the challenges.

When Ksiazek arrived, he found that the demand for facilities in which patients could be isolated exceeded the number of beds available, and the situation did not improve as time went on. This led to an escalation of the outbreak. Unfortunately, in the majority of facilities, infection of healthcare workers was quite common. Ksiazek did not believe that this was due to a lack of PPE per se, but rather that healthcare workers felt at risk and the number of infections supported that belief. Despite the risk health care workers faced and the incidence of disease in their ranks, they did not receive timely compensation for their work. This was not due to a lack of resources at the central level; rather, it was due to a lack of an efficient payroll distribution system. Another ongoing challenge is that there are simply not enough trained medical staff to maintain the existing facilities. Therefore, with the construction of new facilities, those resources had to come from the international community.

Ksiazek then turned to the epidemiology of the outbreak. Table 2-2 demonstrates the spread of the disease to September 2014, and indicates that not only were records lacking, but also the data in these records were often incomplete or non-existent.

TABLE 2-2 National Ebola Situation Report for Sierra Leone.

District	Total Contacts listed during outbreak	Total Contacts who have finished their 21 days	Total Contacts Currently Being Followed	New contacts added in 24h	Contacts seen and healthy in last 24h	Contacts seen and ill in last 24h	Contacts not seem in last 24h	Contacts finished 21 days in the last 24h	% of Contacts seen by Tracers in last 24h
Bo	592	456	136	0	86	8	0	42	69%
Bombali	567	176	391	7	384	4	3	6	99%
Bonthe	84	27	57	52	57	0	0	0	100%
Kailahun	1416	1105	155	19	155	0	0	8	100%
Kambia	68	12	56	38	55	1	0	0	100%
Kenema	2483	1821	589	52	578	0	11	11	98%
Kono	157	80	77	0	71	6	0	0	100%
Moyamba	206	149	57	0	51	6	0	12	100%
Pujehun	333	195	137	0	137	0	0	41	100%
Port Loko	1514	234	1297	97	1155	3	139	51	89%
Tonkolili	533	170	363	0	363	0	0	17	100%
Wester Area Urban	767	436	331	13	331	0	0	0	100%
Western Area Rural	183	0	181	0	181	0	0	0	100%
National	8903	4861	3827	278	3604	28	153	188	95%

SOURCE: Tom Ksiazek, presentation at the workshop.

There appears to be no difference in infection rates among men and women, and the age distribution of infected men and women was approximately equal. Children experience lower infection rates simply because they do not perform some of the activities, such as burial rituals, that would put them at risk. Figure 2-7 shows infection rates by chiefdom compared with infection rates by district. Again, data are incomplete; it is nearly impossible to track infection rates at the tertiary level of geographic or political jurisdictions.

Downward trends in infection rates, Ksiazek suggested, were largely due to a change in people's behavior. By the time Ksiazek departed in late September 2014, officers had been placed in a number of other districts where transmission had begun to pick up, in an effort to forestall infection. However, distribution maps suggest that efforts were not entirely successful. It would take several more months for the outbreak to be declared over in the affected countries of Guinea, Liberia, and Sierra Leone.

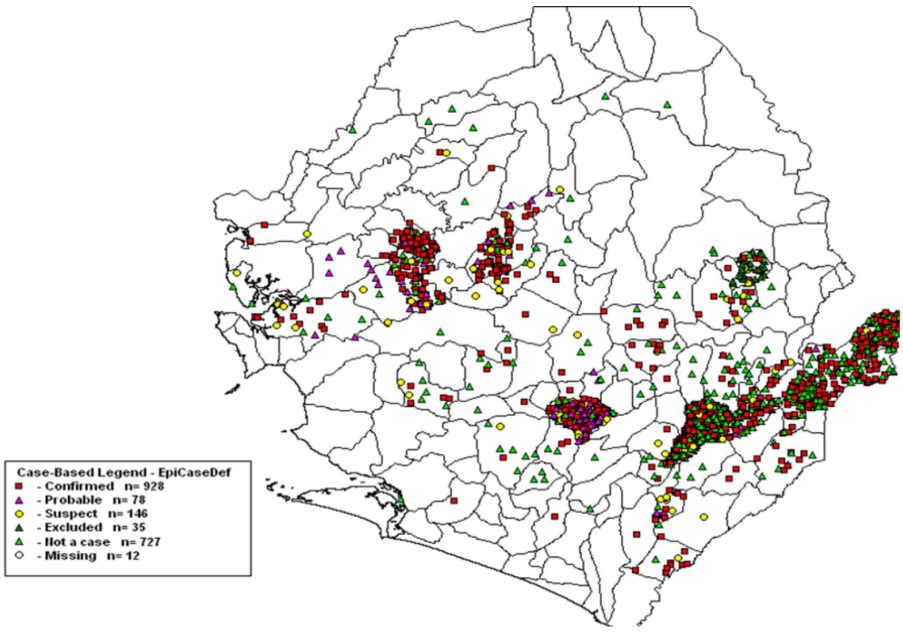


FIGURE 2-7 National Ebola virus detection spot map by cheifdom, Sierra Leone. May 23-September 13, 2014.
SOURCE: Tom Ksiazek, presentation at the workshop.

Discussion

The discussion following Ksiazek's presentation focused on questions about the source and prevalence of the outbreak, including the role of sequencing, transport of samples, and WHO data.

Using Sequencing to Determine the Origin of Outbreaks

A participant asked Ksiazek about one theory regarding the original case in Guinea, that one child and his mother ate infected bat meat. Since that first case, the population reportedly continues to go to the forest and eat dead animals found there. Was there any evidence that new infections occurred as a result of this practice? Ksiazek responded by referring to sequencing issues. He did not think that there had been sufficient

examination of sequences that could determine the source of the outbreak with greater accuracy. However, it appears that in spite of the mutations, there is an accumulation of snips in the viruses that do occur. Ksiazek believes that all of the viruses clearly have the signature of the outbreak virus. He further believes that if there were another introduction, it would most likely have a slightly different signature that would fall outside of the bounds of, for instance, the sequences that occurred in hundreds of individuals. There is an accumulation of some mutations in the virus, but throughout outbreaks in the past these mutations were usually part of the outbreak itself. However, not enough sequencing had been done in all of these sites to fully determine what happened.

Issues with Transporting Viruses

Ksiazek also noted that it is hard to transport these viruses for sequencing and other sample testing, due to the constraints of biosecurity measures. There are efforts to make transport possible, but not in an acceptable real-time fashion, which would be much more helpful.

Discrepancies in WHO Data

A participant asked about the missing set of cases on the graph that Ksiazek presented (Figure 2-8). Did the missing cases include confirmed diagnosed cases? Ksiazek responded affirmatively and explained that when a patient came to a facility, a blood sample was taken upon admission, so these were patients that were definitely seen. The problem is that they were admitted to a hospital but the records did not indicate their outcomes. Even their relatives still do not know what happened to some of them.

This led to a follow up question about why WHO reports these case numbers if it is clear that they are incomplete? Ksiazek replied that the case numbers underrepresent the true number of cases, and that varies from country to country. There are many problems with the data, but in Sierra Leone, for instance, the way this system was put together was entirely lab-based from the beginning, so essentially the only cases reported were people whose specimens were drawn and sent to one of the three laboratories that were initially conducting diagnostic testing. They are real numbers, but the problem is that undoubtedly there were patients that no one counted, because they did not have a record established. In Sierra Leone, there were very few suspect or probable cases; they were almost all confirmed cases. The patient's outcome was unknown in about

30 percent of the cases. In spite of their efforts, it was very difficult to locate either a hospital record that recorded the outcome for patients or a burial record. Ultimately, the mortality rate was approximately 65 percent.

THE EBOLA CONTROL STRATEGY IN INDIA

Ratnakar Sahoo focused his presentation on some of the measures the Indian government took to identify and isolate suspected cases of Ebola entering India. He began by recounting that as of the date of the workshop, there were six or seven suspected cases in India.

As is well known, transmission of Ebola occurs through close contact with bodily fluids of infected humans or animals. Figure 2-8 shows the epizootic life cycle that usually affects fruit bats as they come into contact with gorillas, chimpanzees, and monkeys, which in turn come into contact with humans. Human-to-human transmission then occurs and the virus is spread.

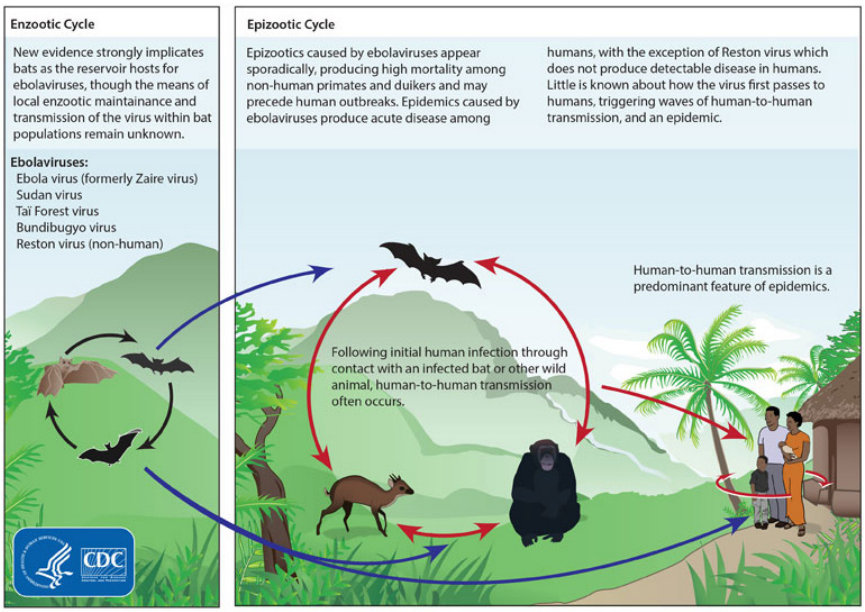


FIGURE 2-8 Life Cycles of the Ebola Virus.
SOURCE: Centers for Disease Control and Prevention (http://www.cdc.gov/vhf/ebola/resources/virus-ecology.html accessed November 2014).

Symptoms of Ebola include headaches, weakness, fever, and fatigue. The incubation period is a maximum of 21 days. When the disease progresses, it produces severe vomiting, abdominal pain, diarrhea, pharyngitis, difficulty breathing and swallowing, conjunctivitis, intensive bleeding, high body temperature, and prostration and bleeding that could lead to shock. Clinical diagnoses and laboratory testing of blood samples can confirm the existence or absence of the virus. The Ebola virus is classified as a Risk Group 4 virus by the WHO.[6] Enhanced clinical samples should be collected using all universal precautions, including PPE (long gloves, gowns, and eye shields), and then handled and kept in BSL-3 or BSL-4 labs. Before dispatching the sample, disinfectant (diluted bleach solution or sanitizer solution) should be used on all surfaces of the container. All vials containing Ebola-suspect samples should have bold labeling. Sample collectors should safely pack vials using the triple packing system and should transport the samples in accordance with the BSL-3 reference lab regulations. Usually, samples from Delhi are sent to the National Institute of Immunology and to the Indian CDC. Other BSL-3 labs across India have also been strengthened to handle potential Ebola cases.

Indian experts are concerned about a potential outbreak of Ebola in India because there are nearly 45,000 Indians now living in West Africa. Further, government health services, especially in rural areas, struggle to provide even basic health services on a daily basis. Another concern is that open defecation and urination is common especially in smaller towns and villages, increasing the potential for transmission.

As a precaution, Indian air transportation authorities have begun to use affordable, thermal scanners that beep if an incoming passenger has a temperature of over 37 degrees Celsius (98.6 degrees Fahrenheit). If a passenger has a higher temperature, health teams then place the person under surveillance. As of the date of the workshop, 22,150 passengers have been screened, of which 54 were identified as high risk and seven were identified as medium risk, and the others were categorized as low risk. The Minister of Health has instructed that thermal scanners be used at all of India's 18 international airports. All planes are disinfected after passengers arrive, and the passengers on the next flight are allowed to board only 30 minutes after the disinfection process. Sanitizers can be

[6] Each country is responsible for classifying pathogens into risk groups, and all countries agree that Ebola is in Group 4.

seen at the entrances of Indian airports, and airport staff and other officials also can be seen wearing masks, goggles, and gloves on duty as a precaution. Figure 2-9 shows authorities in gowns and PPE at airports in India.

Preparations at designated hospitals have also been made and the facilities have been inspected by central teams in all states across the country. These central teams are comprised of a physician and a microbiologist. Doctors, nurses, and others at designated hospitals have been provided with infection control training and full body protection to deal with Ebola cases, should they arrive. Figure 2-10 shows the proposed layout of a designated isolation ward with ten beds. The area is around 1,000 square meters.

FIGURE 2-9 Indian Health Authorities in gowns and PPE at India's airports.
SOURCE: Ratnakar Sahoo, presentation at the workshop.

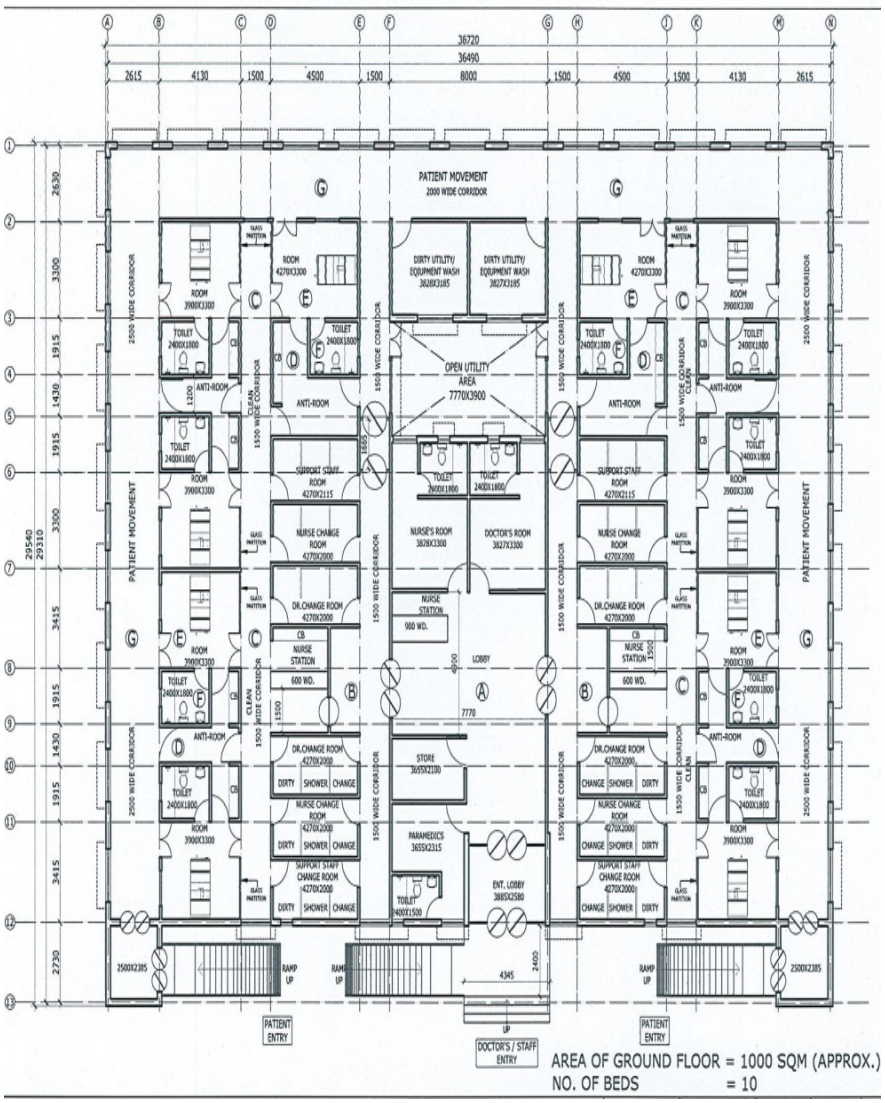


FIGURE 2-10 Proposed conceptual layout plan of isolation ward and rooms for Ebola in existing premises.
SOURCE: Ratnakar Sahoo, presentation at the workshop.

Discussion

The discussion following Sahoo's presentation focused on the factors used to determine risk levels for Ebola.

A participant asked how high-risk, medium-risk, and low-risk categories are determined? By the temperature reading on the scanner? Sahoo replied that high-risk cases are those arriving from pandemic areas with symptoms. Medium-risk cases only have an elevated temperature. The lowest are those arriving from non-pandemic areas. The participant further inquired as to whether other symptoms are used to elevate risk-levels. Sahoo replied that if symptoms are seen and the person is arriving from an affected area, they are categorized as high-risk, as are those suspected of having a history of travel to an affected area or close contact with someone who had symptoms of the Ebola virus.

3

Human and Animal Health: The Way Ahead

David Franz opened the session by saying that infectious diseases do not respect geographical borders. We also know that they do not always respect boundaries between species. **V. M. Katoch** mentioned the concept of One Health and that working together across human and animal health professions has considerable value. It is also important for scientists to work across geographic borders, since that is what the pathogens do.

BIOCONTAINMENT SOLUTIONS FOR POULTRY RESEARCH WITH VETERINARY AND ZOONOTIC PATHOGENS

David Swayne focused his remarks on specific aspects of the containment of dangerous pathogens. He and his colleagues[1] work under the principle that there are three different components that define containment: (1) facilities or building structure; (2) safety equipment; and, (3) the people and the policies and procedures they follow. Swayne believes that the most important of these are the people. No matter how good the containment facility or the equipment, if people do not follow procedures correctly, there will be problems.

Swayne's presentation outlined some vital containment situations that he and his colleagues had to face and challenges they had in discussing these issues with other institutions that work with laboratory

[1] Swayne thanked his staff who worked on this project: Andrew Clark who was with U.S. Department of Agriculture/Animal and Plant Health Inspection Service in Egypt at the time; Terry Tumpey at the U.S. Centers for Disease Control and Prevention (CDC). The project was funded by the U.S. Agricultural Research Service and CDC.

animals. Different laboratory animals pose different challenges to the research environment. Birds, which unlike other animals have different eating habits, have different metabolism, and have feathers, not fur, which leads to unique containment issues. First, birds are not mammals with feathers, they are completely different. They have a different kind of metabolism, and consume a different kind of food. Terrestrial birds, such as chickens and turkeys, excrete nitrogenous waste as dry urates. They have a higher body temperature than mammals and, therefore, for example, day-old chicks require a much higher temperature to remain alive. If the temperature is too low, the chicks become stressed, which introduces a variable that is not designed in the experimental protocol. Since these birds have feathers, starting with down and then full pin feathers and finally vein feathers, they can produce abundant feather dander, which can clog filters. For example, equipment with HEPA filters requires several pre-filters, to avoid the destruction of the HEPA filters, and often must be changed mid-experiment.

Generally cages should have negative pressure, HEPA-filtered intake and HEPA-filtered exhaust. The intake air comes from the room most of the time, and the exhaust could go back into the room, but they have ducted the exhaust through the building duct system. The exhaust is HEPA-filtered before it goes in the duct system and the duct system then goes through a double HEPA filter on exhaust.

Other critical aspects that Swayne and his colleagues consider are biosafety and biosecurity. The facility at which he works was built in 1976, when the U.S. Agricultural Research Service actually wrote the manual for facilities and created the category of BSL-3-Ag. According to the select agent program, Swayne's facility is a BSL-3-Ag facility, although it is not pressure decay-tested because the facility pre-dated the regulations. For over 20 years, the facility had permits at a BSL-3-Ag level. An inspection was conducted in 2008, at which time the lab's level was reevaluated, and the inspectors determined that the facility would only be a BSL-3 if it did not pass a pressure decay test. As a result, the lab is now designated as a BSL-3 enhanced lab, which means researchers were required to change some of the practices that had been conducted in open rooms. Flexible film isolators, which also have HEPA filters, were installed. They draw air from the room and then they recirculate it back into the room after it goes through the HEPA filter. For example, in the animal rooms, they have necropsy tables encased by flexible film isolators. They may also have freestanding cages of chickens for studies using egg layers; this is designated as a containment area. In this case,

the entire space is considered contaminated, and the researcher wears personal protective equipment when entering the space with the animal.

Swayne then discussed how they use containment facilities to conduct studies with zoonotic H5N1 viruses. Many human cases of H5N1 have been detected, and when epidemiologic studies have been conducted, in approximately 70 percent of the cases the infected person was found to have had exposure to poultry. Generally most of these exposures have been in markets or through household poultry production and slaughter.

Swayne's group started a project based on research they were conducting in Egypt where most of the H5N1 cases are found in women and children who are the primary caregivers for the household and rooftop poultry. They were trying to understand how the infection occurred, so they partnered with several people to conduct their work. The first experiment was conducted in a room with a concrete floor, concrete walls, and a concrete ceiling. There was directional air flow, HEPA filter intake and exhaust from the room, a shower outside of the room and outside of the building. They had attached an incinerator on their clean-dirty corridor pass-through autoclave. They always wore appropriate PPE because they were in the room with infected birds that they euthanized and processed. These birds were H5N1 inoculated and asymptomatic, which occurs in the first 24 hours after inoculation when they shed a lot of virus.

First they slaughtered the bird on the table. Then they did sampling at three different points in the room at varying distances from the table. Next, they simulated a home Halal slaughter method in five steps: (1) following animal care and use regulations, they tranquilized the birds; (2) once tranquilized, they cut across the carotid jugular; (3) placed the birds into a bucket; even tranquilized, birds still have involuntary muscle contractions for approximately a minute to minute and a half; (4) they hard scalded the carcass at 66 degrees Celsius (150 degrees Fahrenheit) to loosen the feathers; and, (5) then they manually defeathered the birds, eviscerated the carcass, and cleaned up. During the whole process, Swayne's group ran a negative air ionizing sampler to collect any particles from the air, and later they ran a particle sampler to determine the size of the particles. Figure 3-1 shows the number of virus-infected particles measured at different distances from the table during the first experiment.

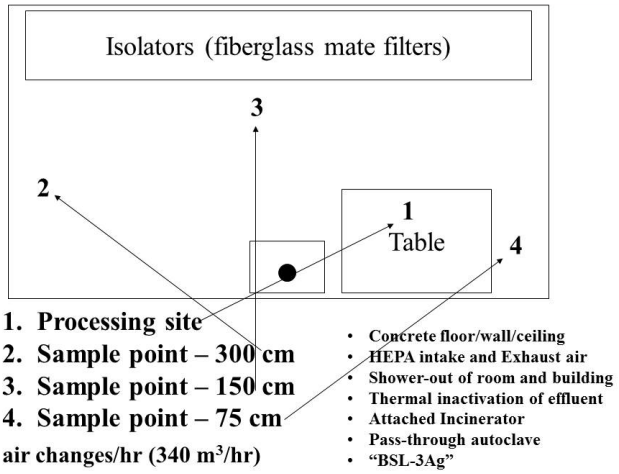


FIGURE 3-1 Home slaughter simulation: Airborne virus generation.
SOURCE: David Swayne, presentation at the workshop.

At two different distances from the table, significant numbers of particles were detected during the home slaughter simulation process. They then measured for virus and recovered virus from the air and the farther away they were from the source of the slaughter, the less virus was detected, which would indicate that respiratory droplets are definitely involved in detecting virus. They also put naive chickens in the same air space while they conducted the slaughter process. They found that all of the chickens exposed to airborne virus become became infected and died.

Next, Swayne's group studied the effects of exposing ferrets, which are the model for human infections, to the avian influenza virus. They conducted the first experiment with the ferrets at 150 centimeters away from the chicken slaughter site. Three of the four ferrets became infected and died of the virus carried by the chickens. Thus, airborne exposure through breathing occurs at the same proximity during the slaughter of infected chickens, and the virus can be transmitted to both chickens and ferrets.

Swayne and his colleagues then investigated how to develop changes in the process to avoid infection. Swayne's colleague **Andrew Clark** suggested conducting the slaughter step in a plastic bag. Clark worked for Animal and Plant Health Inspection Service (APHIS) at the time and had traveled to villages in Egypt to observe women slaughter chickens.

He observed that they cut the carotid jugular, and threw the chicken on the dry ground in front of their houses. A large plume of dust could be seen rising around the chicken. Children were often playing nearby and a woman would often stand over the dying chicken.

Clark hypothesized that this was the source of the exposure. Swayne proposed an alternative hypothesis: that the exposure occurred when the women defeathered the birds because there is a great deal of virus in the feather follicles and a vacuum is created when a feather is pulled out of the follicle. When the surface of the skin is broken, the pressure is released and the virus is aerosolized and forms respiratory droplets.

To test these hypotheses in the lab, Swayne and Clark used two groups of chickens, one that had been vaccinated and one that had not. The result was recovery of virus from the oral pharynx and the cloaca of non-vaccinated birds at high titers. The amount of virus recovered from vaccinated chickens was significantly lower. During the experiment, they conducted the standard slaughter on five chickens. They recovered virus in five out of the five non-vaccinated birds from the kill, scalding, and defeathering steps, and then during the evisceration and clean up steps, they recovered virus in four of five non-vaccinated birds.

Next, they switched to conducting the kill step in a bag. The tranquilized chicken was placed in the bag with the head out. The carotid and jugular were cut and the head was placed back in the bag and the bag was placed in a bucket so the chicken flopped within the bag. Using this method, they switched from a negative air ionizing sample to a large impinging sample, and found that there was a reduced number of samples from which virus was recovered following the chicken slaughter and the titers are lower in each of these cases. In the end, they demonstrated proof of principle: if that one step—slaughter—was done in a bag, the amount of virus was reduced greatly. Next, they repeated the experiment using vaccinated birds, which secreted less virus, and they could not recover virus from the air regardless of the process used.

Then they exposed non-vaccinated ferrets to the slaughter of non-vaccinated chickens. Three of three ferrets became infected and died when exposed to the same air space as that of the open slaughter. On the other hand, if the kill step was conducted in a bag, only one of three ferrets became infected and died. With vaccinated chickens, there was no difference in the type of slaughter: no infection in the ferrets was found.

It is clear that vaccination is very important in many parts of the world, but the problem is that vaccination of chickens in the village sector rarely, if ever, exists. Developing countries have abandoned

vaccination of domestic poultry in the village sector and it is largely conducted only in the industrial sector. The other problem is that plastic bags are quite variable in quality.

Following the plastic bag experiments, Swayne's group considered different slaughter processes, using household items that everyone has available in Egypt, such as a halal pot (a big pot with a lid), and a bucket with a lid. First they used a standard open barrel for the kill step, and then they conducted the kill step in a halal pot, and at the end of a two-minute time span, they lifted the lid off the pot, which they thought might actually create some kind of aerosols and vapors, or aerosols and respiratory droplets.

The other way they conducted the experiment was by placing the chicken in the halal pot during the kill step and then sliding the lid off after some time. Next they used a bucket and placed the bird in it during the kill step and snapped the lid on. The lid had a small hole in the top. Scalding water was poured into the bucket to settle everything out. The experiments with the halal pot and the lidded bucket were conducted using a different table arrangement because over the course of the overall series of experiments, the lab had changed from a BSL-3-Ag to a BSL-3-enhanced lab. The experiments were conducted in a flexible film isolator, i.e., a bio-bubble. They also switched to using the Cyclone sampler because they could collect three different particle sizes by dividing aerosols and respiratory droplets in the sampler.

The results using the standard open-barrel method versus the halal pot or bucket and pouring scalding water into the covered receptacle then sliding the lid off demonstrated that they could reduce the size of the larger, respiratory droplets or even reduce the airborne virus below detection levels. This covered-receptacle method seems to have worked. They compared the results when sliding the lid off the pot versus lifting the lid, and there was a bit more virus in the sample from the lifted lid method, but it was not significantly different. Using the modified bucket method, they could not recover virus if they sampled from the air versus sliding the lid off of the bucket at the end of the kill step.

In concluding his presentation, Swayne noted that there are many physical needs for birds that are different from those of mammals, which translates into diverse housing needs. Birds are diverse and housing variations may be needed to accommodate their unique physiological differences.

For infectious disease housing, isolation cabinets are preferred. They aid in maximizing floor space by having more groups in the same space.

If cabinets of the correct sizes are used, researchers and workers are able to reach in and handle the birds easily. This also allows researchers to maximize the number of birds to obtain statistical significance.

In addition, different kinds of enhancements for containment can be used, such as glove port systems. Birds can be transferred through either vaporized acid transfer boxes or through dunk tanks. Swayne and his group prefer to use the large HEPA filter ventilated flexible film enclosures for inoculations, swabbings and necropsies, and other bird procedures such as slaughters.

Discussion

The discussion following Swayne's presentation focused on specifics of his experiments, religious considerations for the slaughter step, and educating the public.

Jens Kuns opened the discussion by asking three questions of Swayne: How many chickens did Swayne kill at a time for each experiment? Was the anesthesia used a requirement? Did Swayne and his colleagues receive religious input about whether the bucket slaughter would still be considered a proper halal slaughter if it was conducted in that manner, that is, with the hole in the lid? Swayne replied that during the first experiment, ten chickens were killed and then this number was reduced to five; typically five chickens are killed per experiment. He clarified that they tranquilized the birds, and did not use anesthesia. And he confirmed that their collaborators in Egypt took the proposed original project to the Islamic Council in Cairo, from whom they received a letter approving the bird-in-the-bag project and saying this would protect human lives and it did not interfere with halal slaughter.

Swayne continued by saying they have not experimented with the bucket process in the field. Clark returned to Egypt in 2013 and conducted the halal pot slaughters with focus groups of women and it was well received by a large number of participants. Subsequently, they produced posters in Arabic about the process and they are preparing to transfer that material to colleagues in Egypt for distribution. They will try to educate households by educating children who in turn convey this information to their parents. Researchers have found that children have more influence on the adult family members than do case workers distributing posters. Hopefully this will be successful, which may help reduce the number of human H5N1 infections.

HIGH SECURITY ANIMAL DISEASE LABORATORY, BHOPAL: CONTAINMENT OF ZOONOTIC INFECTIONS

Shiv Chandra Dubey began his presentation by noting that the High Security Animal Disease Laboratory (HSADL) in Bhopal, India, was upgraded and designated as the National Institute of High Security Animal Diseases (NIHSAD) in August 2014. Now NIHSAD is an independent institute directly under the jurisdiction of the Indian Council of Agricultural Research (ICAR) and, hence, the institute leaders will be in a position to make decisions as per international requirements.

The lab was designed over a 15-year period with the help of international experts, and with the financial assistance of the Food and Agriculture Organization of the United Nations. After the design and financing phase, it took nearly ten years to fully construct, commission, and validate the facility. Since early 2014, the NIHSAD has been online, and it has delivered the required services, particularly in the wake of avian influenza cases in India.

The institute has a three-floor design. The first floor is dedicated to the air-handling units. The ground floor contains the laboratory as well as the animal wing, and the basement, which is up to five meters down, is dedicated to effluent collection and risk processing. Another special feature is that the majority of the structural engineering components and equipment are of indigenous origin. This has saved a great deal of money, Dubey said, and the overall annual maintenance cost of this lab is less than ten percent of the installation cost. The lab was constructed by the National Dairy Development Board because at that time it was the only agency that had experience with a biocontainment lab, a lab located in Hyderabad which focuses on foot and mouth disease.

The mandate of the HSADL, Dubey noted, includes the building of this facility and developing competence with respect to the handling of exotic animals. HSADL is also responsible for sharing the transferrable technology with partners to help with diagnostics in the wake of or at the emergence of an infectious disease. The HSADL also prepares the biosafety protocols based on indigenous and international requirements; they also educate people about these protocols. Dubey and his colleagues have been associated with training of Indian experts and those from neighboring countries for some time.

The primary biosafety barriers are biosafety cabinets, isolators, personal protective equipment, and personnel training. The secondary barrier includes a double wall structure and a complete cement structure

in the animal area. It also has an air-handling unit for reducing aerosol transmitted pathogens, a rendering plant, and an autoclave. At the time of construction, the facility met all biosafety level 4 (BSL-4) requirements. However, given the advancement of technical requirements for BSL-4 facilitates, the facility is now considered a BSL-3+, and currently there are no plans to upgrade the facility to a BSL-4 level. Since there are annual outbreaks of avian influenza in India, laboratory leaders decided not to renovate the facility at this time because part of the laboratory would have closed and that would have created difficulties in handling the large number of anticipated samples.

After the first outbreak of avian influenza, two facilities were added to HSADL, a specific pathogen-free unit and a transmission electron microscope. During his presentation, Dubey was asked how the response to avian influenza was addressed in such a large country, and he replied that this laboratory is part of the response system that has been developed with the government of India through the Ministry of Agriculture. Fortunately, he said, both the Department of Animal Husbandry, Dairy, and Fisheries, and the Department of Agricultural Research and Education, are in the same ministry that has primary responsibility for international affairs at ICAR. In the event of an outbreak of an exotic disease, the laboratory becomes involved and communicates with World Organisation for Animal Health (OIE) officials. Contingency plans have been developed for specific diseases, particularly avian influenza. Quarantines have been established at the major airports and around-the-clock control rooms can become operational if needed.

HSADL has also been fulfilling its responsibility with respect to diagnostics, training, and active and passive surveillance of samples received at the lab. The animal husbandry departments work in collaboration with the Indian Department of Animal Husbandry, Dairy and Fisheries.

At this point, HSADL has offered these services to the nation for nearly 15 years. Over this time, a few diseases were stopped at the entry point itself, including avian influenza, H7N7, malignant catarrhal fever (MCF), and exotic strains of bovine viral diarrhea (BVD).

HSADL also responded to emergencies following the September 11, 2001 attacks on the United States (9/11) when hundreds of envelopes suspected of containing anthrax spores were sent to HSADL for diagnosis. Fortunately, no anthrax was found. The lab has also been able to confirm the existence of certain diseases not native to India, based on clinical confirmation. The lab was also able to confirm the existence of

avian influenza, both low-pathogenic and highly pathogenic; BVD, MCF, and Bovine immunodeficiency virus infection; swine influenza in 2010; border disease virus in 2011; and West Nile fever and Crimean-Congo haemorrhagic fever (CCHF) in 2011. Routinely, screening for many other diseases occurs at this lab.

Since 2006, Dubey stated, nearly 0.8 million avian influenza samples have been handled at HSADL and have been reported to the OIE. Over the years, the virus has been found in nearly 13 of the 29 states of India. The work carried out at HSADL revealed that until 2007, the declared virus clade of the H5N1 was 2.2; then, after an outbreak in Myanmar, it changed to 2.3, and based on a 2010 isolate from Nepal, they declared the virus clade to be 2.3.2. The clade of the virus detected so far since 2011, in Bhutan, India, and Nepal has come to 2.3.2.18 so this has been the overall molecular composition of isolates handled at HSADL, which has been reported internationally.

In India, crows have been central to the epidemiology of avian influenza. Samples from crows have been received at the lab and the virus was isolated and confirmed. However, there have been no zoonotic implications thus far in India, whereas there have been zoonotic cases in Bangladesh, Myanmar, Pakistan, and other neighboring countries.

The emergence of amantadine resistant influenza A viruses has also been detected by scientists at the lab. Before 2010, CCHF was considered nonexistent in India, but the lab positively identified it in tick samples from Gujarat after a CCHF outbreak in humans between 2010 and 2012. In addition, antibodies of West Nile fever have been detected in ducks in northeast India, and MCF has also been detected in a few places.

After ten years of working at HSADL, Dubey believed it important to work with experts to prioritize the establishment of laboratory guidelines. He led a brainstorming session on guidelines and experts recommended that the lab should have preparedness and surveillance functions for certain diseases and diagnostic preparedness for a number of other diseases, which have not yet been tested or which have been tested serologically.

Dubey and his colleagues have prepared a proposal with technical details on upgrading the lab, and submitted it to the government of India. The plan has been approved and the funds have been allocated, and upon the completion of this plan, the HSADL will have two integrated BSL-4 facilities and the older lab will continue to operate as a BSL-3 facility.

FIGURE 3-2 Working floor layout of the integrated BSL-4 facility.
SOURCE: Shiv Chandra Dubey, presentation at the workshop.

After a great deal of discussion and after political and legal matters have been addressed, the new, integrated lab in Bhopal can go forward (see Figure 3-2).

One side of the facility will contain the laboratory, and the other side will contain the animal wing. There is a series of showers and sprinklers next to the lab. The lab has a controlled entry and a clean corridor for entry to the lab from the showers. There are two changing rooms, an entry changing room as well another changing room inside the lab with a shower in between.

The HSADL was a unique effort by the government of India, particularly ICAR, to build such a facility prior to the existence of the current understanding of biosafety. It was difficult to convince politicians and administrators, which is why it took 15 years for the development of the plans and 10 years for the construction for the facility.

Discussion

The discussion following Dubey's presentation focused on international collaboration and community acceptance of the lab.

International Collaboration

Indira Nath noted that when she saw the data presented by the WHO representative at the workshop reflecting the paucity of BSL-3 and BSL-4 labs in the South Asian region, she wondered whether other countries have access to Dubey's lab, and if there are any problems. Dubey replied that they do receive samples from the other countries. After receiving influenza disease status from the OIE, neighboring countries can have access to HSADL. Also international experts are trained at HSADL, OIE, and by other organizations. This is a regular practice and the epidemiological information received through HSADL processing is provided to neighboring countries, and results are provided as quickly as possible. With respect to Bhutan, when a sample is received at 11:00 a.m., the results are returned via email by 4:30 or 5:00 pm that same day. During peak days of the Bhutan outbreak, scientists and the team at HSADL worked for 16-18 hours a day, and the overall handling of samples sent was very good.

Nath further asked about the bureaucracy involved when international scientists want to access Dubey's lab. If a scientist in Nepal would like to have a sample tested, does he/she have to contact the Ministry of External Affairs or the Ministry of Health? Dubey replied that the guidelines are similar to those of the government of India and the guidelines for transport of samples follow OIE procedures. The NIHSAD website clearly details ICAR guidance regarding the type and size of individual disease samples that can be sent, how they should be packed, and how they should be transported.

Gaining Acceptance from the Local Community

Franz asked about community concerns regarding the building of the lab. Dubey replied that one of the politicians from Uttar Pradesh who was a minister in the government of India and former chief minister of Uttar Pradesh was involved, and he was able to address community concerns. Also, whenever there were difficulties from the administration or from various other agencies, he was always involved and his involvement directly or indirectly was able to convince the other politicians and administrators to solve the problems. Dubey noted that

the Uttar Pradesh politician was also a member of parliament from his district and remained accessible for the entire 8 to 10 years during which the lab was built. He was a problem solver and other politicians were equally responsive to HSADL requirements.

4

The Biotechnology Revolution: Exploring New Territory Together

Raghavendra Gadagkar introduced the fourth workshop session by referring to opportunities and challenges presented by the emerging capabilities of the biotechnology revolution, and stating that India and the United States can explore this new territory in the life sciences and related technology together.

EMERGING CAPABILITIES IN THE LIFE SCIENCES AND CHALLENGES FOR GLOBAL HEALTH

David Relman began his presentation with the point that one of the keys to understanding why and how infectious disease events occur is related to recognizing ecology and evolution. These events occur in an ecosystem under stress; an ecosystem in which infectious agents (microbes), hosts, and the environment are evolving. All three—microbes, hosts, and the environment—concern us.

In addition to the loss of human life and suffering as a result of the Ebola outbreak, there are also important effects of events like these on public health infrastructure, on social infrastructure, and economic and political infrastructures as well. Sometimes these events have as much of a detrimental effect on the overall ecosystem as they do upon individuals. These events reveal a number of important needs. We need to understand how and why these events occur, both from the point of view of the agent as well as from the perspective of the larger system. To overcome existing challenges, we need interventions such as diagnostics, drugs, vaccines, and the means to deliver them in a rapid and flexible manner. This is the context in which we can discuss science and technology and what is occurring today.

Relman then turned to history because the revolution in the life sciences did not begin yesterday. It began more than 50 years ago with the first description of transmissible inheritable material, DNA. Over the subsequent 20 or so years following the discovery of DNA, the tools for manipulating DNA and what is now referred to as recombinant engineering were developed. Some have described the mid-1970s as the beginning of the age of biotechnology. Thereafter it became possible to both sequence and later synthesize DNA, and hence to understand and manipulate it for positive purposes. Genetically modified plants first became available in the 1980s, and the ability to sequence an entire genome was realized in the 1990s. The commercialization of all of this technology then became possible. Since the turn of the last century, these trends have escalated enormously such that today's trends show an exponential growth in technology and a simultaneous decrease in costs. Relman cautioned that there is a difference between information, which is what is gained in these advances, and insight, which is not always measured in such dramatic terms, but one hopes insight follows information.

About 8 years ago, Relman had the opportunity to help organize a study at the U.S. National Academy of Sciences (NAS) that examined these trends and asked what their impact might be on our future.[1] As part of that study, experts were trying to grapple with the many diverse types of capabilities that might fall under the umbrella of biotechnology. First, they considered ways of trying to classify all of these technologies in simple terms. Relman admitted that it is not simple, but the idea was that there is a group of technologies whose purpose is to generate a great deal of diversity that would not necessarily occur normally in nature. This is an immensely important capability and it is exemplified by DNA synthesis, DNA shuffling, and other types of technologies.

Second, there is a related but distinct type of technology that is motivated by the goal of deliberately designing a particular life form. There may be a code for an existing agent. One may have a code in mind for something that does not exist; there is now the means of making that agent in the laboratory as well.

[1] National Research Council. 2006. *Globalization, Biosecurity, and the Future of the Life Sciences*. Washington, D.C.: The National Academies Press. Available at: http://www.nap.edu/catalog/11567/globalization-biosecurity-and-the-future-of-the-life-sciences; accessed April 10, 2016.

Third, there are technologies that assist in understanding how complex systems operate and learning what might be the small critical vulnerabilities or opportunities for intervention, which is called "systems biology," and there are many other technologies to fall in this category.

Finally, there are biotechnologies involved in producing, packaging, and delivering all kinds of products including DNA itself. All of this has led to an immense number of benefits and one could spend a great deal of time counting the types of important results that have come from these technologies.

A particular development illustrates what biotechnology might offer. Scientists have created in the laboratory a yeast strain that contains all of the genes and the pathways for making artemisinin, a very complicated molecule that is now one of the most important anti-malarial drugs. It was previously only available from its natural source, the yew tree in China. But those supplies have been dwindling and the costs have been rising. Now, through bioengineering, one can make this drug in a much cheaper form in the laboratory.

This is just one of many examples. There are numerous other examples, and Relman selected a few to discuss, although he noted that all of them should cause us to think about not only the benefits that these technologies provide, but also some of the other ways in which they might be used or perhaps inadvertently misused. One example is the means to remake living things. In other words, one can remake most viruses from just the sequence. This is certainly true of RNA viruses and most DNA viruses. This technology is actually quite old. In 1994, a German report documented the formation of rabies. This was one of the first examples of how one might take, in this case, cloned cDNA for an RNA virus and cause it to be expressed in the laboratory with the necessary proteins present at the same time and allow the virus to form in tissue culture. This type of work has continued for 20 years and there is a large, important capability, from this technology in understanding how viruses operate, understanding pathogenicity, and being able to manipulate them for many very useful purposes.

Relman then described his collaboration with Craig Venter and a recent example of Novartis vaccines. They use synthetic capabilities to make the seed stocks for some new influenza vaccines starting with sequencing and then ordering the DNA or the cDNA that would encode the necessary antigens and produce it in synthetic form. This saves a fair bit of time in a process that is very sensitive to timeliness. This same capability to remake viruses has also allowed people to study viruses that

have not been known to exist before. Relman referred to Ralph Baric and his group, who have been conducting very interesting work examining coronaviruses, such as SARS, and trying to determine where they originate. If one creates an evolutionary tree of all of the related viruses known today, one can extrapolate back in time and say there ought to have been an ancestral virus that matches. From that hypothetical sequence, Baric and his colleagues made the virus in the laboratory and showed that it had the properties we could predict from the evolutionary studies of viruses existing today. This same technical capability to remake viruses, shuffle their genomes, and ask whether there are other properties that can be created is now very powerful, and widely used, especially in commercial sectors. It can also lead to the ability to take a virus that normally has liver tropism and give it a different organ tropism, or to take, for example, a virus that had low yield in the laboratory and give it high yield, and so forth. There are many examples of this kind of capability.

What Relman thinks is even more interesting today, he said, is the idea that one could engineer entire communities of organisms, not single organisms, but organisms that normally interact together so that they feed each other synthetic, newly-engineered compounds and help each other make resulting products that no organism alone might have produced. With the help of advanced technology, kits are available for experiments that might have taken months to years in earlier times. Today this work can easily be conducted in weeks. More and more of these kits are becoming available.

These capabilities have led to work such as the creation of reengineered mosquitoes that may have lost their fertility, causing the deliberate extinction of species that carry malaria. However, we must think carefully about the ripple effects in the ecosystem of such experiments.

The mo*in*dification of genes is now being proposed as a possible cure for inherited genetic diseases. Currently, work is being conducted in mice, but the same idea is also being considered in humans. One can begin to ask very interesting questions: What are the implications of the availability and capabilities of these types of technologies? What if a user does not have entirely beneficial purposes in mind? Relman raised these questions because when he was a student, his teacher, Stanley Falkow, one of the fathers of pathogenesis in bacteria, frequently said that nature is the ultimate creator of all that might be. Over many years of evolution, there has been so much natural experimentation that what

we see today is something that humans could not hope to outdo. How could we possibly create something that would have greater adaptability than what has been found in nature? The new capabilities available today have caused Relman to rethink this question.

He then discussed another experiment conducted by Lee Riley of the University of California, Berkeley. Riley studies tuberculosis and he had a strong suspicion that the Mycobacterium tuberculosis mce1 operon was necessary for the virulence of tuberculosis. He set out to knock out the operon and his prediction was that the tuberculosis would be attenuated. Instead, he received the opposite result. It turned out that these genes control the replication of the bacterium within host cells in a way that suggests that nature may have deliberately caused tuberculosis bacteria to replicate slowly as a means of long-term survival. There is no point in killing the host very quickly the way this mutant did if it plans to survive for a long period of time. On the other hand, if this organism were set loose today, it would take quite some time to become eventually readapted to humans. In the meantime, over the successive years, humans, as hosts, would suffer the consequences of a poorly-adapted Mycobacterium tuberculosis. In other words, this discovery led to the realization that many pathogens are actually naturally attenuated and when we identify these genes, we are now able to unattenuate them, to intentionally make them more virulent if we chose to do so.

This story is true for many pathogens, which led Relman to discuss highly pathogenic avian influenza. Observations in nature have raised some compelling questions and he was the first to admit that these questions are exceedingly interesting and potentially very important. With regard to H5N1, one of those questions is: Why has the virus not been able to become more easily transmitted between mammals? Some have argued that since this has not yet occurred, there is something about this virus that does not allow for enhanced mammalian transmissibility while being able to maintain the proper hosts and other properties that it has chosen. Others have argued that transmissibility will happen with time. It was this latter agreement that led to the work behind two widely-cited gain-of-function publications.[2]

These experiments were a deliberate effort in the laboratory to see if H5N1 viruses could acquire enhanced transmissibility between

[2] For a brief overview of this research, see: http://www.nature.com/news/the-risks-and-benefits-of-publishing-mutant-flu-studies-1.10138; accessed April 10, 2016.

mammals, ferrets in this case. The first study, by Ron Fouchier, began with a highly pathogenic Indonesia influenza isolate and he created deliberate redesigns of the genome as well as passaging and found that he could isolate a virus that had the property of enhanced transmissibility and, to our knowledge, no great reduction in virulence. A subsequent follow-on study has provided everyone with the five mutations that together allow this virus to have these properties. These results indicate the immense power of this technology, Relman noted, and the means of achieving ends which nature certainly has not yet achieved, and might not achieve in the future.

These experiments and their results also raise important questions about whether this type of experiment is necessary. When Fouchier's paper was published, the world obtained the sequence, the five mutations, needed to remake the virus because influenza, like other RNA viruses, can be remade in the laboratory by anyone who has the appropriate technology. Some have reacted very dramatically to that particular finding. It certainly caused people to stop and ask questions.

When examining the whole world of microbes, we can see that nature has been very successful through many trials and errors in creating pathogens that are relatively rare. Pathogens are exceedingly rare as a fraction of all microbes on this planet. It is a trait that would probably be very difficult to achieve, even with insights gained over time, so it would be hard to recreate nature's balance. However, Relman stated that nature certainly has not tried all of the sequence possibilities that scientists could try in the laboratory. Success in nature is different than success in the laboratory.

Further, even when people are absolutely well-intentioned, accidents will occur. They happen everywhere, even in the best of laboratories. Therefore, if we have a virus or an infectious agent with new enhanced properties, what is the likelihood that it will escape despite all best efforts?

Relman concluded with several challenges and questions. The challenges in confronting emerging infectious diseases include: (1) immense diversity, even in nature; (2) the importance of maintaining essential science and technology; and, (3) the challenge, but also the potential danger, of relying upon certain kinds of oversight approaches that may provide a false sense of security. Relman is concerned that, at least in the United States, people have become very dependent upon lists of specific organisms that we think we can define and identify as dangerous. These lists, however, are incomplete. Our ability to identify

an organism, even Bacillus anthracis, is problematic. There are some Bacillus cereus strains that behave just like anthracis, but they are not on the list. When we have lists, we may stop thinking thoroughly. Relman suggested that perhaps there might be better approaches to this problem.

The empowerment of individuals as a result of new technology for very good and noble purposes also raises potential risks. In the United States, there has been some consideration of these issues, and experts in India could help those in the United States in challenging some of these definitions and considering alternative approaches to overseeing and thinking through what some of these experiments might mean. Our concern is that science in the form of innovation of knowledge should not be in the wrong hands as it could be a significant threat to all living beings and the environment. One must rethink how to mitigate these risks.

Each of these issues deserves serious discussion. For example, the issue of possibly regulating access to organisms, technologies and/or knowledge is worth discussing. Relman is dubious that this approach would work well, but under certain circumstances it may be an option. He supports the idea of promoting awareness and sensitizing all of the relevant communities, especially the science communities, to the potential benefits and risks of research. He noted, however, that scientists must accept the fact that despite all efforts, there could continue to be outbreaks, both natural and potentially man-made, and the public health infrastructure and other countermeasures used as defenses must be strengthened in order to mitigate the negative effects.

Just several weeks prior to the workshop, the United States announced a pause in conducting certain types of experiments due to the concerns regarding the risks of these experiments.[3] What should be gained from a pause in research, and when should research resume? How are we going to assess risk and measure it against benefit? These issues are hard to quantify, if even possible, but there must be some kind of effort to weigh the two against each other. To what degree can risks be anticipated? Many of the often-cited scientific discoveries were unexpected. How will we know in advance that there might be a potentially risky outcome? Who decides whether there might be

[3] Julie Steenhuysen. "White House Issues Report on Improving Biosafety at Federal Labs," Reuters. October 29, 2015. See: http://www.reuters.com/article/usa-whitehouse-biosafety-idUSL1N12T4EV20151029; accessed April 10, 2016.

experiments that ought not to be undertaken? What are our collective responsibilities to society? For example, what would those people who did not attend the workshop, or who are unaware of this research, think about it? They may not know the details of the science, but they certainly care about whether scientists undertake experiments that put them at risk. Scientists must consider this and how to reduce risks, and the most effective approaches to pursue science and technology safely, for the betterment of society.

Discussion

The discussion following Relman's presentation focused primarily on the importance and influence of ecology in the study of viruses.

Referring to mutations in viruses, a participant asked Relman about the example of HIV. From the day a person is infected, many changes occur continuously in the host. Despite there being 1,000 variants, the virus that survives has some advantages. Relman agreed with this point, which has to do with the importance of understanding the selective forces in nature, in situ, that drive evolution. We often mistakenly think that the evolution that we engineer in the laboratory is necessarily the same evolution that occurs in nature. Some of the end results may look similar, but the paths that the virus took—HIV in particular—are different. David Baltimore has shown very clearly that the route to drug resistance in nature is often quite different from the route to the same mutation in the laboratory.[4] Therefore, were Relman in West Africa, he would conduct sequencing and accompanying clinical studies of what is happening to the Ebola virus and what are the phenotypes associated with these new variants arising in nature. He added that he does not think scientists need to create these viruses in the laboratory. Nature is creating them for us. Consequently, we need to spend much more time studying these developments in nature.

The participant added that the ecology in the lab, in the body, or in the environment, could be equally important. Where could these ecologies be incorporated into the models? Is it possible to have a common model or would one have completely independent models? Also, so many of these pathogenic infections have arisen in central Africa. Are there environments in which some of the surviving mutations

[4] For more information on David Baltimore's research, see: https://www.bbe.caltech.edu/content/david-baltimore, accessed April 10, 2016.

can become pathogenic, or are non-pathogenic infections equally important although we are not often concerned with them because of the limited human health effects. It may be that the non-pathogenic viruses are keeping the balance.

Relman replied that the answer to the first question is that the ecology is immensely important. The only reason it does not appear in the models is because it is so complex that humans try to reduce the complexity and study the pieces, the components, the individual viral pathogen, the individual host. However, the question is correct; the interactions are most important and one can begin to conduct more complex investigations in nature and that deserves to be done. There are many interesting ways of doing such investigations.

Relman also reiterated the need to move away from lists of agents. A participant asked what other solutions there might be for governments or policy-makers besides these lists. Relman replied that this discussion was raised when he served on the National Science Advisory Board for Biosecurity (NSABB). The NSABB recommended that NAS conduct a more deliberate study of alternatives to a nomenclature-based list.[5] NSABB considered whether the properties of concern could be described rather than relying on names of organisms. The study was undertaken and the report came out several years ago. The answer was very difficult. This, however, does not stop Relman and others from continuing to think hard about whether we can describe these phenotypic properties (the behavior of the organism) and begin to predict them from the genotype or sequence. That is the critical issue. Can one take a sequence and predict how the organism will behave?

Continuing his response, Relman acknowledged that the point about ecology is also important because how virus A behaves in one individual is very different from how it will behave in another individual, depending upon the indigenous microbiota, diet, and where the individual lives, and other contacts made with the virus and with the individual.

A participant noted that not only is it important to understand emerging diseases, but it is also important to understand when diseases fade out. This is generally not taken into consideration. Relman agreed that this is also potentially immensely important. The reasons that a

[5] National Research Center. 2010. *Sequence-Based Classification of Select Agents: A Brighter Line.* Washington, D.C.: The National Academies Press.

disease fades out are probably quite diverse, but they most likely include continued evolution or selection against the properties that make them so obvious and dramatically attenuated, the adaptation of the host, or some kind of accommodation. Those would be excellent aspects to understand when or if they happen. Sometimes it is just stochastic. Early outbreaks of Ebola ended because insufficient numbers of people were close together to propel the outbreak forward and the proper medical and infection control responses were effective because of logistics, population density, and so forth.

FROM GENOMICS TO PUBLIC HEALTH

G. Balakrish Nair began by stating that his presentation was partially inspired by the cholera outbreak in Haiti after the earthquake in 2010, and by the number of people that were killed in a part of the country where there was previously no cholera.

Nair described hospital-based surveillance, culture-dependent and independent methodologies, and the relationship between pathogens associated with co-infections such as community diarrheas, fecal microbiota of healthy children, and the gut microbiome of Indian children with varying nutritional status.

Nair described a simple hospital-based study that he and his colleagues conducted on the etiology of diarrhea in Kolkata a few years prior to the workshop.[6] There were patients with diarrhea admitted to the infectious diseases hospital. Every fifth patient admitted with diarrhea on two randomly selected days in a week were enrolled in the study. The diarrheal samples were taken to the bacteriology, virology, and parasitology labs, and the pathogens were detected using a variety of techniques. The pathogen diagnostic data and the antimicrobial resistance data were tracked for data management. The study traced 26 different pathogens across the spectrum of bacteria, viruses, and parasites. This was perhaps the first time this was done in this setting.

[6] Nair thanked those who contributed to this research: Dr. Ramamurthy and his colleagues at the National Institute of Cholera and Enteric Diseases; colleagues at the Yakult Probiotic Research Centre; Dr. Mande, Sharmila Mande, from the Tata Consultancy Services in Pune, who conducted the computational analysis; Dr. Mike Levine, Dr. Sur and the Global Enteric Multi Centre Study, and; Professor Yoshifumi Takeda, Director of the Okayama-NICED Research Program in Kolkata..

Next, Nair's group conducted a routine etiologic study of the data. They found that Vibrio cholerae was the most common pathogen across all age groups, and when the data were sorted by age, rotavirus was the primary cause of illness. Among the parasites, Giardia lamblia was the most common found in this outbreak.

Nair and his group then decided to examine the data differently. From November 2007 to 2009, 45,004 patients were admitted to the hospital. Samples were taken from 2,519 patients. Their analysis of 26 pathogens indicated that 42.9 percent of samples contained sole pathogens, 29.2 percent of samples had a mixture of pathogens, and in approximately 27 or 28 percent of samples no pathogens were detected. In the mixed pathogen group, the number of different pathogens varied from two to six or more in the same sample. This intrigued Nair's group. Normally what they did was discard the mixed pathogens because of the added complexity that could confuse the data. Instead, in this study, they analyzed further to understand what the other pathogens were doing and what the polymicrobial infections were in these settings. qPCR, a culture-independent method, was used to identify the microbes present within a sample, and a couple of the parameters used for the bacterial pathogens are listed below.[7]

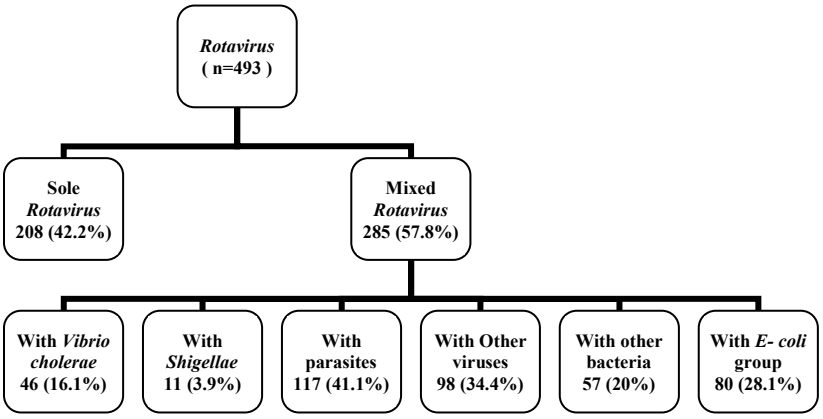
Vibrio cholerae	- 16S rDNA, *wbe* O1, *wbf* O139
Vibrio parahemolyticus	- 16S rDNA
Campylobacter spp.	- 16S rDNA
Shigella spp.	- *ipaH* invasion related gene
Diarrheagenic *Escherichia coli*	
	ETEC – Heat labile (*lt*) and Heat Stable (*st*) toxin gene
	EAEC – *aggR* adherence factor gene
	EPEC – *eae* pathogenecity related gene

A subset of stool samples was examined by culture techniques; 59 samples contained sole pathogens, 9 samples had mixed infections, and 54 samples had no detectable pathogens. When they followed the

[7] For more information, see: Gopinath Balakrish Nair, et al. "Emerging trends in the etiology of enteric pathogens as evidenced from an active surveillance of hospitalized diarrhoeal patients in Kolkata, India." *Gut Pathogens*. (2010) 2:4. Available at: http://gutpathogens.biomedcentral.com/articles/10.1186/1757-4749-2-4; accessed April 10, 2016.

culture-independent method, they found that of the 59 samples which were thought to have sole pathogens, only 25 samples actually contained sole pathogens and 34 samples contained mixed pathogens. This was surprising. The key message after this study was that more than two-thirds of the hospitalized diarrhea cases had DNA of more than one enteric pathogen in their fecal samples.

Nair's group continued to examine these samples and tried to understand the relationship between pathogens associated with co-infections. This was done in collaboration with Colin Stine at the University of Maryland in Baltimore. Two of the main pathogens in the hospital study were rotavirus and Vibrio cholera. There were 493 cases in which rotavirus was detected in the study series, of which 42.2 percent contained only rotavirus pathogens, and the majority (57.8 percent) of samples had rotavirus mixed with other pathogens: that is, rotavirus with Vibrio cholerae, with Shigellae, with parasites, with other viruses, with other bacteria, and with E. coli.



Note:-
Vibrio cholerae :- Vibrio cholerae O1 + Vibrio cholerae O139 + Vibrio cholerae non O1 non O139
Parasites :- Blastocystis hominis + Entamaeba histolytica + Giardia Lamblia + Cryptosporidium spp.
Other viruses :- Adenovirus + Norovirus G1 + Norovirus G2 + Sapovirus + Astrovirus
Other bacteria :- V. parahaemolyticus + Vibrio fluvialis + Aeromonas spp. + Campylobacter jejuni + C. coli + Salmonella
E- coli group :- EPEC + ETEC (LT) + ETEC (ST) + ETEC (LT + ST) + EAEC

FIGURE 4-1 Rotavirus with Mixed Isolation, November 2007-July 2009.
SOURCE: Gopinath Balakrish Nair, presentation at the workshop.

They then started testing the possible associations. They used Fisher's exact test to compare pairs of pathogens, one, both or neither, with an independent assortment based on overall frequency with which pathogens were detected. To establish criteria for statistical significance, they calculated p values, odds ratios, and 95 percent confidence intervals.

Figure 4-2 also shows the odds ratio of rotavirus co-occurring with various other pathogens. For example, Shigella did not seem to have any association, but three of these seemed to have a positive association with the presence of rotavirus: enteroaggregative E. coli, Cryptosporidium, and Adenovirus where the odds ratios were as high as six. Because there seemed to be some association, they researched the cholera literature and found that the rotavirus, which is an RNA virus, and the adenovirus, which is a DNA virus, possibly had different sites of pathogenesis, and therefore a presence of both together could have made the infection much more severe. There were a couple of reasons why they thought these associations may exist, but they are still examining this question. Likewise, Vibrio cholera exhibited an odds ratio with various pathogens that appear to be associated only with Giardia lamblia.

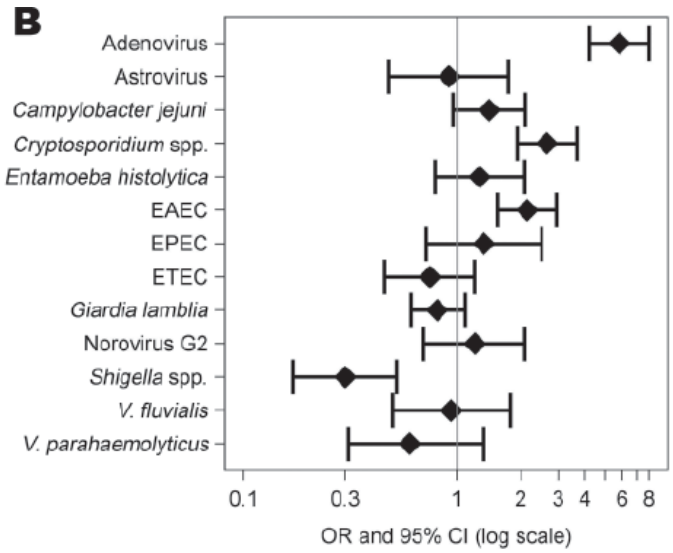


FIGURE 4-2 Odds ratios showing odds of rotavirus co-occurring with various other pathogens.
SOURCE: Gopinath Balakrish Nair, presentation at the workshop.

Several questions emerged from the culture-independent study: What are the potential implications of polymicrobial infections? Do cases of diarrhea caused by Vibrio cholerae or rotavirus and a second pathogen differ from those caused by Vibrio cholerae or rotavirus alone? Does one pathogen lead the way for another to successfully infect a person? Do the pathogens behave synergistically to escape immunologic detection, or does the age or season affect polymicrobial infections? What is the temporal sequence of pathogen infection?

Another key message from this study is that polymicrobial infections associated with Vibrio cholerae and rotavirus in this series were non-random associations. The group is continuing to investigate these interesting data from the hospital-based study.

Another study, the Global Enterics Multi-Center Study,[8] was a case-controlled study performed on community diarrheas, which are different because patients were not required to be hospitalized to test the results. This study was conducted in Kolkata and at two other sites in Asia and four sites in Africa using the same criteria for selection of cases and controls. There were 141 collection sites in Kolkata, as shown in Figure 4-3.

They calculated the excess rate of infection and certain pathogens. The excess rate of infection is where the excess rate of isolation is attributable to diarrhea – this is a difference of isolation rate between cases and controls. Pathogens like Giardia lambliam, enteroaggregative E. coli, typical enteropathogenic E. coli, typical enteropathogenic E. coli EPEC and salmonella were detected in apparently healthy, non-diarrheal cases. Rotavirus was the single most common pathogen, followed by Cryptosporidium, and similar results were found in samples from other sites in the GEMS study. Thus, the third key message is that apparently healthy children living in poor sanitary conditions ingest a high concentration of fecal bacteria that colonize the small intestine.

Nair then discussed a study of the fecal microbiota of apparently healthy children who participated in a community-based trial of a probiotic in Kolkata. In other words, they first conducted a hospital-based diarrhea study, then a community-based study, and then they studied healthy children who participated in a probiotic trial.

[8] This study was funded by the Gates Foundation, and the principal investigator was Myron Levine from the School of Medicine at the University of Maryland.

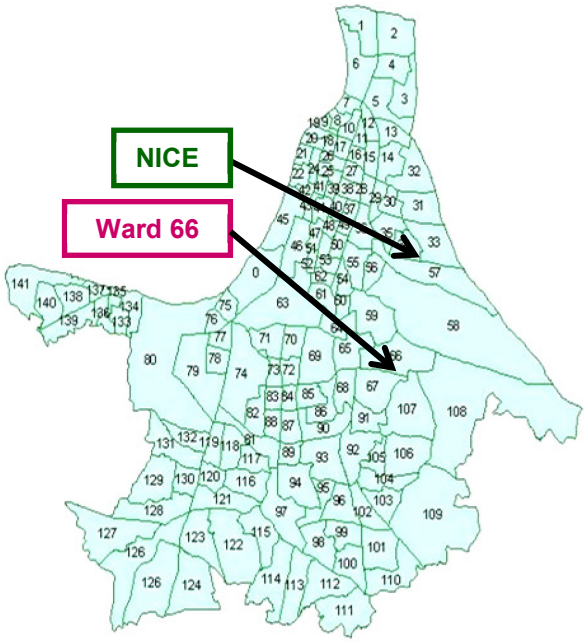


FIGURE 4-3 Map of Kolkata collection sites.
SOURCE: Gopinath Balakrish Nair, presentation at the workshop.

This was one of the largest community-based studies for children. For 12 weeks, the probiotic was given, and for another 12 weeks the children were followed. For this study, they conducted fecal microbiota analysis, in collaboration with researchers at the University of Osaka, Japan, using a sensitive culture independent reverse transcription RNA-targeted quantitative PCR. At 5 points during the study, stool samples from the study group and the control group were collected and analyzed: at the start of the study, then 6, 12, 18, and 24 weeks after the beginning of the study. At every collection period, healthy children were found to be excreting Vibrio cholera, V. parahaemolyticus, Campylobacter jejuni, Salmonella typhi and Salmonella typhimurium, and rotavirus. The enterobacteria as a group was much less represented.

FIGURE 4-4 Photograph of Kolkata probiotic study site.
SOURCE: Gopinath Balakrish Nair, presentation at the workshop.

What surprised Nair and his group was that these were healthy children excreting toxigenic Vibrio cholera. The collated data showed that 52.6 percent of the 133 healthy children examined had detectable Vibrio cholera at different frequencies and at different bacterial counts. The bacterial counts were low, so if they had followed the culture results, they probably would not have identified these pathogens. In 31.6 percent of all samples, Vibrio cholera was only detected during one collection time. In 21.1 percent of the samples, Vibrio cholera was detected twice or more during the study. In 12.8 percent of the samples, Vibrio cholera could be detected during two consecutive sampling timepoints and only one case continued to have detectable Vibrio at all 6 sample collection timepoints.[9] Again, there seems to be a transient colonization of what

[9] Gopinath Balakrish Nair, et al. "*Vibrio cholerae/mimicus* in fecal microbiota of healthy children in a cholera endemic urban slum setting in Kolkata, India," *Microbiology and Immunology*. Vol. 56, Issue 11, 789–791, November 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1348-0421.2012.00497.x/abstract; accessed April 10, 2016.

one would think are fully pathogenic Vibrio cholera. How do the children manage? They also examined the detection of other pathogens in the feces collected from the 70 carriers of Vibrio cholera and they found that many of them shed Campylobacter jejuni and E. coli, and many fewer shed the ETECs or the E. colis. The fourth key message was that the intestines of apparently healthy children carry enteric pathogens for extended periods of time at low levels in disease endemic settings reflecting the effects of constant exposure to fecal bacteria and enteric pathogens.

The next study in this sequence examined the gut microbiome of Indian children of varying nutritional status. This study was conducted at Birbhum, which is in West Bengal. They did not have large numbers of children in the study; approximately 20 children were selected with the exclusion criteria normally used in such studies. This study was from a larger study known as the Birbhum Population Project, which is a health and demographic surveillance system. To assess the health of children in the study, Nair used the three z-scores recommended by WHO to assess child growth. They made a cumulative z-score that was a cumulative nutrition index in which the 20 gut metagenomes were divided into three groups: apparently healthy, borderline malnourished, and severely malnourished.

The microbial membership in these 20 samples was the main phyla and were not unusual. They were the ones generally found in these kinds of studies. The microbe was Prevotella, which is not unusual for this region. It is the kind of genera that one finds in people consuming dietary fibers, dietary peptidoglycans, and other polysaccharides.

Using the 20 samples taken, Nair's group examined the variation of microbial groups with nutritional status. A consortium of pathogens—Escherichia, Shigella, and others—was found and the abundance of pathogens increased with decreasing nutritional status. This meant that as the nutritional status declined, these genera were dominant. In other words, Nair believes that the presence of common, beneficial bacteria, showed a direct relationship to nutritional status, where the beneficial bacteria decreased with decreasing nutritional status. These undernourished children enter the whole infection cycle. Beneficial bacterial were found more frequently in the apparently healthy group, which correlates with positive nutritional status of the child in these settings.

For another part of the study, they analyzed the genera co-occurrence networks obtained for the gut microbiomes among apparently healthy,

borderline malnourished, and severely malnourished groups. An interesting set of sequences showed that despite having contrasting trends in abundance, some of them showed strong positive associations amongst each other. However, as the nutrition level declines, there seems to be a network formed by the pathogens, which becomes more tightly bound when it appears in the severely malnourished state, which means that there was a consortium of pathogens in the malnourished child or in the undernourished child. They found positively correlated clusters of orthologous genes (COGS), and negatively correlated COGS, with the positively correlated tending to reflect function in terms of digestion and similar functions whereas the negatively related COGS were related to the infection process or the virulence.

In summary, pathogenic microbial groups seem to abound when the nutritional status declines or when there is an impaired nutritional status. There is also a depletion of several commensal genera. There is a higher number of virulence genes in children with a lower nutritional index.

Nair noted some of the research questions that have arisen from the studies that they conducted. What are the pathogens doing in an apparently healthy child's gut as shown in the case-control study? When is the balance between pathogen and commensal intestinal microbiota disrupted? How does the host deal with the presence of pathogens? Immunologically, how are multiple pathogens perceived in polymicrobial infections? What is the nature of the immune response to pathogens in the healthy child?

In addition, Nair noted, the environment did contribute to the presence of pathogens and a lack of nutrition contributed to the proliferation of pathogens. Therefore, this is something that depends on the individual's immunologic response. The extent to which this relates to epidemiology, transmission, and to a whole set of other variables is an interesting facet of research that they are increasingly trying to address.

Discussion

The discussion following Nair's presentation focused on sanitation issues and the potential protective nature of pathogens at low levels.

A participant asked if the cases with multiple infections were using shared toilets or perhaps open toilets. Is it possible to provide them with private toilets? Nair replied that this is difficult in a setting where there are many people in a very small space. The transmission of fecal pathogens is intense. Among healthy children, anything that goes into

their mouths probably carries pathogens, and yet most of them do not seem to suffer from infection. Nair then suggested that the presence of these pathogens in low numbers may be protective in an endemic setting, although this was not part of the research conducted.

A participant asked if it is possible that Nair and his colleagues were just measuring pass-through rather than something that is actually colonized in the gut. Nair replied that they conducted frequency studies and there were some children which excreted steadily for a couple of weeks. The questions that they keep asking are: How do they colonize? Why do they prevail there? For how long? Is their presence protective? Nair acknowledged that he and his colleagues do not have answers for all of these questions, but he wanted to share these results with the experts at the workshop.

Another workshop participant had reread Robert Koch's original writings, and the second of his three postulates for causation is that the pathogen should not occur in hosts who do not have the disease. However, the participant realized that this is very difficult to achieve because the participant has seen the telltale bacteria in the stool of humans who do not have diarrhea and yet that bacteria causes cholera. Even Koch saw that there was asymptomatic carriage in people with the cholera organism. It is an interesting and very difficult problem, almost a teleological problem. What does constitute true colonization and what are transients?

INNOVATION IN MOLECULAR DIAGNOSTICS FOR RESOURCE POOR SITUATIONS

S. R. Rao introduced his presentation by stating that containing or mitigating problems related to infectious diseases requires early diagnosis, and he provided examples of collateral damage that occurred due to delayed diagnoses, and how it can be prevented. He also provided examples of innovative steps that are being taken in resource poor situations to improve diagnostics.

For Rao's first example, he described fungal keratitis, which is a very common disease that causes blindness. In India, the disease is especially correlated with agricultural activity particularly the harvesting of crops. If the plant matter touches a person's cornea and leaves some fungal deposition, it leads to fungal keratitis. The eye heals in almost 40 percent of the cases, but the cornea is scarred and vision is compromised.

This fungal parasite sits on the cornea and produces enzymes for its nutritional purposes, which, in turn, degrade the cornea.

An antifungal drug eliminates the infection when it is treated, but in the meantime the fungus could have consumed the cornea, leaving a scar and compromised vision. In approximately 60 percent of cases, the antifungal medications did not work, requiring keratoplasties to remove the cornea as the only treatment option, possibly leaving the patient blind. Thus, there is a critical need to develop novel therapeutic approaches for treating fungal keratitis.

Rao and his colleagues examined fungal keratitis under several conditions as organisms in culture, and found them to be very clever organisms. If they are grown on casein, they will produce casein enzymes. If they are grown on coleitem, they produce colidenen enzymes. In other words, the organism produces different enzymes to adapt to different substrates.

As part of the study presented at the workshop, Rao's group examined the types of enzymes that are produced when organisms are grown in cultures, in different tissue substrates; the appearances of normal and infected corneas; and the production of different enzymes produced by the fungus. Their study identified all fungal and host responses that are associated with corneal damage. They then produced a rabbit model and developed a combination of particular enzymes and antifungals that were able to completely cure the disease. They have a combination of protolytic inhibitors that prevent the damage and also remove the fungi. The problem is that, as with any other eye drug, when a person blinks, the drug is removed. This requires continual reapplication, which is difficult.

They then considered developing a nanotechnology-based approach for this problem. The important parameter is an increase in time that the antifungal would remain on the eye because the fungi have some mucosal properties. They stick on the cornea. To counter those properties, the residential period of the drug is increased. The drug contains alternative substrates for host and fungal enzymes so that the cornea is protected from degradation by fungal enzymes. Inflammation also needs to be controlled, so this component is added to the drug particle. This is the concept with which they designed something similar to a smart nanoparticle. The nanoparticle is a polymer that is biocompatible and biodegradable. When the fungi produce enzymes, they can consume this nanoparticle instead of the cornea. The particle is decorated with peptides so that it can be utilized for this purpose. These

peptides have corneal penetrating capabilities, cornea binding properties, plus anti-inflammatory properties.

In addition, Rao's researchers included integrin-binding peptides because once the damage to the cornea cells occurs, mucin is not available. Integrin starts coming out. If application occurs later, integrin-binding peptides, anti-inflammatory peptides, and antimycotic material are available. This process can continue on the eye for more than 24 hours, which means one drop or one dosage per day should be sufficient.

That is the type of drug that Rao's group developed. At this point in the production process, having excised and characterized particular nanoparticles, they prepared the peptides and attached them to the nanoparticles. The drug has been tested in vitro. The corneal binding and anti-inflammatory effects of the nanoparticle have been tested on human lenses.

Rao then turned to molecular diagnostics. His group started a project several years ago on a novel molecular diagnostic for eye diseases. The object of the project is to develop a rapid, simple, and inexpensive diagnostic method to detect mutations of eye diseases and a signature sequence of pathogenic organisms.

They asked eye hospitals in India to identify the types of organisms existing in their patients. Once Rao's group received a list from the hospitals, they looked for the signature sequence for all of these organisms and made a unique multiplexed PCR-based system with unique probes and targets. They have 54 primers and 27 probes in one piece and the diagnostic was developed. When they developed the diagnostic, they were unaware that it is not easy to make a multiplex piece with the 54 primers. This is very complicated but they started anyway. They attempted to address all of the possible issues, although when they made the final, commercial product, it was made into several elements. The probe selection was the key step in the molecular based technologies.

Based on the success of this platform, Rao's group is developing a chip to detect septicemia, a chip to detect accutane kuflitis, and a chip to determine antibiotic resistance. Rao said that they were at the clinical trial stage and it should be available in a year or two. Now they are addressing the question of whether they can use microfluidics or paper microfluidics, which would make them affordable. This is where they can develop novel diagnostic approaches.

S.R. Rao's goal is to develop and evaluate easy-to-use, low-cost, point-of-care diagnostics for infectious diseases. Many of the workshop

participants, Rao noted, are familiar with the criteria of affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free diagnostics that are available to end users. These are the parameters one would like to have in a diagnostic kit, the so-called 'assured approach.'

Paper microfluid devices will be ideal for this purpose because they are very cheap, and the cost of medical diagnosis can be reduced significantly for the developing world. Disposal is also easy; they can be thrown away or burned. During this diagnostic process, biological fluids spread through the paper devices—through the fibers and the micropulse available in the paper—without the need for electricity, an external pump, or any other devices. However, because the fluids spread, a device was needed to place the reagents at different locations so that they diffuse only in specified directions, not everywhere. Rao's group has developed this diagnostic by using computer algorithms to draw the desired design with wax. They dissolve the wax in particular solvents and make a solution that can be put in a pill, and with a blotter the structures can be drawn onto the paper diagnostic chip.

CHALLENGES OF SYNTHETIC BIOLOGY

Pawan Dhar spoke about synthetic biology in a very broad sense, providing a foundation on current issues for workshop participants, and then moved to more practical aspects. Biological systems have traditionally been studied by reducing the complexity of systems to individual components and by down-regulating the expression of the genes. In other words, by creating junk out of what was a gene or throwing the gene out (gene knockout), we have learned biology. From that, scientists ended up with many parts of genes, and the question they asked was whether they could do anything with these parts because it is very hard to understand them. Can they be tied together? Can a computational model be created? The answers are yes; however, modeling has its own limitations because it involves collecting the essential features and subtracting some information, which will be lost. Another group of scientists then asked, Can a genetic system be created from scratch given the raw materials? The process of linking genetic materials together is known as molecular biology. Systems biology is the process of creating computational models, and synthetic biology is the process of creating genetic systems from scratch. Dhar was at MIT when, in June 2004, the field of synthetic biology was launched. He recalled this latter definition because since its inception so many variations of the

concept of synthetic biology have evolved that sometimes the original message is lost.

Engineering organisms is a new area of synthetic biology by which scientists attempt to build organisms from scratch. Rules of composition and standards are needed to create well-behaved systems. However, IEEE standards that engineers enjoy do not exist in biology simply because the problems investigated are human problems. Organisms evade standards because each is unique. However, from an engineering point of view, one needs to create some restrictions and that is where the standards enter. The science of synthetic biology is the development of a rational design and control construction because control is very important. Many times there is little control over what one creates, and only once the creation has begun is there raw data to analyze.

In comparing engineering and biology, Dhar noted that they are quite similar in terms of their robustness, multitasking, and so forth. There are many dissimilarities between engineering and biology as well. For example, with an electronic circuit design, one is dealing with digits, defined laws, and known forces among structures that are under the designer's control. Biology, on the other hand, is predominantly analog and the only laws that are known are the laws of inheritance called Mendel's laws of genetics, although some debate even these laws. They are not useful, unfortunately, because these laws were not designed for construction purposes and they zoom in and out from phenotype to genotype. They are not designed to explain what happens to the information just below the phenotype. Therefore, new ways of examining and implementing new approaches are needed.

An engineering approach makes sense, Dhar continued, because engineers are successful in creating systems. Unfortunately, absolute engineering solutions do not exist for biology due to the many different sources of contextual data. The solution is either to be found in a top-down approach or a ground-up approach, where the system is built one part at a time, hoping that the solution will be found somewhere in the middle. However, the key message is that this type of construction must be controlled. Dhar then turned to the extent to which biology has been converted into an engineering discipline. Looking at publications addressing a variety of biology topics, truth tables and data sheets are often found. A truth table in a biological setting is essentially a metric that indicates if there is a certain input concentration, a promoter or repressor, and what the output concentration would be in terms of protein. When there are a number of these concentrations, a continuous

state exists based on a series of variations that were inputs to the system. *Latent time* and other terms normally used by engineers are now being used in the biological community. There are also many publications that use biological equivalents of switches, logic gates, oscillators, and so forth. The lac operon is one such example, wherein if the repressor is on, the product is off, and if the repressor is off, the product is on. This is a typical example of a NOT gate that engineers use. When an enzyme and a substrate come together and make a product, this is an end gate. Likewise, there are other examples that demonstrate similarities between engineering and biology. And recently, a special community of biologists has been working on developing standard compositions.

There is a bit of concern, however, about whether the recombinant DNA technology is going to be obsolete in the future because if one can create a recombinant vector on the computer, email the sequence to the DNA synthesis company, and receive the entire vector, does one really need to copy and paste small sequences here and there?

In Dhar's lab, they asked the question, Why did nature place these start and stop signals in a particular location? Did nature try all of the possible combinations? Are there experiments still to be conducted? Traditionally, we know that there is a protein-coding region and an RNA-coding region that comprise the bulk of the genome, and there is a small portion that does not do anything. Dhar's group developed a technique by which they can make the protein-coding genes and the functional proteins from the non-coding area (or as some like to call it, 'the dark matter of the genome'), and they are examining the resulting combinations and applications. They have found many examples and this is just one of them. When Nobel Prize winner Martin Chalfie visited Dhar's lab, he asked if they had considered reversing the protein-coding sequence to determine if they could create a new protein. Dhar's group did this in E. coli and when the coding sequence was reversed, an enzyme was created.

Dhar mentioned an Organisation for the Prohibition of Chemical Weapons meeting he attended, where some people asked him if his group can make a brand new genome, that is, make a brand new microbe by converting junk into a gene. His response was that they had never thought of that. Ever since, they have been trying to match their potential genes against those in the existing genome database, just to be safe.

Several good applications have emerged recently, in addition to automation, and some companies are now using a synthetic biology approach. For example, E. coli makes isoprene and this is used for

making rubber tires. Likewise, OPX Biotechnologies makes a BioAcrylic from organisms, which is used in making paints, and Metabolics Company converts sugar into a biodegradable plastic. There are many such companies and some people are speaking of making high-value chemicals from microbes.

However, Dhar pointed out that there are certain aspects about which scientists need to be careful now that the biological community is assuming the role of a creator. Do we really understand what we have created? A synthetic organism is different from a traditional recombinant DNA biology experiment where the entire genome is cloned or copied. Likewise, there are worries that if an organism is created that is not completely controllable, a minority organism could divide and overtake the majority, leading to a loss of control. There are many issues that are still unsolved, and this is the right time to address them.

In 2014, a synthetic yeast chromosome was designed at Johns Hopkins, and more than 5,000 edits were made to the genome—and this was a 300-kilobase sequence. It took 5 years for the group to chemically synthesize a brand new DNA. Even more fascinating is that a group in the United States created a six-base DNA. We have heard of Alignable Tight Genomic Clusters, and now we have X and Y also in the DNA. Scientists at Scripps have created chemical molecules that are part of the DNA, and the most interesting part is that it is not just a structural composition, but it is a DNA device.

Where are we going to stop?, Dhar asked. Some people argue that if a microbe is created completely from synthetic chemistry, nature does not have any way to support the existence of this microbe. Even if this microbe escapes the lab, they say that it will die in nature. However, we do not know this with certainty.

The outcome of the first Delphi study in India was that the public perception of synthetic biology is almost nonexistent. The scientific community does not use a common definition of synthetic biology because everyone seems to think of something different when discussing it. The trouble is that without a common definition and without clear-cut rules, there is little or no guidance for scientists. The biosafety regulatory processes are good, but much more needs to be done. Synthetic biology currently is self-regulated and scientists do not want to do anything wrong. However, the situation may become more precarious because many publications are being released, therefore, intent and sufficient funding may result in nefarious actions. Some of the future engagements that may be conducted are to differentiate between anxiety and risk, and

what is real and what is speculative. A great deal of what is discussed in the synthetic biology community from biosafety and biosecurity aspects still reflect anxiety because robust safety and security measures do not yet exist. It is also very important to model misuse scenarios and to devise a policy that is predictive, not just reactionary. This is especially true, said Dhar, because some people are speaking of reviving extinct organisms by using synthetic biology. Releasing new organisms into the wild in the name of biodiversity may also be risky because there are insufficient safeguards.

Sensing the alarming situation that might arise in future, the top-most gene synthesis companies have come together and formed a consortium, which represents 80 percent of the commercial global synthesis capacity. This is difficult to regulate because these companies are now investing in creating desktop DNA synthesis printers. If this occurs, DNA printers will proliferate widely, including in labs, and it will be nearly impossible to control this spread of synthesis capability. This situation provokes important questions: How can the distribution of desktop DNA synthesizers be tracked? Is it time to attempt to predict the safety level of emerging synthetic microbes? Would it be helpful to design and distribute unique synthetic DNA barcodes so that we can know where a design originates?

Dhar also noted that there is a need to develop standard assays to measure predictability, reliability, robustness, and evolvability, because the designs currently being created may evolve. A cell is an evolving system and it may be necessary at some point to halt this evolution, which is very difficult. It would be helpful to add safety data to the design parts, devices, and circuits. Currently there are no safety data for the devices, circuits, and parts, because no one knows how to acquire that safety data. If synthetic biology is moving in the direction of making brand new organisms, then it would be helpful to design less competitive organisms, and to design organisms that could be under external control so that they could be switched off at will if something goes wrong.

The questions Dhar posed are being debated in almost every meeting on synthetic biology, and no one has a clear answer. There are useful aspects of synthetic biology, and we need to be careful not to stop the good science at the cost of perceived risks.

Discussion

A participant briefly commented that the World Health Organization, with the influenza Global Influenza Surveillance and Response System (GISRS) network, has developed a Pandemic Influenza Preparedness Framework that allows scientists to distribute viruses more freely between members within the GISRS network and the research community.[10] The question of placing the Pandemic Influenza Preparedness Framework into the context of sequence data has arisen because there is concern that once a sequence is known, the virus is known. This is worth considering, the participant said.

[10] For more information on WHO's GISRS, see: http://www.who.int/influenza/gisrs_laboratory/en/; accessed April 10, 2016.

5
Laboratory Regulatory Oversight: Finding the Balance

INDIAN REGULATIONS AND ANIMAL AND HUMAN HEALTH SAFETY

Nitin Jain opened the session with a presentation on Indian regulatory mechanisms. In 1993, considering the increasing risk associated with the use of new technology in laboratories, the National Biotechnology Board issued guidelines for ensuring the safety of laboratory workers. While drafting and preparing these guidelines, the review committee considered local factors, such as resistance to infection, the host-parasite burden in the community laboratory environment, and chances of survival and growth of altered organisms under tropical conditions. Prior to that, in 1986, the Indian government enacted environmental protection rules and regulations defining procedures for handling genetically modified organisms (GMOs) and hazardous microorganisms. These rules, finalized in 1989, are known as the rules for the manufacture, use, import, export, and storage of hazardous microorganisms, genetically engineered (GE) organisms, and cells which were not included in the 1986 Environment Protection Act (EPA).

The 1986 rules outlined six regulatory committees by topical area of research, each with its own set of guidelines.[1]

- Recombinant DNA Advisory Committee (RDAC)
- Institutional Biosafety Committee (IBSC)
- Review Committee on Genetic Manipulation (RCGM)

[1] For more information about India's regulatory committees, see: http://www.moef.nic.in/division/genetic-engineering-approval-committee-geac; accessed April 10, 2016.

- Genetic Engineering Appraisal Committee (GEAC)
- State Biotechnology Coordination Committee (SBCC)
- District Level Committee (DLC)

IBSC and RCGM are involved in approving cases involving the use of genetically modified organisms (GMOs) or living modified organisms (LMOs) in research, and they also conduct biosafety assessments. The 1989 rules describe the approval required for the use of GMOs in plants and medical biotech products. For environmental release of GMOs or LMOs, or for large-scale production of them in the country, approval must to be obtained from the Genetic Engineering Appraisal Committee. DLCs basically function as regional monitoring groups to ensure compliance with the act and associated rules.

Jain provided an overview of the IBSC, including how it functions and its composition, and then briefly described the RCGM and SBCC.

The IBC is a statutory committee constituted by the Provisions of Rules (1989) of the EPA (1986). Organizations undertaking recombinant DNA activities with GMOs, LMOs, or rDNA materials, must have an IBSC, which must be registered with the Department of Biotechnology (DBT) under the Ministry of Science and Technology. An IBSC is initially constituted for three years and thereafter is renewed every two years. Its role is to examine the experimental protocols submitted with applications for research permission. It evaluates the ability of the investigator and his or her staff to conduct the proposed work, and it evaluates the facilities available within the organization to conduct research involving the recombinant DNA technology. The IBSC evaluates any potential danger associated with the work. It also evaluates the biological containment plan and facilities as per the recombinant DNA safety guidelines, and determines whether additional expertise should be considered. If there is need of any additional expertise, the IBSC may solicit expert comments.

An IBSC consists of one chairperson, three internal members, one member secretary who is also an in-house scientist, and one outside expert in the relevant discipline, typically in molecular biology. An IBSC should also have one biosafety officer with medical qualifications adequately trained to offer advice on specialized containment requirements. Finally, one member is nominated by DBT. IBSC members are appointed by the head of the organization, and can be reappointed at the end of a three year term. Membership is usually reviewed annually and appropriately modified based on participation and the requirements of the proposed recombinant DNA research and

developments involving recombinant DNA technology. DBT is to be notified within 2 weeks of any change in IBSC membership or chairmanship.

An IBSC is responsible for reviewing all research and development activity involving recombinant DNA technology of that particular organization. Depending on the category of the experimentation, the IBSC can simply note the information, grant permission for initiating the experiments, or refer the proposed research to RCGM for further review.

Next, Jain described the DBT RCGM, which functions in the Department of Biotechnology, and is responsible for reviewing the reports of all approved/ongoing projects involving the high risk category and control field experiment research in four areas: human and animal healthcare, agriculture, industry, and environmental management. This committee is empowered to visit the experimental facilities where projects with biohazard potential are being pursued prior to the commencement of research to ensure that adequate safety measures are taken as per the recombinant DNA safety guidelines. The committee is also empowered to issue clearance for the import and export of etiologic agents and vectors, germplasm, and so forth, necessary for recombinant DNA experimental work, training, and research.

Lastly, the GEAP functions under the Ministry of Environment and Forests, and is responsible for examining research proposals from the perspective of environmental safety on a case-by-case basis. It is also responsible for examining the environmental aspects of activities involving large scale use of hazardous microorganisms, recombinants in research, and industrial production. Proposals relating to the release of GE organisms and products into the environment, including experimental field trials, are considered by the GEAC. It also examines large scale use of recombinant DNA in products or the elements of GMOs.[2]

Jain then provided a brief history of regulatory efforts by the Department of Biotechnology from 1990 to 2014. The Department considered the RDAC's proposed guidelines, which were issued in 1990 (Recombinant DNA Safety Guidelines), and in 1994, the Revised Guidelines on Safety and Biotechnology were issued. To ensure biosafety in India, DBT also developed the following guidelines:

[2] There are two websites that provide information on activities of RCGM and GEAC: www.dbtbiosafety.nic.in, and www.igmoris.nic.in. Accessed April 10, 2016.

- Revised Guidelines for Research in Transgenic Plants
- Guidelines for Generating Pre-clinical and Clinical Data for Recombinant DNA-Based Vaccines, Diagnostics and Other Biologicals
- Guidelines and Standard Operating Procedures for Confined Field Trials of Regulated GE Plants
- Guidelines for Safety Assessment of Food Derived from GE Plants
- Guidelines and Handbook for Institutional Biosafety Committee (revised in 2011)

Then, in 2012, DBT issued Guidelines on Synthetic Similar Biology and Regulatory Requirements for Marketing Authorization in India.

Issues related to genetic engineering of human embryos and the use of embryos or fetuses in research and human germline gene therapy are excluded from the scope of the 1990 Recombinant DNA Safety Guidelines. Those guidelines cover areas of research involving GE organisms, genetic transformation of green plants and animals, recombinant DNA technology applicable in vaccine development and large scale production, deliberate/accidental release of organisms, plants, animals, and products derived from recombinant DNA technology. Under these guidelines, four levels of risk have been assigned. Classification of organisms within these levels is based on the pathogenicity of the agents, the modes of transmission, the host range of the agent, the availability of effective preventive treatments or curative medicines, the capability to cause disease in humans, animals or plants, and an epidemic caused by microbial strains in India. The guidelines are based on those issued by the World Health Organization.

Jain provided an overview of all the recombinant DNA guidelines:

- Chapter I: defines the scope of the guidelines, including research activity, large-scale operation, and the involvement of risk associated with the accidental or deliberate release of recombinant DNA organisms.
- Chapter II: defines the recombinant DNA classified pathogens, and describes elements of biological and physical containment, such as laboratory safety, safety equipment, facility design, and so forth; the procedure for obtaining approval for large scale experimentation or manufacturing for release of GMOs in the

environment is also covered in this chapter.Chapter III: discusses the scope of their various committees, and the functions and implementation structure.

- Chapter IV: describes the containment facility and biosafety practices to be followed while conducting research involving GMOs.
- Chapter V: describes the recombinant DNA safety considerations, and classifies microorganisms on the basis of risk. It also provides the general scientific consideration for the risk assessment while working with microorganisms, hazardous microorganisms or recombinant DNA microorganisms.

Based on the level of the associated risk and the requirement for approval from competent authorities, research activities have been classified into three categories. Category I research activities are exempted from the approval process of the competent authorities, which are RCGM and GEAC. Experiments under Category I involve self-cloning using strains and inter-species cloning of organisms in the same exchanger group, such as organelle DNA including those from chloroplast and mitochondria. This type of activity does not require that the researcher notify RCGM or GEAC.

Category II research activity requires prior notification to the competent authority or RCGM. Experiments falling under the Containment Levels II, III, and IV are considered under Category II, as are experiments involving non-pathogen DNA vector systems and regeneration from single cells. Category II experiments also include those wherein DNA or RNA molecules are derived from any source except viral genomes and transferred to any non-human vertebrate or any invertebrate organism and propagated in containment. Large-scale use of the systems exempted in Category I, such as the large-scale use of recombinants made by self-cloning, are also considered under Category II. Proposals in this category are examined by IBSC, and the researcher must also notify RCGM for record purposes.

Category III research requires prior review and approval by the competent authority. Examples of Category III research include all toxin gene cloning experiments producing LD50 less than 50 micrograms per kg of body weight of vertebrates or large scale growing, research including cultured human cells of recombinant DNA molecules containing complete genes of potentially oncogenic viruses or transformed cellular genes, experiments involving the use of infectious animal and plant viruses in a tissue culture system, experiments

involving gene transfer to whole plants and animals, experiments requiring field testing and the release of recombinant DNA microorganisms or plants, and experiments involving engineered microbes with deletion and certain rearrangements. Category III experiments must be reviewed by the IBC and the RCGM.

Prior to 2003, large-scale research was defined as experimentation using fermentation beyond 20 liters, and it fell into Categories I, II, and III. In such large-scale research, safety criteria are to be compiled first. These criteria include a description of the host organism and the vector, and adherence to good laboratory standard operating procedures (GLSP) when working with genetically-modified organisms. Guidelines also specify the principles of professional safety and hygiene for GLSP as well as the level of containment. The import or receipt of etiological agents and or vectors for human and animal diseases or their carriers is subject to quarantine regulations. Further, if an import is for research purposes, RCGM is the competent authority granting approval, but if the import is for industrial purposes or large-scale manufacturing and further commercializing purposes, the approval-granting authority is GEAC. The 20-litres threshold was relaxed in 2003. The RCGM, using its discretion, may, on a case-by-case basis, permit the applicant to conduct experiments using fermenter capacity of greater than 20 liters exclusively for research purposes, and only to produce sufficient GMOs required to generate pre-clinical and other relevant data to create the product for commercial use. The threshold was also relaxed to ensure that sufficient material is being generated to conduct pre-clinical trials.

Discussion

A participant asked about the Biotechnology Regulatory Authority of India (NBRA) bill being considered by the India parliament at the time of the workshop. Jain replied that the bill was introduced in the 15th Lok Sabha, but with the dissolution of the parliament, that bill was also dissolved, however, it was to be reintroduced at the parliamentary session following the 2014 elections, and he said that it will be included in this Lok Sabha in session at the time of the workshop.

A participant asked if Jain could clarify the qualifications of a biosafety officer on the IBSC. Jain replied that this person is to have medical qualifications, specifically the person is to be a practicing doctor (MBBS) who also understands containment issues.

Another participant asked about the process for the IBSC to identify suitable expertise in complex cases? Is it a regular process across the country, or does each local institution have its own process for identifying the right people? Jain replied that an IBSC functions independently and the chair is empowered to call upon any person he or she may consider suitable.

T. S. Rao added that when the biosafety guidelines were initially created, DBT nominated the biosafety committee members. Since then, however, the number of laboratories and industries conducting this type of research has increased.

A participant noted that sometimes only one or two people physically attend IBSC meetings in the United States. Is there a system in India of defining minimum attendance for a valid meeting? Jain replied that DBT has received inquiries about whether members can join via Skype, so a policy on this will soon be released.

REGULATORY OVERSIGHT OF BSL-3 LABORATORIES

John Kenneth opened his remarks by saying that biosafety per se, as the word suggests, is based primarily on the risk posed by pathogens known to cause primary disease and are classified according to risk level into biosafety levels 1, 2, 3, and 4, in an ascending order of risk. Biosafety containment provides a barrier between disease-causing pathogens and healthy persons and the environment.

There is a tendency for people to focus on one area of specific concern, based on professional interest, be it the environment, a laboratory, etc., but biosafety measures block pathogens from being transmitted between lab workers, hospital staff, general staff, and the public at large. The basic tools to do this are: engineering controls, or the way a facility is designed and constructed; personal protective equipment, and safety equipment; and safe work practices.

Next, Kenneth provided details about BSL-3 laboratory regulations. Indigenous or exotic agents that may cause potentially lethal disease are studied in BSL-3 laboratories because these diseases can be contracted through inhalation. BSL-3 facilities are also required for clinical work, teaching junior scientists, and training that accompanies research. Diseases causing near-certain death are studied in BSL-4 laboratories. Due to the biosafety concerns, everything that goes into and everything that comes out of a BSL-3 laboratory must be regulated, including the

people, the air, the articles, the samples, containers, and waste. Access is controlled and there is a physical separation from other corridors. The air flow is negative pressure, which means that the pressure sucks air into the area, and it does not let air out of that particular area without proper filtration, and it is not recirculated out into the environment. The air quality inside the lab is also controlled.

Physical entry only occurs through an air-lock or an anteroom so that air does not pass unfiltered outside the facility. There is self-closing double door access, and personal protective equipment must be worn inside that air-lock or anteroom. Biosafety cabinets are used inside the facility, and waste and clothing are decontaminated at the exit and removed through a second door. See Figure 5-1.

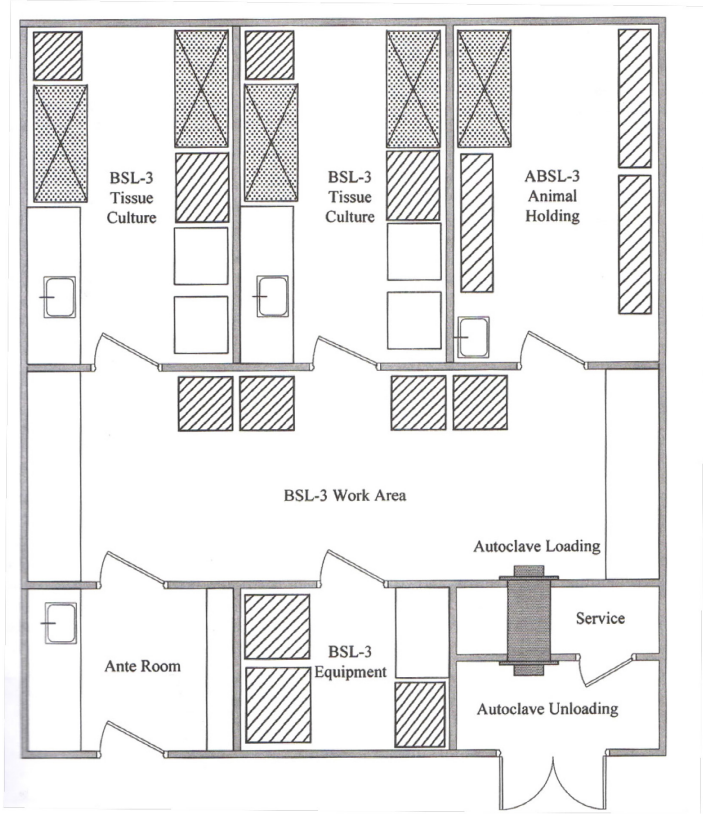


FIGURE 5-1 Design of a basic BSL-3 facility.
SOURCE: Fleming, Diane O. Hunt, Debra L. 2006. *Biological Safety - Principles and Practices, 4th Edition*. American Society for Microbiology. Reprinted with permission of the American Society for Microbiology.

The basic principle is to have an inlet, which is an anteroom, and an outlet. Everything in between is totally controlled. Airflow must be unidirectional, and the air change rate must be between 15 and 20 air changes per hour, filtered at the entry. A HEPA filter is required so that the number of pathogens and the number of organisms, entering is limited. The air has to be at least Class D, fewer than 1,000 particles of less than 0.3 nanometers per cubic meter, and have a negative pressure of minus five to 15 centimeters of water. The anteroom is also pressurized, and there is no leak to the external environment. The entire area is engineered so that there is no deposition of organisms. There is a totally smooth and cleanable area that does not have any crevices or niches where organisms can multiply.

The essential issue for personnel safety is "training, training, and more training." All personnel must have protective equipment, and basic laboratory training. They need to be recertified periodically and all of them must be vaccinated and educated. Consent must also be obtained, because laboratory work can be potentially harmful. Workers are strictly monitored to avoid errors or lapses in concentration, just like airline pilots who cannot work longer than a specified period of time. The importance of training cannot be overstated. Internal and external audits are also necessary.

An ideal BSL-3 team, Kenneth said, would include an experienced team leader, HVAC engineers, engineers for facility and instrumentation, infection control, doctors and nurses, and those who can conduct periodic reassessments and certification.

There are several existing standards, such as the ISO standards, GLP standards by the U.S. Code of Federal Regulations, the Australian National Association of Testing Authorities standards, and checklists for BSL-3 labs developed based on the Biosafety in Microbiological and Biomedical Laboratories (BMBL 5th edition) published by the U.S. Centers for Disease Control and Prevention (CDC).[3] The ISO 15189:2012 guideline for medical laboratories is a mature standard.

[3] For examples of two BSL-3 checklists, see: http://www.selectagents.gov/resources/Checklist-BSL3.pdf; and http://orf.od.nih.gov/PoliciesAndGuidelines/Bioenvironmental/Documents/BSL3CertificationGuidelinesFINAL_508.pdf; accessed April 10, 2016.

In addition to the requisite standards and assessors, India also has a National Accreditation Board for Hospitals. The best experts are chosen to conduct examinations for third party certification. A module to assess BSL-3s is needed, and laboratories need to be overseen with regard to specific areas like air flow, training, readiness, waste disposal, and so forth.

It would also be helpful to extend assessments to include isolation and high security care. Currently, there is no comprehensive oversight of laboratories on an international basis. Every country has its own oversight mechanisms, but it would be ideal to have international standards. However, they most likely would be impossible to implement.

Discussion

The discussion following Kenneth's presentation focused on accreditation and certification of laboratories.

Kenneth noted that since most research conducted in BSL-3 labs in India involves microbiology, certification of clinical laboratories belongs to the National Accreditation Board for Laboratories. T.S. Rao noted that having third party certification is very important, and welcomed any input on how to organize this.

Another participant followed up on the ISO 15189. The National Accreditation Board trains assessors in India, however, none of them has access to BSL-3 facilities, therefore, in the participant's view, a third party should be involved in the assessment and accreditation of these labs. Similarly, the third party could seek to have specific assessors who have relevant knowledge and who have passed specific exams, including an additional component on the ISO 15189. T.S. Rao then asked about the guidelines for a BSL-3 model. He believed that this needed to be defined.

Another participant asked if India had a national certification system. Kenneth replied that India has a link to the International Asia Pacific Lab Accreditation Committee as well as to the International Laboratory Accreditation Committee. They audit one another. The participant followed up, asking if this system was specifically for BSL-3 labs. Kenneth replied that no, this system existed for all labs.

A participant noted that there do not appear to be any procedures for other laboratories in India, such as animal science laboratories, other than procedures for medical labs. The existing certification is missing a biosafety component in its overall approach. That should be introduced

in the ISO 17025 accreditation process so that it covers all types of laboratories, including medical and animal science laboratories, the participant said. There is also a lack of expert groups in India who can provide assessments of biosafety laboratories; this aspect is also needed.

Kenneth made a final point. When molecular biology was new, National Accreditation Board for Testing and Calibration Laboratories (NABL) did not have experience in these fields. There were very few who had such experience, so when a specific organization applied for molecular biology certification, he was called to examine it. He proposed that there could be four or five people who are well-trained to assess labs and they could be called upon to assist with lab certification.

One of the workshop participants recounted the initial consideration among scientists of building a BSL-4 lab in India. The government of India was opposed. Together, India and international technical experts visited a number of countries to understand the international experience and an Australian lab was selected as the model for the Indian lab. However, after further analysis, they concluded that BSL-4 labs are very expensive. Another group was later formed, and they visited additional laboratories around the world and selected the Holland lab as a model. The biosafety officer atthe Holland lab assisted in preparing the architectural drawings for the Indian lab along with an architect from Delhi. It took nearly five years to complete the requirements on paper. It was a rigorous exercise. Following this, structural equipment was imported, sold to fabricators, tested, re-tested, and then manufactured. Another participant continued by noting that this experience provided Indian experts with valuable knowledge about designing and operating laboratories to the highest standards, however challenges remain.

An alternative perspective was offered by another participant who cited a great deal of education among laboratory managers and staff in India, sufficient to address problems that may arise independently and with the assistance of international experts. DBT has a full-fledged engineering group, and once the decision has been made to build a lab, the group does so according to the specifications of that particular laboratory. The specific requirements are determined on the basis of a preliminary outline or draft. Rigorous discussions among engineers from all relevant fields follow and a final design is then endorsed. The previous speaker agreed, emphasizing the need to translate that expertise into reality. T.S. Rao requested draft recommendations from workshop participants regarding how to create such a facility.

The previous participant expressed the view that Indian experts are good at fabrication as well as engineering, including pumps for negative pressure, HEPA filters, etc. NABL accreditation is not mandatory for all laboratories. There are many private labs around the country that do not seek NABL accreditation. A regulatory body to certify and recertify labs would be helpful. **T.S. Rao** noted that the government is still creating the new regulatory, accreditation structure, but NABL could be empowered to do this rather than create a new entity. Another participant reiterated that DBT has the expertise required to build biocontainment labs in India.

Rao stated that the government will assist whenever additional expertise is needed, or wherever there are uniquely governmental functions required because, "we need to make things happen," and "we need to drive reality." In response, the need to empower DBT with a greater role was noted because the only BSL-4 lab in the south Asia region is in India, therefore, India has a responsibility, not only to the country, but also to the region. The Indian government is also interested in strengthening the region.

The United States is always concerned about the development of BSL-3s and BSL-4s, noted another workshop participant. In particular, it is important to consider how these labs fit into the global community of well-operating, -managed, -maintained, -certified laboratories. One of the outcomes of this meeting, if it is useful to the Indian government, may be for Indian National Science Academy and the National Academy of Sciences to produce background papers that could provide information on existing animal health and human health laboratories, and on which regulatory structures exist and where gaps still remain. Perhaps at another stage the academies together could provide DBT with a set of recommendations on the types of regulatory needs associated with these labs. These needs could include types of structures and guidelines for oversight and/or advisory bodies as the rapidly expanding BSL capacity comes online in the next decade. Rao agreed that such recommendations would be excellent, and that India would appreciate this assistance.

Another participant noted that there are many BSL-3 labs in India, and in Delhi itself there will be at least four or five; and they are all functioning well. However, they are extremely expensive to maintain. In addition, the reliability of BSL-3 labs needs to be certified over a period of time, not only at the point of initial operation. There have been efforts to try to identify people to certify and recertify these labs. Recertification may require some sophisticated equipment, which will in turn require the

generation of an entirely new type of business. A certification company could certify BSL-3s or BSL-4s in the country. Only with such a model would it be sustainable to invest in this equipment at a national level. Regular funding for maintenance is similarly a critical aspect of sustaining BSL-3 labs and the government lab. Since these labs are extremely expensive, universities or institutional centers may not be able to support them from their own budgets. Rao agreed that the long-term sustainability is an important aspect to continuously consider. This prompted the comment that perhaps it is better to consider BSL-2+ labs for some research instead of BSL-3 labs, because there are probably not more than 13 or 14 labs that actually adhere to the requirements of a BSL-3 lab.

REGULATORY OVERSIGHT OF BSL-4 LABORATORIES

Tom Ksiazek began his discussion of the regulatory framework for BSL-4 labs in the United States with the advent of genetic engineering. In the early 1970s, the book and film *The Andromeda Strain* triggered concern in the general public about that scientists might inadvertently create and release a superpathogen in the laboratory by manipulating E. coli. Scientists agreed that there ought to be some consideration given to the safety standards under which these experiments were conducted and convened the Asilomar Conference in 1975. The Asilomar Conference led to the National Institutes of Health (NIH) becoming the regulatory agency that established the RAC, issued the NIH Guidelines for Research Involving Recombinant DNA Molecules, and provided assistance to local committees in the application of those guidelines Asilomar also led to the Biosafety in Microbiological and Biomedical Laboratories (BMBL) regulations and guidelines.

The RAC guidelines were published in 1981, and the first edition of the BMBL was released in 1984. They serve as the regulations and guidelines under which all biosafety levels are regulated in the United States. With some caveats, prior to the advent of these guidelines, research conducted in laboratories was regulated through permits. Permits largely regulated exotic organisms and their importation or redistribution in the United States. If Ksiazek wanted to bring Japanese encephalitis into the United States, for example, or obtain Japanese encephalitis from Rockefeller Lab, he would have to obtain a permit to move an exotic agent from one place to another. However, there are no inspections associated with obtaining the permit, so he would have to

describe the facilities, the training, and the type of personnel that would be handling the agent. The same is true for exotic animal pathogens, especially livestock pathogens. These pathogens were and still are regulated by the U.S. Department of Agriculture Animal and Plant Health Inspection Service.

The BMBL and another document called "Chapter 9" became the standard for the operation of these laboratories. The BMBL standards are performance-based rather than prescriptive. They describe the qualities that facilities are to meet to be in compliance with the standards required under other laws. "Chapter 9" actually prescribes the physical constitution of the laboratory in much more detail, which does not leave the architects and engineers with the ability to meet performance standards in the same way. As technology has advanced, laboratory operations have evolved a great deal. With performance-based standards, operators have the obligation to meet them, but the manner in which they do so is not specified because technology continues to develop.

It has been approximately 30 years since the first edition of the BMBL was released; about every 5 to 6 years these documents are modified by the regulating agencies. In the case of human health research, NIH and CDC jointly modify the documents. Outside experts are involved for specific groups of organisms and/or for specific levels of labs. The BMBL is now used as a regulation, although it was clearly developed as a guideline. Under the Select Agent Act, laboratories must be inspected every three years. BSL-3 laboratories receive certification for three years, and there is often one surprise inspection within that three year period. In practice, BSL-4 labs are inspected annually.There are two elements involved in establishing the level of laboratory appropriate to specific types of research. The first is a risk assessment conducted on the organisms themselves. Each organism is assigned to a specific risk group. The qualities that are assessed when making that determination are in Table 5-1.

Determination of the risk is made at a local level, where organisms are assigned to a laboratory that meets the standards for performance. The general principle underlying the risk assessment is personal protection rather than environmental containment. For example, if a researcher is handling a common human pathogen that is found in the community, it is much less important to try to protect the environment more rigorously. However, if the agent is not found in that location and is likely to cause a public health emergency in that community, it is more important to try to rigorously protect the environment.

TABLE 5-1 The Factors Considered in Assessing Organism Risk for Laboratory Biological Safety Levels

Personal Risk	Environmental Risk
Human Pathogen?	Contagious?
Laboratory Infections?	Indigenous?
Vaccines Available?	Aerosol Infectious?
Treatment Available and Effective?	Agricultural Risk?
Aerosol Infectious?	

BSL-4 labs require the building of a box inside of another box, followed by the development of a very strict regimen of procedures. Specific equipment is also designed to keep organisms inside the specified boxes. When Ksiazek began his career at Fort Detrick in the 1980s, regulations were just emerging, and the primary concern of security was the safety of all people who worked in the laboratory facility, so the goal was to keep organisms inside the appropriate location.

Much of the biosafety technology used today was developed at Fort Detrick and transferred to the many other U.S. BSL-3 and BSL-4 facilities: The air supply and exhaust systems are filtered and double-filtered; all of the sewage is incinerated; and, all of the waste exits the facility through autoclaves that are validated with each run. A great deal of effort is expended to certify that this material remains inside the laboratory where the individuals themselves are protected by very rigorous use of personal protective equipment.

There are also secondary safety barriers in facility design. Engineering controls are an important part of these laboratories. Often it is difficult to determine the exact cost of equipping and running them because BSL-3 and BSL-4 labs have traditionally been part of a large physical structure such as Fort Detrick or CDC. Generally, if there was a centralized steam plant or a water chill plant, one could not separate the cost of that particular part of the facility incurred by the lab. Both BSL-3 and BSL-4 facilities generally have what is called single pass air, therefore, whether in summer or winter the cost of air conditioning the lab, for example, remained hidden in the overall physical plant operation of the large enterprise. To provide a sense of scale, the cost of electricity for the high-containment laboratory building at the Galveston National Laboratory in Texas is approximately $2.2 to $2.5 million per year.

Emerging infections continue to create surprises and public health emergencies of considerable size, not only by threatening human health, but also by creating economic consequences to the countries affected. SARS, HIV, and zoonotic pathogens exist in human populations, and can politically destabilize a number of countries. Ksiazek described naturally-occurring emerging infections as the principle biosecurity issue currently facing the United States, although terrorists, as individuals or groups, may use organisms against people in a way that could create considerable problems. He argued that there is less thought given to pathogen risk analysis than perhaps there ought to be. Under the framework of the Select Agent Act that went into effect in 1997 in the United States, training must be documented in ways not previously required.

In December 2013, the select agent regulations went into effect, causing a significant response among the microbiology community due to the number of agents on the official U.S. Select Agent List. There was some agreement within the scientific community that not all agents on the list posed equal risk. As a result of these concerns, there was an effort on the part of the American Society for Microbiology and other large organizations to elevate a small number of agents, perhaps smallpox and 1918 influenza, to the status of Tier 1 agents with the remaining agents being listed at a lower level of risk. What happened in the end was that a fairly extensive list of pathogens became Tier 1 agents, and a smaller number of agents were removed. As a result, if a lab has a Tier 1 agent, the lab must put in place a greater number of biosecurity measures with regard to personnel reliability, the security of data maintained about the agents themselves, and the security of information and data related to the physical plant. Physical security requirements were also increased at facilities that held or were working with Tier 1 agents. There are real costs associated with being able to handle select agents, and those costs have increased with the advent of the Tier 1 category. In Ksiazek's view, there are Tier I agents that do not have some of the attributes ascribed to them. Some of the individuals involved in the classification of these agents have agreed with Ksiazek.

Ksiazek returned to personnel reliability measures. The Select Agent Act requires that researchers working with Tier 1 agents obtain a security clearance prior to obtaining permission to conduct their experiments. The clearance is granted by the Department of Justice, implemented by the Federal Bureau Investigation, and confirms that the person does not have a criminal background and that there are no other issues that would, in

their view, disqualify that person from handling these agents. When the Act was initially enforced, there were specific instances when clearance investigations discovered that individuals who had worked in these labs for many years had incidents in their past, and they were removed from their positions. Ksiazek stated that there is no ability to appeal these decisions.

Discussion

In response to a question regarding which of the U.S. regulations should perhaps not be replicated in other countries, Ksiazek replied that, as a microbiologist and a public health researcher, he would modulate some of the security regulations. Safety is very important, and the code of practiceBMBL, does a good job of addressing these issues.

Another issue, Ksiazek added, is that prior to the adoption of the Select Agent Act, NIH held the researcher and the safety committee accountable for adherence to the BMBL standards. In other words, if funding came from the federal government, researchers had to meet these requirements. With the advent of the Select Agent Act, the BMBL shifted from being standards to being a regulatory mechanism.

An Indian participant noted that when Indian experts studied the classification of biocontainment labs by biosafety level, there were initially just a few parameters taken into account: an agent's capability to infect the person working with the organism, the risk posed to the community by the agent, and the availability of preventive and therapeutic measures. There are now four BSL levels. However, there are many other internationally recognized levels, such as BSL-2+, BSL-3+, BSL-3 NRs. What are the distinguishing features between BSL-2+ and BSL-3 labs? Some say that a BSL-2+ lab has different physical structures, whereas a BSL-3 lab has different practices as well.

Ksiazek noted that officially the category of BSL-2+ labs does not exist in the United States. There are instances where, for all practical purposes, these labs do exist. For instance, during the 2009 emergence of H1N1, a special category of lab was created that allowed BSL-2 labs to operate with BSL-3 lab practices to initially handle specimens. There is a laboratory category called "BSL-3 enhanced for individual organisms. The BMBL does have lists and recommended risk levels for these instances. In the United States, BSL-3 labs are not required to have HEPA filtration, although no one would build a facility without it.

ETHICAL CODES RELEVANT TO MEDICAL AND HUMAN HEALTH RESEARCH LABORATORIES

Vasantha Muthuswamy began by defining ethics as a modern code of conduct that determines right and wrong. There are many codes of conduct in the form of guidelines with which individuals voluntarily comply. The first code for biomedical research in India dates to 1980, when it was released as a policy statement on ethical considerations in modern research on human subjects. When these various guidelines were developed, the Belmont Report[4] and international guidelines were consulted, and equity, accessibility, and affordability were also taken into consideration. In 1996, a committee that was established by the government of India developed new ethical guidelines, which were listed in the Indian Council of Medical Research (ICMR)-NIH forum in 2000. At that time, Justice Venkatachaliah agreed to chair the committee on one condition: that these guidelines one day be passed as a bill in the Indian Parliament, or made mandatory, so that they would be followed by all. Nearly 20 years later, the bill has not been passed as far as medical research is concerned.

In the meantime, a number of other guidelines have been developed. In 2006, the ethical guidelines for biomedical research of 2000 were revised and newly titled, Ethical Guidelines for Research in Human Participants. Guidelines on stem cell research and therapy have been brought to DBT, and the draft of biobanking guidelines have also been brought forward. There are also guidelines on GMO food safety, and, in the summer of 2008, good clinical laboratory practice (GCLP) guidelines were introduced. ICMR-DBT jointly released guidelines for probiotic research and ICMR recently posted the Code of Conduct for people conducting life-science research online. Another recent development is the ICMR ethics bill, soon to be released. The basic tenets of these guidelines include: autonomy, justice, beneficence, and non-maleficence, as in the Hippocratic Oath.

The 2000 guidelines, updated in 2006, are followed across India. The most recent version of the bill introduced in Parliament will incorporate mandatory adherence and will also establish a biomedical research authority that will ensure the accreditation and registration of all ethics

[4] The Belmont Report can be found at: http://www/hhs/gov/ohrp/humansubjects/guidance/belmonth.html; accessed April 10, 2016.

committees and Institutional Review Board (IRBs) in India. Likewise, all clinical trial site investigators must be accredited. If the ICMR ethics bill is enacted by Parliament as scheduled, it is to come into effect at the end of 2015.

Muthuswamy then turned to biosafety, biosecurity, and human health safety issues for workers and research participants. The ICMR/GCLP guidelines issued in 2008 are clinical laboratory practice guidelines pertaining to specimen collections and pre-analytical collections.[5] Good clinical laboratory practice guidelines are not for reporting quality test results or day-to-day research results, but they are to be followed by medical researchers to generate quality data.

Now that these guidelines are in place, the primary concern is compliance. The laboratory GCLP guidelines pertain to all labs involved in biomedical research: microbiology, serology, hematology, blood banking, molecular biology, molecular pathology, clinical pathology, clinical biochemistry, immunology, immunohematology and immunobiochemistry, histopathology/pathology, and cytology. An issue raised in the United States as well as in India by modern biomedical research is biobanking: The 2006 guidelines addressed DNA and cell line banking, repository collections, research samples, primary use and secondary use, and general principles to be followed. They also enumerated responsibilities given to the IRBs and the IECs to oversee and guide researchers on practices to follow and not to follow. This has become a very important issue for more recent guidelines due to large numbers of existing samples. Efforts are being made to educate people about the significance of addressing stored samples. They are attempting to answer critical questions, such as what types of samples currently exist: coded samples, unknown samples, and samples that must be anonymized. Guidelines should provide details about the benefits of laboratory research with stored biological material, while also addressing concerns such as informed consent. These challenges are not unique to India, although they may be more acute in some countries due to a lack of awareness, even among scientists. Specificities exist in India regarding informing research participants and seeking consent after explaining potential risks and benefits due to the number of languages spoken and varying literacy levels. Several ethical questions remain,

[5] In international collaborations where the transfer of biological materials is involved, the Indian Ministry of Health's Screening Committee provides oversight, though the ICMR is also involved.

including the type of consent required for the safe use of biological materials while maintaining privacy. When should waivers of consent be allowed and what are the necessary precautions to be taken?

There are many ways that ethics committees can function. It is common in India to assign compliance grades to institutions from zero to 100 percent, and many institutes receive outstanding assessments. Yet there are other institutions that still lack ethics committees despite many years of efforts. In still other institutes, committees exist on paper only. The primary focus currently is building the capacity of IRB members themselves. There is a tendency to perhaps villainize the IRB. Some members do not realize they are there to guide researchers in doing their work properly; they do not have a policing role. Given that they have considerable responsibility to oversee research across the country, it is essential that members understand their roles clearly.

Modern biology and biotechnology have novel ways of manipulating basic life, Muthuswamy noted; therefore, codes of conduct are needed, particularly with regard to dual-use research. Scientists engaged in such research activities should be aware of the potential associated risks of a broader range of applications (including hostile applications). They should not only be aware of, but also comply with, the requirements of international conventions and treaties relevant to their research work. The aim of codes of conduct for scientists is to ensure that all research activities involving microbial or other biological agents or toxins, whatever their origin or method of production, are only of the types and quantities justified by preventative research or other peaceful purposes. In order to prevent the use of scientific research for purposes of bioterrorism or biowarfare, all persons and institutions engaged in any aspect of scientific research should abide by their codes of conduct.

Responsibility rests with the institution to make the appropriate precautionary arrangements when allowing their laboratories to conduct certain research. To provide all necessary biosafety precautions, risk must be minimized and due care and caution must be taken. The institutions are responsible for having the appropriate committees to oversee the research. They are also involved in decisions pertaining to the publication of dual-use information and knowledge where there are reasonable grounds to believe that there are significant risks that the information and knowledge could be readily misused or inflict serious harm. Once established, the ethical principles upon which the guidelines should be based are transmitted to all who are, or may become, engaged in the conduct of biomedical research.

In 2011, the Association of Microbiologists was formed in India. On that occasion, a new paper on guidelines for microbiologists was published in the *Indian Journal of Microbiology*. This widely distributed paper was intended to ensure that all microbiologists follow the guidelines. However, even if all the members of the association are aware of the guidelines, we still do not know a great deal about the overall implementation of the guidelines.

Further, capacity building is needed for all those who are involved in this research. At this point, it appears that only those who are involved in GMO research are aware of biosafety and bioethics. Biosafety now applies not only to recombinant DNA research, but also to research on many infectious agents. Researchers working in a BSL-3 or BSL-4 institution may not be aware of the differences in these labs or what steps are to be followed when handling infectious agents. In 1997, the Medical Council of India issued a notification that all medical schools should make bioethics education part of their curriculum, but for various reasons this is still not universally mandatory except at a few institutions. Capacity building, bioethics education, and biosafety training must be part of the curriculum. International collaboration on bioethics and biosafety issues warrant focused attention.

Muthuswamy concluded by underscoring that guidelines need constant updating, new ones must be formulated, and legislation is needed to regulate these guidelines. Regulation is not the final answer, but it is one step forward in informing people about the challenges that these issues present. Unfortunately, even with all of these elements in place, unethical activities will occur. The majority of law abiding people, however, want to follow the rules, and it will be helpful to have laws that guide them as they conduct particular kinds of research.

Discussion

The discussion opened with a question about international collaboration and sample exchange. In many respects, sample exchange is difficult in India due to domestic regulations and the regulations of other countries. Muthuswamy commented that biological samples can be sent to and from India, following the appropriate guidelines, and consent must be obtained from both countries. The purpose of the exchange must be stated, and the appropriate ethics committee must also provide clearance. The approval is handled through the Ministry of Health's Screening Committee which consists of all relevant government

departments. A subcommittee reviews all applications and provides recommendations for approval or denial of permission for the samples exchange.

T.S. Rao added that he has been involved with the Hatfield Marine Science Center (HMSC) and the development of the sample exchange guidelines of 1997. He has found that it is difficult to ensure that proper credit is given to the researchers in India, and that the rights of the individuals whose samples are transferred and used are protected. Another participant added that at times, if a researcher wants to do a particular test not available in India, it can be done in the other countries and then those samples can be sent back to India, and permissions are given for this to occur. However, all authors must be given proper credit. The Health Minister's Screening Committee was also concerned that a lot of material would be leaving India without due credit being given. Despite this concern, sample sharing continues. There are some institutes, such as the Institution of Science, where directors have the authority to send some material without the Steering Committee's approval. Sample exchanges by DST and DBT do not require approval. However, the institutions that actually send requests and submit applications for clearance are far fewer than the actual number of exchanges between Indian organizations and international organizations and institutions. The extent of such research becomes clear when papers are published, and it is unclear as to how samples were sent from India. Who gave permission for so many samples to be garnered for such studies? The majority of institutions do not seek approval from HMSC; there are only a few that are aware of the regulations and apply for approval. Those who do apply go through bureaucratic procedures that delay the process and they often become frustrated. There is so much being done in India, but it is small in comparison with the size of the potential.

Another participant raised the connection between the restrictions on sample exchange and biosecurity concerns. Under export controls, there is a SCOMET list that contains special chemicals, organisms, materials, equipment, and so forth. While DBT did clear some of these samples for exchange, industries send samples to their own facilities after gaining approval. It was under that system that there were some checks on exports.

Rao closed the discussion by reiterating the need for independent regulatory oversight of BSL-3 and BSL-4 labs. He also underscored his request for Indian-U.S. cooperation to develop regulatory guidelines

based on the experience of CDC. He proposed the designation of two Americans and two Indians to develop concrete recommendations.

6

Applying and Using New Tools and Knowledge Safely

Over the past 20 years, **Robert Martin** was of the opinion that while efforts to strengthen laboratories rely on various factors, including education, training, accreditation, and so on, the importance of leadership and management responsibilities has been underestimated. He therefore focused on the critical importance of strong leadership and management in order to create a culture of safety in the laboratory.[1]

Martin noted that a baseline definition of safety when working with potentially infectious microorganisms addresses a combination of laboratory practices and procedures, and of laboratory facilities and safety equipment. Another definition of biosafety addresses why researchers would implement those practices, namely the reduction or elimination of individual and environmental exposure to potentially hazardous pathogens. It should be clear that there must be a biosafety policy from laboratory leadership. And there must be someone designated as the person responsible for the implementation of strong biosafety practices.

From those rather simple definitions, a great deal of work has arisen. There is no dearth of material available to those interested in learning more about biosafety and the implementation of biosafety practices. They can look at *Biosafety in Microbiological and Biomedical Laboratories*, published by the U.S. Centers for Disease Control and Prevention (CDC)[2] and the National Institutes of Health (NIH); resources from the American Association for Laboratory Animal Science; the

[1] Robert Martin was unable to attend the workshop in person and his presentation was provided via recording.

[2] The *Biosafety in Microbiological and Biomedical Laboratories* can be found at: http://www.cdc.gov/biosafety/publications/bmbl5/; accessed April 10, 2016.

Laboratory Biosafety Manual,[3] published by the World Health Organization; and the *Laboratory Biosafety Guidelines*,[4] published by the Public Health Agency of Canada. There is even a journal called the *Applied Biosafety Journal* from the American Biological Safety Association.[5]

Given all of the material available, and numerous training activities held by institutions, and the standards written and legislation passed in countries, why do safety practices appear to be so hard to implement? In Martin's opinion, part of the reason is that when training of laboratory workers is discussed, there is an implication that the workers are ultimately responsible for biosafety. There is often no mention of management responsibilities in these documents or discussions. In a article, "Why Is Safety So Hard?," Dan Hebert addresses the topic by stating that the majority of accidents occur because organizations have failed to implement best practices and guidelines on process safety.[6] Despite widespread reference to safety in corporate mission statements and communications, the changes in culture that basic safety principles entail have not sufficiently permeated the entire workforce.

Clearly, not having demonstrable and visible commitment by leadership throughout the organization sends a signal to employees that safety requirements are suggestions, as opposed to requirements. An unfortunate example to drive this point home was a deadly fire at a University of California, Los Angeles (UCLA) laboratory in 2009. A young student died as a result of burns from this fire (see Figure 6-1).

UCLA was found negligent and was fined, because several significant safety weaknesses were uncovered. The student was working with a liquid that was combustible when exposed to air, had not been properly trained in the techniques used to manipulate the substance, was

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[3] The *Laboratory Biosafety Manual* can be found at: http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf; accessed April 10, 2016.

[4] The *Laboratory Biosafety Guidelines* can be found at: http://www.phac-aspc.gc.ca/publicat/lbg-ldmbl-04/index-eng.php; accessed April 10, 2016.

[5] The *Applied Biosafety Journal* can be accessed at: http://apb.sagepub.com/; accessed April 10, 2016.

[6] Dan Herbert. "Why is Safety so Hard?" Available at: http://www2.emersonprocess.com/siteadmincenter/PM%20DeltaV%20Documents/Articles/ControlMagazine/Why-is-Safety-so-Hard.pdf; accessed April 10, 2016.

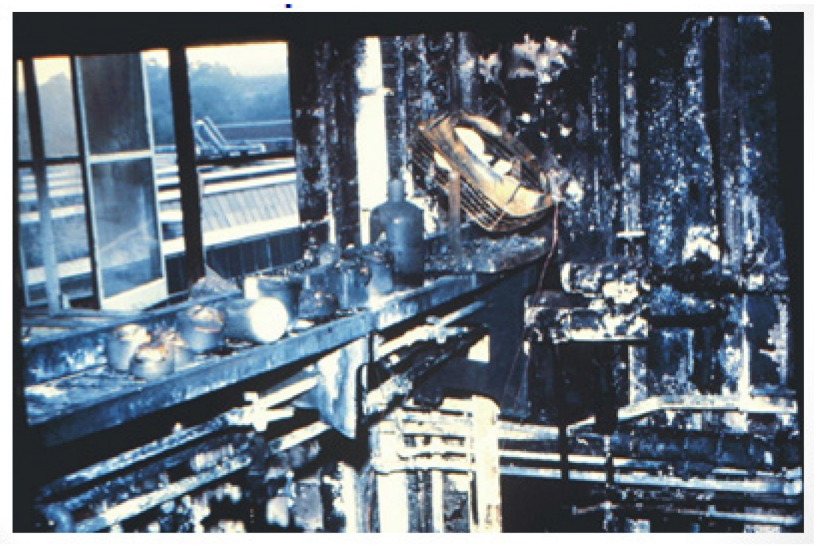

FIGURE 6-1 University of California, Los Angeles laboratory after the deadly fire in 2009.
SOURCE: Robert Martin, presentation at the workshop.

not wearing a lab coat, and there were other volatile chemicals unrelated to her experiment in the hood in which she was working. Although the principle investigator claimed the student had received training, there was no documentation indicating safety training had taken place at all.

In 1986, a survey by Vesley & Hartmann of 4,000 laboratory workers in 54 public health and 165 hospital laboratories in the United States revealed that in hospital laboratories the rate of laboratory acquired infections was 3.5 per 1,000, and in public health labs, the ratio was 1.4 per 1,000.[7] Exposures were cited as resulting from needle sticks, aerosolizations, hood failures, and microscope contamination. A review of weekly morbidity and mortality reports also documents a number of laboratory acquired infections. While it is not possible to eliminate accidents, it is clear that we can do better.

Sometimes the individual laboratory worker involved is the source of the problem. Some individuals may feel safety training and safety practices are cumbersome, an attitude that may lead to excessive risk

[7] D. Vesley and H.M. Hartmann. "Laboratory-acquired infections and injuries in clinical laboratories: a 1986 survey." *American Journal of Public Health*. September 1988. 78(9):1213-5.

taking. Sometimes they are pressured to complete work more quickly or cheaply, and corners are cut. Often employees are not aware of the infection risks they are taking. For example, even now some laboratory workers are more concerned about contracting HIV from a blood sample, when there is a much greater risk of contracting hepatitis B, or in some countries, hepatitis C infection from samples. So while all these are reasons why accidents may occur, many of these issues stem from a lack of leadership and poor management practices in the laboratory. It is the laboratory director's job to ensure that adequate safety training has taken place, that adequate instructions have been provided on working with equipment and reagents, that adequate space is available, and that there is ongoing oversight of safety practices in the laboratory.

Martin then outlined the 12 Quality System Essentials related to the international standard for medical laboratories, or ISO 15189. They include the following elements:

- Organization
- Personnel
- Equipment
- Purchasing and Inventory
- Process Control
- Information Management
- Documents and Records
- Occurrence Management
- Assessment
- Process Improvement
- Customer Service
- Facilities and Safety

In many countries, there is a drive to ensure that laboratories are accredited, not only to provide better services for health care, but also because accreditation of laboratories is a significant step toward assuring that a country meets its obligations under the International Health Regulations of 2005. To implement the quality management system, it has become clear that laboratory directors not only need technical knowledge, but they also need to be leaders and managers as well, and often leadership and management skills are lacking. In part, those skills are lacking because many laboratory directors have come into their position through seniority or through a strong

grounding in technical skills, but they have never received training, or they have limited skills, in leadership and management.

The University of Washington created a nine-month blended learning certificate program that helps improve skills related to leadership and management for mid-career senior managers and laboratory directors. This program was developed because a laboratory director or manager has the ultimate responsibility for the laboratory and its practices. He or she is the recognized leader and has the responsibility for not only ensuring accuracy and timeliness of testing, but is also responsible for assuring that testing is carried out safely. The laboratory director certainly needs technical knowledge, but he or she also must possess good leadership qualities to ensure a high functioning laboratory.

In addition to a director who clearly accepts responsibility for safety in the laboratory, the laboratory requires a biosafety officer and quality assurance officer who are organizationally positioned to be independent of the section supervisors, and who report directly to the laboratory director. In some cases, a biosafety officer may have other responsibilities inside one of the sections, and while there may be some small laboratories where that is necessary, in a larger laboratory biosafety is a full time job, as is quality assurance.

Although implementation of safety practices is dependent on multiple champions—the laboratory director, the biosafety officer, the quality assurance officer, supervisors, as well as laboratory staff—the laboratory director must be viewed as the ultimate champion for laboratory safety. That individual must ensure adequate funding for personnel and resources and must develop an environment of trust that enables a reporting culture. These attributes will help lead to a culture of safety. These leaders, the laboratory director, biosafety officer, and quality assurance officer, have responsibilities to encourage compliance with the safety program by both new and long-term employees. They have to manage change towards the safety culture. They must establish effective health and safety committees, and collect and provide essential information and statistics relevant to a culture of safety.

Within the laboratory, a safety management system is directed by the safety officer who has responsibilities for the development of the safety manual where laboratory specific policies and procedures are maintained, and where standard operating procedures are maintained. There must also be training available to laboratory staff that aims at identifying risks in the laboratory and safety procedures to mitigate those risks. Even if all of these steps are taken, unless there is demonstrable

interest by the laboratory director, the biosafety officer, and supervisors of the laboratory, attitudes of employees will not change and the level of safety awareness will not be what it should be.

In summary, the key to creating an environment of safety is to ensure that leaders and managers have the skills to do their job properly, that there is an identified biosafety officer who has responsibility for developing a safety manual and appropriate standard operating procedures, that ongoing training is provided, that appropriate risk assessments are conducted, and that adequate space is available for the laboratory experiments being performed.

Neglecting laboratory safety can be extremely costly, as in the case of the UCLA laboratory, a life was lost and the reputation of the facility was damaged.

Discussion

The discussion after Martin's presentation focused how levels of leadership influence safety and the kind of oversight required for clinical laboratories.

Joseph Kanabrocki underscored that leadership at multiple levels is critical. One often hears that leadership from the top is most important, but he believes that top-down and bottom-up leadership are equally important. The culture of safety must be established at both the top of management structure and at the front line. If people at the front line hold their peers accountable, then the situation will be much safer. In the select agent world, people have to look out for one another, as well as focus on personnel reliability and security issues.

A participant asked whether it is necessary to have one manual on biosafety for public health labs and a different one for clinical labs. Are the requirements sufficiently different to warrant this? Kanabrocki answered that the oversight of clinical laboratories is much more regimented. There are certain standards that have to be met. In the United States, clinical laboratories have to satisfy certain certification requirements. This is different on the research side. There are some certification requirements, but they are not as rigorous or extensively documented as it is on the clinical side. Kanabrocki added that in the clinical realm, the same procedures must be followed exactly the same way each time for reproducibility and assuredness. Another participant added that researchers in Monterey, California work closely with the Monterey County Public Health Laboratory and they not only test blood

samples and urine, they also test water, food, and conduct many other types of testing that has very little relationship to clinical laboratories.

A participant stated that facilities in India have biosafety officers. That position now includes fire safety, physical safety, chemical safety, and radiological safety. Therefore this person is now called a safety officer, rather than biosafety officer.

ANIMAL VACCINE MANUFACTURING

B.M. Subramanian began by stating that vaccines, like any other drug, must be produced under strict, current good manufacturing practices (CGMP), and the biocontainment component must also be followed when the vaccine involves the use of infectious agents.

When vaccine research is conducted in India, a proof of concept is developed by academia, and then it is transferred back to the cell line for industry to continue the process. The vaccine goes to the drug controller and clearance is obtained to make clinical grade material under its CGMP production facility. Clinical trials are the next step. Research results are then returned to the controller and market licensing is granted along with market authorization. At the point that industry takes over, CGMP is required, so many in academia work tirelessly to follow CGMP. If they do not have a CGMP facility, the company that pursues the product has to create the virus banks and the cell banks in their facility as per CGMP requirements, and this process continues back and forth. In India's animal vaccine development industry, this transition is not seamless. Subramanian then gave a brief introduction about CGMP. The practices of developing and implementing primary barriers, and the associated documents, are similar to those in biocontainment labs. But the actual facility design is significantly different for CGMP than for biocontainment facilities. In biocontainment facilities, infectious material is kept inside the room and progressively negative pressure ensures that the material does not escape. In CGMP facilities, such as the CGMP enabled clean room that Subramanian's institution is building, progressively positive pressure environments aim to protect the drug from outside contaminants. The number of air exchanges and particle counts are strictly monitored, but they are much higher than what is followed in a BSL facility.

Next, Subramanian discussed foot and mouth disease, which under U.S. Department of Agriculture (USDA) classification is a BSL-3Ag

agent. The vaccine used around the world is produced by a known attenuated strain of the virus. The kind of facility that works with this vaccine is built with negative pressure; however, the facility also follows the CGMP procedures because negative pressure will bring all the contaminants inside, which is not allowed by CGMP. At the Indian Biological Center, researchers try to develop novel platforms to work within the biocontainment requirements for these kinds of organisms.

Subramanian and his colleagues also conducted work on the rabies virus isolates collected by others from various parts of India between 2002 and 2012. Nearly 40 samples were sequenced, and two distinct pathogenic lineages for the Indian isolates were found. The predominant one has an Arctic-like lineage, and the other one has a Sub-continent lineage. The Sub-continent lineages were also found in the viruses from Nepal and Sri Lanka. They also conducted some evolutionary analysis, and found that the Arctic-like lineage in India appeared very recently compared with the Sub-continent lineage, and has spread south from the Arctic region. They also found that in India, the majority of rabies cases is due to dog bites. Little is known about the role of wildlife in the spread of rabies in India.

Further, wildlife in India is not vaccinated against rabies, unlike in European countries and America. In the Kheda district of Gujarat in December 2012, around a dozen buffalo and cattle died showing symptoms of rabies. There was also another case in Gandhinagar, a nearby district. A large number of buffalo died. Brain samples were collected from one of the dead buffalos and rabies and its sequences were identified. After three months, they found another district, Surendranagar, in which nilgai (a wild form of cattle) were infected. They isolated rabies virus from these animals also. After almost 15 months, in March 2014, they isolated the rabies virus from a mongoose in the same district of Gandhinagar. When they mapped these samples on the phylogenetic tree, they all had the Arctic-like lineage virus. The buffalo and mongoose isolates were from the same district, but the virus was isolated with a 15-month gap between collection dates. The other two, the nilgai and the buffalo, came together on the lineage map, and they were found only 50 kilometers apart. This indicates that although dogs are the major carrier and transmitter of the rabies virus in India, the role of wildlife has been neglected thus far.

Although there is no government policy on the vaccination of wildlife against rabies, when it is tried, the inactivated viral vaccine is commonly used. Subramanian's group used the rabies virus

glycoprotein-free based subunit vaccine during experiments in mice. They vaccinated, boosted, and challenged the mice with the rabies virus, and after 35 days there was enough serum conversion to protect the animals. His group is also trying to develop another platform using a viral pseudotype technique. Due to the nature of the research, it can be conducted in labs without biosafety levels. One of his colleagues went to the United Kingdom and spent time with the viral serum tech groups to learn their technologies and how to incorporate them. Subramanian's group is now trying to implement these techniques in their institute for some of the high risk activity viruses.

In addition, they are working on bovine tuberculosis (TB). The organism was isolated in non-pasteurized milk and in pasteurized milk. They are trying to diagnose bovine TB from the release assay, because of the viscosity in the reagents.

They tested their diagnostic procedure on a bovine farm, and found four of the 10 animals examined for TB tested positive using the IFN-gamma kit. They sent these ten samples to Chennai for spoligotyping, and four of those samples were confirmed positive for lung tuberculosis. Some wild animals also tested positive for tuberculosis, including a sloth bear. They tried to diagnose TB inwildlife, but the World Health Organization (WHO) does not recommend this approach. However, Subramanian's group recommends serology for bovines, and they also recommend the serology for wild animals due to other logistical problems. Therefore, they tried to develop a lateral flow serology test specifically for pathogenic tuberculosis. Then they developed a kit and presented it to some of the wildlife rescue centers, such as Wildlife SOS. Using Subramanian's kit, postmortem animals were tested for tuberculosis, and from that they created a collection of serum samples that tested positive. They send these kits to wildlife institutes all over India for TB testing; they are also using them to predict tuberculosis serology from elephant and bear samples. Further, they are trying to develop BCG knock outs as a vaccine against bovine tuberculosis in collaboration with Bruce Martin and Chris McFadden at Surrey.

Discussion

The discussion after Subramanian's presentation focused on biosafety measures for rabies surveillance.

One participant asked Subramanian about the rabies survey, stating that the work is very important in terms of surveillance. How were the

specimens handled, and how were the specimens gathered at the field site? These steps also constitute important aspects of biosafety measures. Subramanian agreed that biosafety measures are critical, right from the collection of samples. These locations are remote, and the people who collect the samples place them in double bin containers. These are then hand-delivered to the researchers. All of the laboratory staff, from the cleaning staff to the engineers to the scientists are vaccinated annually, and the serum neutralization end-point titer is checked. If the person is found to have less than one international unit, the person receives a booster.

Subramanian continued by noting that in the field, brain samples are collected from various parts of the brain, not only the hippocampus. Generally the postmortems on animals are not done in laboratory areas. They are conducted outside only. They try to conduct a proper inspection of the body, and then dispose of the body with antiseptic and boric acid solutions. With that they also bury the carriers deeply. That is a very important aspect to be considered in terms of biosafety measures.

PUBLIC OUTREACH ON BIOSAFETY

In his presentation, Kanabrocki shared some of his experiences conducting and supporting laboratory research at the University of Chicago. The university is a mid-sized academic research institution at the Hyde Park campus, one mile from Lake Michigan, about six miles south of downtown Chicago. It is also the home of the University of Chicago Medical Center, which is one of the major medical centers in the Chicago metropolitan area. UC Medicine is one of the four designated hospitals for the Chicago metro area to receive Ebola patients, should they arrive in or near the city. In addition, the Ricketts Regional Biocontainment Laboratory is a biosafety level 3/Agricultural Biosafety Level 3 (BSL-3/ABSL-3) facility built on the campus of Argonne National Laboratory (ANL), managed by the University of Chicago.

Kanabrocki shared a quote from Jim Welch, who is the Executive Director of the Griffin Research Foundation: “The collateral damage of unsafe research is science itself.” The safe conduct of research is a shared responsibility. It is the responsibility of scientists to perform a comprehensive risk assessment of their research—before they begin that research—to weigh the risks and benefits of the work itself, whether it should be undertaken, and, if so, under what conditions? It is the responsibility of scientists to convey to the public the importance of the

work they do. By nature, scientists like to work in laboratories, and often they are not the most social creatures in the world, however, such communication is an obligation that all scientists have and it should not be neglected.

It is important for those who work in high-containment laboratories, or who conduct infectious diseases research, to engage the public. It is important that they explain the value of the work itself, and the direct benefits of that research activity to their local community. Finally, it is important to explain the safety and security measures in place that help ease concerns about the type of activities that may be conducted in those laboratories. This work needs continuous community engagement.

A number of incidents that happened in U.S. government laboratories—U.S. Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and Food and Drug Administration (FDA) under the Department of Health and Human Services (DHHS)—in 2014 brought negative attention to biocontainment research and infectious diseases research and created a very negative reaction to scientists in general. When the public is upset, politicians become engaged, and if the politicians are engaged, they tend to act.

During the subsequent biosafety stand down at DHHS laboratories, research was halted, extensive reviews of inventories were conducted, and any strains that were no longer needed were removed. The goals of the stand down were to inventory thoroughly what researchers had in their possession, and to promote laboratory safety as a priority. Following that was a halt from DHHS on funding of gain-of-function research on influenza, Severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). Hence, collateral damage from unsafe research is science itself.

In 2007, the University of Chicago competed for, and was awarded, funding to build one of 12 Regional Biocontainment Laboratories together with two national laboratories that were built through a funding initiative from National Institute of Allergy and Infectious Diseases (NIAID). Kanabrocki was the official responsible for the select agent program, and the biosafety officer for the Ricketts Lab, located at ANL, about 25 miles southwest of downtown Chicago. A security advantage of this site is that Argonne's whole site has restricted access, unlike the University of Chicago main campus.

Before the lab opened, Kanabrocki and his colleagues engaged the public, conducting dozens of tours through the facility for whoever wanted to come. They walked through the facility, and researchers

explained the type of work being done there. The importance of the research at the lab includes the development of vaccine therapeutics, including two Tier-I pathogens. For this reason, the entire facility operates under the Tier-1 regulations. One of the activities they had at an open house early on was a slide show of photos from inside the facility. Kanabrocki also brought a long sheet of paper, and children lined up as far as you could see to use a pipette on the paper. This was another way of engaging the public and saying, "come on in." During that time, the facilities engineers really learned how to run the building. They tested each system and actively failed everything that could fail during that waiting period before approvals for operations were obtained.

ANL also has a legacy of community engagement regarding hazardous material. The laboratory itself stemmed from Enrico Fermi and the Manhattan Project during the World War II era. A liaison committee was formed for the Ricketts Lab that involved leadership from all the surrounding communities as well as people from the ANL and the Department of Energy (DOE), which runs that laboratory. The committee met monthly until the lab opened. Kanabrocki found it interesting that as time went by, and as the date for the opening of the lab grew closer, fewer and fewer people attended the meetings.

Turning to the research benefits to the community and to public health, Kanabrocki explained that the training resources available through the Ricketts Lab have been invaluable. The first focus was on training scientists who would be working at the Ricketts Lab, or at other comparable facilities. Part of the mission as a regional biocontainment lab is to be a resource to the region in the event of a public health emergency, so an emergency response training component was added. The facility has trained local first responders on how to respond to an emergency involving a high containment setting, such as training clinicians for Ebola preparedness. First responders come into the facility and conduct drills with lab biosafety staff and researchers. They enter containment facilities, and evacuations are performed on simulated medical emergencies. Many of the local first responders were anxious when they first walked into the building. Some of them had envisioned vats of anthrax sitting around in the lab, but when working with an organism that replicates, large quantities are not needed at any point of time. That reduced many people's anxiety. Another helpful tool was having first responders enter the lab before it was opened. There were researchers fully dressed in their protective garments, simulating "experiments," and the first responders could ask questions, understand

what scientists were doing, and understand the equipment they were using.

As for biosafety, the lab has a walk-in autoclave with biometric access control and vaporized hydrogen peroxide (VHP) large-space decontamination is conducted. Personal protective equipment (PPE) is worn in containment, and there are Magnehelic differential pressure gauges and readouts for negative air flow. In addition, there are ventilated cage rack systems for animal research, and a Class 3 cabinet for aerosol challenges. Biosecurity is equally important. They have 62 closed-circuit television cameras monitored around the clock, and perimeter accesses control with proxy card and fingerprint access. Once a person is in containment, each individual has a PIN code to enter when moving through the lab. Access records are maintained and examined on a regular basis. The responsible officer receives daily readouts of access records.

A code of conduct has also has been developed for personnel reliability. Beyond plagiarism, fabrication of data, collegiality, and sharing of reagents, the code also contains a statement that commits all those who sign to adhere to safety practices. Very importantly, signatories are also required to report deviations from standard protocols.

Ricketts Lab has a full-time biosafety officer, who is there every day. Kanabrocki is also there one to two times a week. He and the researchers know each other on a first name basis, and researchers come to him with issues, such as problems with someone at the laboratory. They are trying to develop a community environment because it is the heart and soul of their personnel reliability program.

Shared governance is also critical. All of the protocols at Ricketts Lab and all the research activities are reviewed by the Institutional Biosafety Committee (IBC). The committee has membership from UC faculty and staff, members of ANL, members of DOE, and community members. Transparency is the foundation of their engagement. The lab wants the public to know what they are doing and if there are incidents, then the public is told about the incidents, too.

The responsible officer for Ricketts Lab also attends weekly Monday morning meetings at ANL to talk about safety on the Argonne campus. Safety and security are ongoing activities. Although Kanabrocki often does not have anything to contribute during the meetings, he attends because just being there helps to maintain a comfort level between the leaders of both labs.

The Biosafety Training Corps has also been developed at the Ricketts lab, using an approach that integrates the various activities that make these facilities function well. The training is for scientists, students, trainees, some support staff, biosafety professionals, and the biocontainment facility engineers. An environment is created where all of these people can come together and discuss issues. In addition, there is a mentoring program that is probably the most important piece of the training. Along with routine training, a week-long course is offered and anyone that has any role in a containment laboratory is welcome to attend. The lab also has a year-long fellowship program designed to train post-graduate scientists in the realm of biosafety. The fellows do everything the biosafety officers do: they attend IBC meetings, laboratory inspections, and training. When the lab is inspected by external agencies, the fellows are also involved. The fellowship is a full immersion in a biosafety program. There is also an Institutional Animal Care and Use Committees protocol for the course, because they use live animals.

It is critical, however, that training be relevant because otherwise it is ineffective. Every lab is approached as an individual entity and training is provided in that context. Lab inspections are approached in the same way. Kanabrocki and his colleagues do not walk into a lab without knowing exactly what experiments are being conducted, so scientists are engaged in a very active way on their real safety issues. There are no generic inspections.

Kanabrocki then shared his experience with making biosafety "cool." The biosafety officers at the Ricketts Lab wanted to encourage investigators at the Hyde Park campus to think of the biosafety officers as a helpful resource. They developed a poster campaign that used the image of Michael Jackson's Billie Jean album cover with the gloved hand in a creative and effective way.

Scientists often walk in the corridors with their gloves on, so biosafety officers are trying to teach researchers to take off one glove and hold reagents in the gloved hand so they can open door knobs, etc., with their bare hand. Who could better exemplify one glove than Michael Jackson?

Regarding Ebola preparedness, the UC Medical Center is an Ebola-patient designated hospital. It was a major effort to prepare to receive potential Ebola patients. Kanabrocki was surprised to find that infection control at the center was not as robust as he would have expected. To improve infection control, they used the Ricketts Lab standard operating

procedures (SOPs) as a model, first asking for a floor plan of the isolation ward. From there they developed the center's SOPs, and then conducted training for two full days for all clinical staff. The first day of training was basic, donning and doffing PPE, entry and exits, waste management, and movement of materials into and out of the isolation room. Day two covered how to conduct clinical procedures in full PPE; a veterinarian taught that section.

This training effort was received quite well by the University and by the Medical Center, and as a result, they wanted to publicize the preparedness at the Medical Center. There was television coverage on the training, and there was an article in a University of Chicago publication about the biosafety program as the resource for Ebola preparedness training.

In conclusion, Kanabrocki recounted that one of his biosafety officers wanted to film the training, and he obtained permission from the incident commander. The video included elements of popular culture. The success made Kanabrocki conclude that popular culture can promote biosafety and make it cool.

Discussion

The discussion after Kanabrocki's presentation included questions about incidents and safety, the pop culture campaign, and transparency in, and effectiveness of, communications.

To begin, a participant asked if there had been any incidents at the lab. Kanabrocki replied that there have been some near misses, but no exposures. There was one fatal lab acquired infection (LAI), and one very serious LAI about two years earlier; both of which occurred in BSL-2 labs. Kanabrocki does not worry as much about the BSL-3 lab as he does about the BSL-2 labs. In BSL-2 labs, people are not as respectful of the materials they work with and they certainly are not as well trained. Competency is not verified, and that is where there are problems.

David Franz then asked if the ANL director attends the weekly safety meeting. Kanabrocki answered that yes, the majority of the time he does, and if he does not, his deputy director attends.

Another participant asked about the pop culture campaign, and if he has noticed a positive response from the community, and if people ask questions. Also, have there been any negative reactions to the campaign? Kanabrocki said that there have been both positive and negative reactions to the campaign. He does not mind the negative responses because those

still indicate that the people are aware of the message, which means that the campaign is working.

There are other communities in the United States where a public campaign did not have such a positive outcome. There is a potential down side, however, to being so vocal. There is a great deal of concern from a security perspective. How can these negatives be avoided? There's always a lot of concern about showing photographs of the inside of a laboratory, or allowing public access, even before a lab opens. Kanabrocki believes that unless one can develop a roadmap to the pathogen itself, the security concern is not great. They do take precautions such as not photographing room numbers, and during tours, people are not allowed to take photos. As for public backlash, in his view, that occurs if there has not been enough face-to-face communication with the community in advance of a laboratory opening or of a project beginning. Engagement has to happen early, and has to continue throughout the life of the project.

Franz added that he was involved peripherally with the opening of the BSL-3 lab at Kansas State University. There were public meetings, and the same pattern occurred; people finally stopped coming, but the meetings were packed at the beginning. There is a requirement in Kansas to hold an annual public IBC meeting with the details of the meeting to be published in the newspaper. Anything we can do to decrease speculation about what is going on in the lab reduces fear. Anything that implies that the public cannot hear about what is happening, in generalities of course, adds fuel to their concerns. People get bored with the issues once they are familiar with them, and they go on to other matters. Thus, these meetings are very helpful in engaging with the community.

Kanabrocki added that all of the work at the Ricketts Laboratory is funded with public money, so it is already in the public record. As far as security is concerned, there are seven barriers between the person and the agent on the vivarium side, and five on the laboratory side. What is there to keep secret other than how to get to the materials?

Another participant noted that transparency is absolutely paramount, not only because people are concerned and afraid that they might be affected by a release, but also to avoid conspiracy theories on a personal and national level. It is very important that BSL-4 labs are open for people from other countries to at least tour, if not to participate in scientific exchange programs following proper protocols. The worst thing that could happen is that other countries believe that secret research

is being conducted that is prohibited by the Biological Weapons Convention.

Another concern is that scientists often speak a bit too fancifully about their work, and use terms that have very different meanings for the public. For example, the word, "mutation," has a completely different meaning to a scientist than to a person on the street. Another example is a listing of the number of lab incidents in the newspaper: fifteen hundred biosafety incidents in one year may sound ominous to the public, but these incidents are often far from dangerous and may simply mean that a light went out somewhere and it was not clear where the light bulb was located. Perhaps when biosafety protocols are being devised, the scientific nomenclature could be balanced with the use of more common terms. Finally, there are scientists who do not engage, which can contribute to conspiracy theories because few people know what they are doing. However, there are also scientists who engage too much, to further their own scientific programs. Not talking about Ebola is as harmful as saying that Ebola will kill us all. There has to be a middle ground, and a little bit of control is necessary.

BUILDING AN AFFORDABLE AND EFFECTIVE BSL-3 LABORATORY

Rakesh Bhatnagar began by providing an example of the BSL-3 laboratory at Jawaharlal Nehru University (JNU) funded by DBT, created by cutting costs without compromising safety. First, he and his colleagues determined that they would build a two-story building with the BSL-3 lab on the ground floor, and another laboratory on the first floor for experiments not requiring high-containment facilities (see Figure 6-2).

The whole structure is about 8,000 square feet. The left side has a plant room (utility room) with a chiller plant and a generator for complete electrical backup, so that all the critical equipment, particularly those maintaining negative pressure, temperature, humidity, and so forth, do not have an interruption of power. There are panels that can monitor temperature, humidity, heating, cooling, and filters (microbial filters, pre-filters, and HEPA filters). All this information is provided on a computer as part of the building management system. Everything is

continuously monitored and recorded. If there are any problems, the system provides a warning so that maintenance can be performed.

Bhatnagar then described the BSL-3, in which two rooms have been dedicated as an animal facility. The other two rooms are mainly for molecular biology work. There are two air handling units. One takes care of the air in the animal area, and the other air handling unit takes care of the air in the molecular biology area.

Although there is a pass box, everything can be done inside. Both the animal area and the molecular biology area have double door autoclaves. For any infectious material, the outer door is shut, the inner door is opened and the material is put in and the inner door is shut, and the material is autoclaved. The wash room provides the space and necessities to clean cages, and also has washing machines.

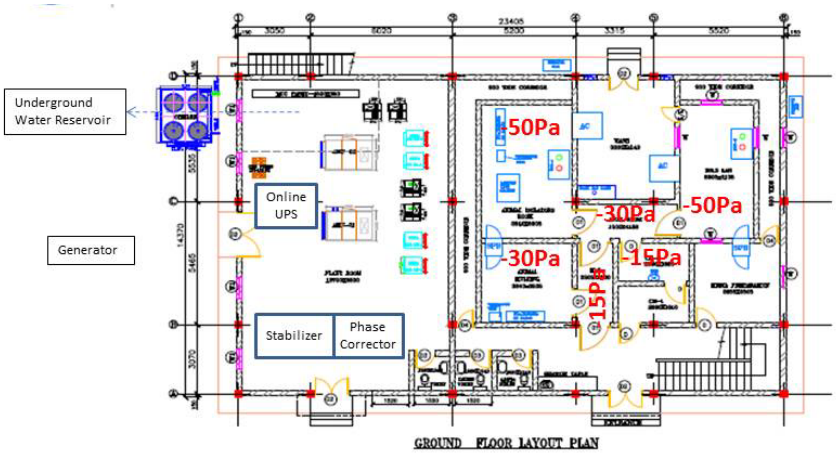

FIGURE 6-2 Layout of Biocontainment facility (BSL-3 lab and animal house) at the school of Biotechnology in New Delhia Facility.
SOURCE: Rakesh Bhatnagar, presentation at the workshop.

When JNU received the funding for the BSL-3 facility, Bhatnagar and his colleagues chose a place behind the School of Biotechnology. It was a green area and the building was constructed specifically for the BSL-3 laboratory. The design and execution were done by a German company, and all of the engineers and workers were from India. The installation, commissioning, and validation were done by M+W Zander and Company. They have commissioned more than 300 BSL-3 labs all over the world. After the lab opened, M+W Zander ran it for about a

month, while local researchers and staff were trained. They have a comprehensive contract with a company called Biosave. There are many BSL-3 labs in Delhi, and Biosave stores all the spare parts that are needed. SOPs and written instructions are provided to all employees who work in the lab and each employee is trained in advance of beginning work as well as periodically thereafter.

The total cost of construction and equipment was approximately $500,000, and it took about one year and eight months total to design, erect, create, and validate the building. Planning began three years prior, for a total of four and a half years from conception to completion. Maintenance costs are also affordable. In conclusion, Bhatnagar said that despite the excellent facilities at the lab, they are unable to do experiments with some viruses which need a BSL-3+ or a BSL-4 lab; such facilities are badly needed in India.

Discussion

The discussion following Bhatnagar's presentation focused on lab validation, determining the appropriate number of BSL-3 labs, the levels and types of labs needed to meet specific needs, oversight and inspection of individual labs, and finally, funding to sustain the labs.

The opening question referred to laboratory validation. Are there certified, validated agencies in India that perform independent assessments? Bhatnagar confirmed that there are some consultants who are trained to validate, however, India does not have an equivalent to CDC. Those trained for validation come to the lab and bring their machine for particle counts, and so forth, and confirm that all equipment is functioning properly. In the end, they ensure that the air is clean and without any contamination; that is what they check primarily. A certificate of validation is then provided. This process is undertaken twice a year to be certain that the environment is safe.

Bhatnagar noted that many scientists from India who have visited the lab have noted that they consider it to be a model. It is a small facility, which is easier to maintain. Often BSL-3 labs are much bigger, and they are much more expensive to maintain. This is also a challenge in the United States. It is important not to build too many or too few labs, and it is critical to learn from each other's experiences.

This raised another question about how to determine the right number of BSL-3 facilities. Is there a correct ratio of the number of labs per million people and how should they be geographically distributed? A

participant responded that perhaps the calculation should be based upon the needs of the work requiring these labs. Those needs may vary not only from one region to another or one country to another, but also may vary with time, which of course makes the issue of sustainability complicated, because what might be needed for a sustained research effort for one period of time, such as for a decade, may evolve into a series of research questions that have been addressed, no longer necessitating the same level of research effort. The United States has not found a solution to the question of the necessary number and location of labs. Many people believe there are too many BSL-3 labs and that much of the work being done in them is not absolutely necessary or could be done with less dangerous organisms at lesser bio-containment levels.

Another participant added that when one considers the kind of load assigned to a specific facility with relation to the population, it essentially means that there is a certain incidence of disease in the population. As the incidence of disease fluctuates, so does the need for such facilities, requiring a dynamic equation rather a stationary situation. Bhatnagar commented that this means there should be a limited number of facilities constantly available for monitoring dangerous organisms which could suddenly arise.

How do we decide what is required for surveillance? Agra has two BSL-3 labs that were built to conduct research on drug resistance. A participant suggested that BSL-4 laboratories could perhaps be placed strategically in state capitals and the central capital for example, due to international flights. BSL-4 labs can also be downgraded and used as BSL-3 labs, and upgraded again if necessary. This upgrade-downgrade solution could be an option.

In India, the BSL-4 labs in Bhopal and Pune are in very large cities, but there are no BLS-3+ or BSL-4 labs in the biggest cities of New Delhi, Mumbai, Calcutta, and Chennai. However, **V. M. Katoch** said that the government of India is taking a regional approach by building ten federal labs in the major metropolitan centers and approximately 48 labs in districts along with smaller medical school labs. There are also plans to extend this lab network to 168 sites with BSL-2 labs. The idea is to be able to detect an epidemic before it becomes even larger. These labs may not be able to detect unknown pathogens, which requires rapid sequencing, cloning, and sequence analysis. The labs in the network are not all planned to be culture labs. Many will be located in medical schools that may be upgraded into culture labs. They are to be epidemiological labs to detect anomalies in a particular region. If

something is identified, the samples will be referred to other labs at higher levels. Some workshop participants, however, were skeptical that these labs would be sufficient to detect outbreaks.

Perhaps, contributed another participant, even within a particular category of lab, for example, a BSL-2 surveillance lab, it might make sense to think about whether all of the labs should be exactly the same or whether there should be specialization, and whether there are certain kinds of tests or certain kinds of surveillance methods or approaches that might be followed in one or a certain subset of the labs while other approaches are followed in other labs. There may be no right answer, but it might be of some value to have specialization and preferred places that develop expertise in a particular kind of disease or syndrome and develop people with the appropriate experience within the facilities. At times it is hard to know where a sample should be sent when the diagnosis is unknown. However, when the syndrome or the suspected problem is known from the start, then a certain small number of places that have specific expertise in that problem may be more efficient and effective. In this way, investments in labs could be made without too much duplication of resources.

The discussion transitioned to the frequency of oversight and inspection. Some participants suggested that here should be standards that are followed, and a third party should oversee and verify the labs and procedures. India needs to develop greater capacity to conduct these oversight and certification functions.

Furthermore, sustainability and maintenance require committed funds, which need to be requested and appropriated from the government, university, or some other source such as outside grants. The United States has these challenges as well. Ten BSL-3 labs were built by NIAID, and two BSL-4 labs were built, one at the University of Texas, Galveston, and one in Boston. The U.S. government is the only entity that has funding for sustainment as a part of the original lab agreement. The lab receives a specific amount of funding each year for a specified number of years. Other labs must identify their own funds. Even military labs now receive a small portion of their sustainment funds from the U.S. government, and approximately 20 percent of the funding comes from the work for others; overhead is included in contract work to help fund the building. Another participant noted that in sustainability models, single income sources will not be sufficient. It is necessary to build a corpus of funders for each biocontainment lab. A corpus is generally built on several principles. One of which is that these are big facilities,

which not all institutions can afford. There will be smaller companies that will want to use a biocontainment lab and this work can be subcontracted at the BSL-3 level with supervision by the regular staff.

Nath added that as the Indian network is considered based on needs and sustainability, perhaps it would be wise to consider the needs of the Asian region, because it was shocking to learn that the Indian BSL-4 lab was the only one in the region, and there are few BSL-3s. If there is an epidemic, it is not going to respect borders. Dengue comes from southeast Asia, and hemorrhagic fever and Ebola, for example, also do not know borders, so India should look outward as well as consider how to help the region. To plan for this, a participant added, it will be important to consider which countries to include. Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, Pakistan, and Sri Lanka are important. The Indian National Science Academy has a joint meeting once a year with experts from countries of the region, and they expanded to include other countries such as Australia, Indonesia, and Malaysia.

MANAGEMENT OF NATURAL DISASTERS

Muzzafar Ahmad opened by noting that there are many definitions of "disasters," including one by World Health Organization (WHO): "Any occurrence that causes damage, ecological disruption, loss of human life or deterioration of health and health services on a scale sufficient to warrant an extraordinary response from outside the affected community."[8] India, along with six other countries, Canada, Indonesia, Italy, Mexico, Philippines, and Turkey, was rated at a 'high risk' for natural disasters in absolute terms, and the World Bank has reported that direct losses from natural disasters is estimated to be up to two percent of India's GDP and twelve percent of central government revenue, which is quite high. Fifty percent of India's landmass is prone to earthquakes. In addition, droughts, floods, cyclones, and tsunamis create hazards for every state in the country.

In addition to natural disasters, manmade disasters such as chemical, biological, radiological, and nuclear disasters as well as road traffic

[8] Rashidi Ahmad. "Roles of the University in Disaster Management," *Malaysian Journal of Medical Sciences.* 2007 Jul; 14(2): 1–3. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442620/; accessed April 10, 2016.

accidents and air traffic accidents also pose threats. India has the world's longest railway network, which, as with all other modes of transport, may be susceptible to accidents. The country has experienced urban flooding, riots, and terrorism.

Ahmad recounted recent and past disasters. Examples included the Kashmir earthquake of 2005, and the Leh cloudburst and mudslide, which was caused by recurring climate and ecological changes. In 2013, almost 6,000 people were missing or dead as a result of the flooding in Uttarakhand. The Bhopal gas tragedy was one of the worst global chemical disasters. In two days of rain in Mumbai, almost 1,000 people died. The Indian oil depot fire in Jaipur led to damages of more than 15,000 crores Indian rupees (approximately 2.5 billion U.S. dollars). Every year, disasters occur where fireworks are made for Diwali in Tamil Nadu, including one in which more than 100 people died. Fortunately, as a result of preparedness efforts, there were no deaths during Cyclone Phailin in 2013, as compared to the 1999 super cyclone of the same intensity when many people died. The cyclone coincided with the biggest festival, Dushhera, and government, in some places, had to use force to evacuate people from the coastline. In September 2014, three days of unprecedented rain led to the worst floods in recent times which caused massive destruction and the near submersion of the capital. The secretariat and major hospitals were also submerged. The medical college hospital was also severely affected and all medical services were disrupted for a number of days.

As a result, Ahmad explained, there has been a paradigm shift in disaster management. Initially, it was relief-centric; now the approach has been on prevention, mitigation, and preparedness. In December 2005, the Indian Parliament passed the National Disaster Management Act, which provides a legal definition of disaster in India, and includes the degradation of the environment. There is also a national policy on disaster management, which has been approved by the government and finalized with a vision "to build a safe and disaster resilient India by developing a holistic, proactive, multi-disaster-oriented, technology-driven strategy through a culture of prevention, mitigation, preparedness and response."[9] India has a dedicated National Disaster Response Force, which was established under the act. It is a specialized force trained not only in search and rescue, but also in response to chemical, biological,

[9] For more information, see: http://pib.nic.in/newsite/mbErel.aspx?relid=133377; accessed April 10, 2016.

radiological and nuclear incidents. Their instructors have been trained in premier institutions, including the U.S. Federal Emergency Management Agency (FEMA), and they are proactively deployed during impending disasters. They also help various state governments with training. The 12-battalion National Disaster Response Force is drawn from various central police forces, and is located in various regions across the country for more efficient deployment. They can be used for international assistance. For example, the force from Andhra was deployed to Japan during the Fukushima disaster.

In addition, there are various nodal agencies in the country involved in the early warning system. Specifically, the India Meteorological Department conducts weather forecasting and earthquake recording. It has substantially improved its early warning capabilities, which was evidenced by the early warning given of the Phailin event. India's Central Water Commission provides early warning of floods and the Geological Survey of India is responsible for landslide warnings. As a result of the 2004 tsunami, they now have advanced equipment. The Indian National Centre for Ocean Information Services, located in Hyderabad, provides early warning to vulnerable areas, including the Andaman Islands, the coastal village of Colva, Mumbai, and other cities; the data is also used by other countries. The National Remote Sensing Centre of the Indian Space Research Organization uses satellite imagery in the prediction of floods, cyclones, and droughts.

Ahmad then turned to the management of response to biological disasters. In July 2008, the National Disaster Management Authority (NDMA) created national technical guidelines on management of biological disasters. A core group of experts, microbiologists and other scientists developed these national guidelines calling for greater attention to the prevention of biological disasters. Pharmaceutical and non-pharmaceutical interventions and biosafety measures were included. This group created a database of inventories of various laboratories handling hazardous microorganisms, and enhanced medical preparedness through the establishment of command, control, and coordination of infectious disease control efforts. They have also worked to develop human capacity and research. Critical infrastructure for management of biological emergencies, institutional mechanisms, public health responses, and provisions for management of pandemics are additional challenges undertaken by NDMA.

And finally, another important goal is the development of mechanisms for enhancing international cooperation, which includes

upgrading the biosafety level of laboratories, developing bio-risk countermeasures, conducting risk and vulnerability assessments of livestock, and establishing legislative and regulatory frameworks and early detection facilities based on risk management practices. These preparations are to be brought together in the development of an all-hazards implementation strategy.

Discussion

The discussion following Ahmad's presentation focused on bilateral cooperation. In particular, **Nirmal Kumar Ganguly** cited a previous Indo-U.S. partnership that aided in rapid assessments that determined which vaccines should be used in which national disaster situations. There are many other critical components of disaster management including epidemiology. Therefore, he recommended adding to the list of areas for potential bilateral cooperation the strengthening of capacity to conduct robust epidemiologic studies during disasters so that the cycles of disease can be broken.

BIOSAFETY NEEDS AND PARTNERSHIPS

Ganguly began his presentation by emphasizing that biosafety is critical at biocontainment labs, and needs to be ingrained in the day-to-day practices of handling human samples. Forty-five million Indians are either infected with or are potential carriers of Hepatitis B, two million are infected with Hepatitis C, and 2.3 million are infected with HIV. Samples are collected in the field, in hospitals, and a variety of other locations. Another example of the importance of biosafety in all areas, even beyond biocontainment labs, is India's recent resurgence of polio. India was free of type-2 polio for many years, and then suddenly in northern India, a type-2 polio outbreak occurred. When epidemiologic investigations and sequencing the virus, investigators ultimately were able to identify the source and determine that this outbreak occurred due to a lack of biosafety. It was determined that there was an Indian company that wanted to manufacture polio vaccine had a reference strain of type 2 wild polio virus that was not contained and led to the outbreak.

Biosafety measures must be followed across the board. One of the major programs undertaken through a partnership with CDC, the Indian Council of Medical Research, and CDC is mapping every public health laboratory and company in the country working with infectious

organisms. The number of these labs is astonishing. The mapping project will not only list these labs, but will also include physical visits to the labs to learn what type of infrastructure, capacity, and training they have. This inventory should also provide a sense of available capabilities that could be drawn upon in emergency situations. For example, should an Ebola outbreak occur in India, it would be helpful to know that there are three or four people in India who have an in-depth knowledge of Ebola. This project would be an excellent target for collaboration between U.S. and Indian scientists and hopefully this workshop can catalyze cooperation that can eventual draw upon this information.

Ganguly noted that the need for cooperation was also demonstrated by an outbreak of plague after the September 1993 earthquake in Beed and Latur. People moved out of their homes to escape potential collapse, but they stored grain in their houses so that the grains would not be destroyed. Both Didorincus and Bandicota bengalensis, which are feral rat species, intermingled with the Rattus rattus norvegicus (house rats), and they started the spread of bubonic plague. By September 1994, it had spread to Surat, where a festival was being held, and the pneumonic plague killed a large number of people. When laboratories in India tried to identify the disease, they identified it as Pseudomonas pseudomallei, the causative agent of meliodosis. Papers were published with these results, but some medical personnel were not convinced and believed that it was a plague outbreak due to clinical observations. This led some experts to look further, and they sent strains to the appropriate labs, where it was identified as Pseudomonas stutzeri, which is a saprophyte.

Then, Ganguly recounted, the next plague outbreak occurred and again partnership was invaluable. To respond to these emergencies, establishing a lasting partnership is essential. Some Indian experts were told that an incidence of bioterrorism had occurred and that plague had been engineered and released in India. Researching this potential case required additional expertise, specifically, a mammologist who was an expert on rats. India has few such experts, so help was sought, which allowed for identification and isolation of bacilli. The next step was to prove to skeptics that the outbreak was not a bioterror event. Ganguly and his colleagues were horrified to find that there is no repository of plague found in India. Ganguly then turned to other outbreak instances and the partnerships that helped end the outbreak. The first outbreak was of the Nipah virus, which occurred in Malaysia, and Australian experts helped them. Then an outbreak occurred in Siliguri, West Bengal, resulting in a high fatality rate. Investigations concluded that it was a

novel strain of measles virus so a sample was sent to CDC for confirmation. The CDC measles group found that the sequences were that of a measles vaccine strain, the Edmonston-Zagreb strain used in India. Through sequencing, they established that the genealogy was different in Malaysia strains, in Indian strains, and in Bangladesh strains.

When the SARS outbreak occurred, Indian scientists found SARS virus not only in people with symptoms, but also in the urine and excretions of people who had no symptoms. They reported these findings; however, few believed that there could be asymptomatic cases of SARS. CDC did have knowledge of asymptomatic cases, and again it offered significant assistance so that the Indian government could be advised that asymptomatic SARS cases, which might carry the virus and excrete the virus, could and did exist.

U.S.-Indian partnership also established a special mechanism between the Indian National Institute of Biology and American institutes through which Indians could receive an expedited visa to the United States. This helped in establishing disease investigative centers in the region such as those in China and Thailand.

The avian influenza outbreak in Maharashtra was addressed through partnership with NIH, which helped in identifying strains that could be used in an H5N1 vaccine because at that time there was no H5N1 vaccine available. This partnership, unlike some others, was less successful in that the cost of the vaccine was unrealistic. The only challenge that emerged was how to address intellectual property rights (IPR) issues when an Indian strain was to be used in a vaccine. The current state of IPR management is much better, but additional work in this area is needed. Perseverance led to the development of the first H5N1 vaccine made in India through a partnership with the U.S. company Novavax. The seasonal flu vaccine in the virus-like particle platform with Novavax and an Indian company completed a clinical trial, and it will be used in India.

Ganguly concluded by stating that there is a need to consider how to connect all of the many existing Indo-U.S. partnerships and to ensure that they are mutually reinforcing and sustained.

Discussion

The discussion following Ganguly's presentation included comments about bilateral cooperation, especially in areas not yet benefiting from

Indo-U.S. collaboration, and the different levels of cooperative relationships.

S.R. Rao identified biosecurity, biosafety, and biocontainment as three primary areas of cooperation, and said there are many other areas that would benefit from partnership and collaboration. General scientific collaboration and cooperation in the area of diagnostics are frequent, but there are very few collaborations in the regulatory sciences and in risk assessment. Perhaps the only sustainable example of cooperation on risk assessment has been with U.S. Department of Agriculture on biosecurity issues related to plant pathogens and the invasion of certain species of plants across boundaries. The National Institute of Plant Health Management in Hyderabad has a sustained collaboration that includes convening workshops, reviewing guidelines, and updating handbooks on a long term basis under the Ministry of Agriculture. India does not have a similar arrangement with the Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA) , and is slowly trying to develop collaboration on regulatory practices and regulatory science, including regulations related to biosafety, biosafety of recombinant products, biosafety of normal products, and biosafety containment facilities.

It is helpful to compare the rules and regulations within the two countries and learn from each other about whether the rules are effective. A bill is before the Indian Parliament that will cover most of the Environmental Protection Act. It will fold many of the EPA requirements into the Biotechnology Regulatory Authority. There is also a biosecurity bill particularly addressing planned quarantine issues raised by the Department of Agriculture, which will be introduced soon.

An important element of collaboration is to compare what is meant by biosafety in the laws of both countries, and what efforts can be undertaken between the two countries. This has been done effectively in the case of agricultural cooperation; the same should be extended to cooperation with the U.S. FDA and EPA, and any other agencies involved in biosafety.

Another issue for India is to examine the 1990 guidelines addressing biosafety labs because they are outdated. There is a need to exchange experiences through a workshop or meeting to help build the capacity to update the guidelines to meet contemporary requirements.

S.R. Rao noted that he is responsible for promoting the establishment of BSL-3 labs. He often experiences a lack of capacity to construct BSL facilities in the country. There is a clear need to share experience in

designing, developing, and maintaining BSL facilities. Further, in his experience, the ability to handle these laboratories after commissioning is poor. Human resources are inadequate: Many young people may choose not to obtain a Ph.D; instead, they are interested in technical skills to maintain these labs. Sustained collaboration is called for in all areas of biosafety, including developing training programs and workshops for biocontainment labs, and India would be very happy to partner with any of the regulatory bodies abroad, especially with U.S. regulatory bodies.

He restated that there is on-going research and collaboration in areas such as HIV research, but there is no solid collaboration between U.S. and Indian regulatory bodies to promote both regulatory scientific investigations and the regulation of existing facilities, as well as continuously building the human resources required for implementing biosafety protocols. S.R. Rao included animal houses in his consideration of biosafety. There is significant need for human resource development regarding how to maintain animal facilities. In particular, researchers are importing new mice and many experimental models from abroad, but when they are put into animal houses they become infected.

India is also creating a biosafety support unit under the Environmental Protection Act related to the 1989 rules that cover both pathogenic organisms and recombinant products. The office will be staffed with 20 to 25 people, one half of them dealing with the medical side, one half of them dealing with the agriculture side, mostly addressing risk assessment. They have asked USDA to help train the employees and a letter of intent has been exchanged. India has proposed to cover all travel costs for those being trained in the United States by USDA, and USDA will cover the training costs. The same approach can be taken for most risk assessment science related to pharmaceuticals and other biologicals. There is also a need to build capacity in the regulatory system to address nanotechnology, gene therapy, and other new products. These serve as outstanding examples of capacity building related to regulatory laws and guidelines, and much more could be accomplished through an organized effort. Thus far efforts to cooperate on these issues have not been well-coordinated. Workshops and other actions in this area are very much needed and requested, in particular to assist in updating guidelines and standards, specifically those dealing with BSL-3 facilities. Such efforts would be an excellent start to many other programs in the regulatory sciences.

Ganguly noted that there is an Indo-U.S. agreement on environmental health, to which EPA is a major party. This mechanism

needs to be effective. Further, the Material Transfer Agreement (MTA) is presently a major hindrance to Indo-U.S. cooperation. He also suggested that all Indo-U.S. agreements should be archived so that all accumulated knowledge is located in one place. **T.S. Rao** agreed that the MTA should be addressed through the inter-ministerial group.

Another participant observed that there are currently four levels of Indo-U.S. cooperation. The first is nation-to-nation collaboration to sign fundamental agreements. The second is institution-to-institution collaboration, and the third is PI-to-PI. There is a fourth that has not yet been discussed: individual scientist-to-individual scientist collaboration, especially among young people. Younger people work more and more through social networks, so perhaps ResearchGate would be helpful. How many people are providing protocols to young people when they inquire? This is peer-to-peer exchange. Ganguly replied that there are many Indian scientists who have returned from U.S. institutes and they often collaborate and publish together. There should be an archiving platform under the Indo-U.S. Science and Technology Forum, for example, to track and monitor these collaborations so that they can be sustained.

Another example of effective cooperation was demonstrated in the visit of a CDC consultant who advised Indian contractors and others on structural changes to NCDC labs to strengthen biosafety and biosecurity.

7

Collaboration and Going Forward in Partnership

Norman Neureiter began by noting that just prior to the workshop, a Joint Committees Meeting of the Indo-U.S. Science and Technology Forum, which is under the chairmanship of John Holdren and Vijay Raghavan, was held in New Delhi. During the meeting, all of the Forum-sponsored scientific activities between the two countries were reviewed.

The Indo-U.S. Science and Technology Forum[1] was established in 2000, at a time when U.S.-Indian relations were not as amicable as they are today. It was created with a small amount of money, which came from the P.L. 480 funds[2] that the United States owned in India, equivalent to $7 million. They were deposited in a bank, and those initial funds continue to gather interest, which is matched each year by the Indian government. This generates approximately $1.5 to $2 million dollars annually from which collaborative efforts are sponsored. It is not possible to have a big research program for $2 million a year, but it is possible to bring many people together for workshops and meetings, and to support travel grants, and so forth. Furthermore, a great deal of interest has been generated among people who have contributed funds from other sources. The total amount expended in 2013 was approximately $7.8 million, and a significant portion came from the Department of Science and Technology or from Indian government agencies that wanted to use this instrument to facilitate cooperation.

To sustain these activities, Neureiter noted that a commitment of funds on both sides is required. What the Forum can provide is the ability for people to come together and speak in detail about what sources might be available for further cooperation. Decisions on which proposals to

[1] For more information, see: http://www.iusstf.org/; accessed April 10, 2016.
[2] Indian currency paid to the United States for purchase of food through a food assistance program.

fund have been made jointly and no proposals are funded without approval from both the Indian and U.S. committees.

Discussion

The discussion following Neureiter's presentation focused on the obstacles that prevent young scientists from being able to participate in international collaborative opportunities and ways to correct them.

Indira Nath noted that although discussion of larger issues is excellent and essential, there are smaller issues that can act as obstacles to cooperation, such as difficulties in obtaining visas. Young scientists face this obstacle in particular. This is a sensitive issue: Senior scientists in India have been fighting for government-sponsored travel fellowships for these young scientists so that they can attend international conferences. However, the recipients of these funds are frequently unable to attend because the visa process is incomplete even days before scheduled departure. Since the funds have been allocated for a certain person, they are effectively blocked because they cannot be given to another applicant on the waiting list with only one or two days left before the conference. It is unclear why applicants do not receive a timely decision on their visas. A U.S. participant expressed a common sentiment: it is unacceptable to have young people not be able to attend meetings, because it is one of the more important ways to foster collaboration.

Ganguly then made six general recommendations to advance Indo-U.S. cooperation: (1) improving partnerships by creating a unified action plan that can nurture and advance them; (2) strengthening regulations so that they are properly executed and not abused; (3) strengthening collaborations and partnerships with adequate financial and ethical architectures; (4) facilitating interaction to identify challenges and benefits, such as the MTA and visas; (5) strengthening existing agreements by examining how they worked and did not work; and, (6) creating a system in which all players, the governments, departments, institutes, and the individual scientists, can interact more fully.

Nath also added that the Global Academy of Young Scientists has been promoting young scientist academies in many countries. INSA has undertaken this initiative to establish an Indian Young Scientist Academy, to be formalized in December 2014. Members are elected from among Ph.D. students and scientists in their mid-forties. Grant also

noted that in the United States there are elected societies for younger scientists.

Nath added that many of the suggestions raised at the workshop were to train younger people on biosafety or research conduct. If these younger researchers from both countries have a mechanism by which they can meet, the culture will continue to grow. This is much better than just holding training courses in one country or another.

The U.S. Global Health Security Agenda[3] was mentioned and some participants pointed out that there are aspects of the agenda that have long been in existence. Nonetheless, the idea of the initiative is to consolidate U.S. activities around global health security and then promote new initiatives. One of the initiatives is to create special partnerships with many countries around activities in global health security. India has taken a global lead in this agenda, and this workshop and the type of collaboration discussed are very consistent with the goals of the program.

CLOSING REMARKS

James LeDuc noted that the vigor of the workshop discussions clearly reflects the interests of experts from both India and the United States and their commitment to strengthening and deepening cooperation. These are important issues, and the only way to make progress is to work together going forward. It is very clear that the tone of the meeting encouraged collaboration, training, and leadership development. The stage is set for real progress in the future.

Raghavendra Gadagkar stated that no one would deny that the bilateral relationships between the United States and India in all spheres, but most certainly in science, hold benefits for all involved. Such positive interaction is never one way.

Diane Griffin's remarks were focused on further concrete steps for cooperation. An INSA-NAS regional meeting, similar to this workshop, is planned for 2016, during which Indian leadership in south Asia will be a focal point for presentations and discussions.

[3] For more information see: http://www.globalhealth.gov/global-health-topics/global-health-security/ghsagenda.html; accessed April 10, 2016.

A

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety

STATEMENT OF TASK

An ad hoc planning committee, under the auspices of the U.S. National Academy of Sciences (NAS) in collaboration with the Indian National Science Academy in New Delhi, India, will convene bioscience experts from Indian academia, industry, and government research laboratories and similar U.S. experts for a workshop to address a suite of issues under the heading of biosafety, biosecurity, and biorisk management. The workshop will feature invited presentations and discussions.

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. The workshop will include topics such as the following: responsible practices in pursuit of the benefits of life science research; matching precautions to risks; facility risk assessment; laboratory certification; mechanisms for reporting laboratory-associated infections; right sizing the regulatory environment; regional transport of samples and specimens; and special challenges and opportunities associated with biosafety level 3 (BSL3) and BSL4 laboratories that were identified in an international workshop held in 2011. This workshop is also intended to inform future discussions of broader topics related to next steps for promotion of biosafety and security in India.

B

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety

VISION STATEMENT

The Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety is designed to encourage scientists from India and the United States to examine global issues related to emerging infections and global health safety, to share experience and approaches, and to identify opportunities for cooperation to improve practice and research in these areas. In general, the workshop participants will address challenges posed by infectious diseases within India and the United States and across national borders. The participants will address both human and animal health because zoonotic infections such as avian flu and anthrax have shown that the borderlines between animal and human health are merging. Because of the evolving nature of infectious disease, in addition to the current status of human and animal health issues, surveillance in real time to detect emerging outbreaks and to predict emerging epidemics is critical.

Sessions will touch on issues associated with the global life sciences revolution and today's challenges with respect to emerging infections and epidemics, and focus on issues that are of particular relevance to India and the United States to achieve the right balance between safety and the advancement of life science research on pathogens.

How to achieve prompt communication of suspected new infections and methods for transportation of infected material will be discussed in the context of the safe use, management, and operation of high containment (BSL 3-4) laboratories in India and the United States. In addition, new and exciting developments in technologies, such as the biotech revolution and synthetic biology as well as the utility of codes of ethics/conduct for avoiding improper use of pathogens will be explored. Regulatory issues in both countries as well as multilateral agreements on these issues will be visited. Finally, sustainability issues in maintaining

surveillance, laboratory facilities and modeling for predicting epidemics will also be explored.

The workshop will begin with speakers outlining the burden of infectious diseases and the importance of pathogen identification, infectious disease control (including the global challenges of influenza and Ebola) and will provide an overview of laboratory diagnostics for virulent and drug resistant pathogens. Subsequent sessions will focus on: 1. The integration of human and animal public health systems and disease surveillance, and potential responses to agricultural pathogens in both countries and ways to prevent economic loss in the event of an outbreak through a discussion of disease modeling, forecasting, and issues related to data sharing. 2. Path changing technologies and innovation in biology as well as containment laboratory issues associated with new developments in life science. 3. Existing regulations and their implementation in the United States, India, and other countries and organizations with regard to recombinant DNA, product development, good laboratory practices (GLP), and the utility of codes of ethics/conduct. 4. Management and training for laboratory networks, effective disease surveillance before and after incidents and how to educate and interact with the public, government, industry, and academia about life science research.

Working group breakout sessions will cover: (1) Research of concern on new pathogens, regulations, and codes of ethics/conduct; (2) Comparison of different biosafety methodologies and the implications of different assessments; (3) Levels of biocontainment; answering research questions about economically viable containment levels and potential alternate methods;(4). Sustainability of surveillance laboratories; cutting costs without compromising safety; (5). Diagnostic and field laboratories; safety considerations for transportation of diagnostic samples and in emergency situations; and (6). Laboratory accidents and laboratory-acquired infections including response, reporting, and planning.

The final session will touch on public health challenges for disaster management in South East Asia and the United States. Workshop participants will be asked to discuss possible areas for collaboration and partnership such as joint training centers and/or the initiation of additional bilateral or multilateral workshops on global health laboratory leadership and biological safety.

The ultimate goal is to jointly share challenges and lessons learned regarding biological safety, laboratory management, and the general

efficient and sustainable operation of laboratories for public health, animal and plant health research, and clinical applications for improving global health safety. A secondary goal is to encourage collaborative partnerships between Indian and American scientists in areas identified by both groups during the workshop keeping in mind the existing multilateral agreements between the two countries.

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C

Agenda

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety
Convention Centre
Indian National Science Academy (INSA)
New Delhi, India
November 18 - 20, 2014

November 18, Day 1

8:00-9:00am	Registration
9:00-10:30am	Chair: Indira Nath
	Opening Welcome by President of INSA and Others
	Raghavendra Gadagkar, President, INSA
	Krishan Lal, Immediate Past President, INSA
Remarks by VIP Representatives	
	V.M. Katoch, Secretary, Department of Health Research (GOI) and Director General, Indian Council of Medical Research, *Emerging Infections on National Development*
	Amy DuBois, Health Attache, US Embassy, New Delhi
	Diane Griffin, Vice President, U.S. National Academy of Sciences (NAS)
	Dinakar Salunke, Vice President, International Affairs, INSA
10:30-11:00am	Tea Break followed by group photograph
11:00-12:00pm	**Plenary, Session 1. Introduction and Framing the Issues**

	Co-Chair: **Indira Nath** Co-Chair: **James LeDuc** Speaker, **David Franz**, *Integrating Safety and Security into the Life Sciences Enterprise* Discussion
12:00-1:00pm	Lunch
1:00-3:00pm	**Plenary, Session 2. Human Health Research; What are the Needs?** Chair, **G.B. Nair** Speaker 1, **Todd Davis**, *Influenza as a Global Challenge for Human Health Research* Speaker 2, **Aparna Singh Shah**, WHO SEARO Speaker 3, T**homas Ksiazek**, *Perspectives on the West African Ebola Outbreak* Speaker 4, **Ratnakar Sahoo**, *Ebola Control Strategy - India* Discussant: **Anuja Krishnan**, Institute of Molecular Medicine, Okhla, New Delhi
3:00-3:30pm	Tea break
3:30-4:30pm	**Plenary, Session 3. Human and Animal Health: The Way Ahead** Chair, **David Franz** Speaker 1, **David Swayne**, *Biocontainment Solutions for Poultry Research with Veterinary and Zoonotic Pathogens* Speaker 2, **S.C. Dubey**, High Security Animal Disease Laboratory, Bhopal; *Containment of Zoonotic Infections* Discussion
4:30-6:30pm	**Plenary, Session 4. The Biotech Revolution: Exploring new Territory Together** Chair **Raghavendra Gadagkar** Speaker 1, **David Relman**, *Emerging Capabilities in the Life Sciences and Challenges for Global Health* Speaker 2, **G.B. Nair**, *From Genomics to Public Health*

	Speaker 3, **Ch Mohan Ra**o, *Innovation in Viral Diagnostics for Resource Poor Situations*..
	Speaker 4, **Pawan Dha**r, *Challenges of Synthetic Biology*
	Discussion
7:30 pm	Key Note Speaker, **K. Vijay Raghavan**, Secretary, DST & DBT, Govt. of India at Multipurpose Hall, India International Centre (IIC), 40, Max Mueller Marg, Lodhi Road, New Delhi, followed by **Welcome Dinner** hosted by USNAS

November 19, Day 2

9:00-11:00am	**Plenary, Session 5. Laboratory Regulatory Oversight; Finding the Balance**
	Chair, **T.S. Rao**
	Speaker 1, **S.R. Rao / Nitin Jain**, *Indian Regulations in Animal and Human Health Safety.*
	Speaker 2, **John Kenneth**, *Laboratory Regulatory Oversight for BSL 3 Laboratories*..
	Speaker 3, **Thomas Ksiazek**, L*aboratory Regulatory Oversight for BSL 4 Laboratories*
	Speaker 4, **Vasantha Muthuswamy**, *Ethical Guidelines, Codes and Equity in Human Health Research*
	Discussion
11:00-11:30am	Tea Break
11:30am-1:00pm	**Plenary, Session 6. Applying and Using New Tools and Knowledge Safely**.
	Chair, **Joseph Kanabrocki**
	Speaker 1, **D.D. Kulkarni**, *Practical Issues to be Addressed for Biosafety and Biosecurity in India*
	Speaker 2, **Robert Martin**, *Management of Biosafety Practices - Creating a Sustainable Culture of Safety*
	Speaker 3, **B.M. Subramanian,** Tamil Nadu Veterinary and Animal Sciences University (TANUVAS), *Translational Platform for Veterinary Biologicals*

	Speaker 4, **Joseph Kanabrocki**, Public Outreach on Biosafety
	Discussion
1:00pm	Lunch
2:00-3:30pm	**Breakout A (three concurrent), Session 7.** (*open to all participants, indicate choice*)
	1. Research of concern on new pathogens. Regulations and codes of ethics.
	Chairs: **David Relman**, Rapporteur: **Jens Kuhn** (Convention Centre)
	2. Strengthening management practices to support biosafety in laboratories.
	Chair: **Robert Martin**, Rapporteur: **Gray Handley** (Lecture Hall, Convention Centre)
	3. Levels of Biocontainment facilities: Answering research questions at economically viable containment levels or with alternate methods. Chair: **Jaya Tyagi** *Rapporteur:* **Ashley Grant** (Multipurpose Hall, Jubilee Building)
3:30-4:00pm	Tea break
4:00-5:30pm	**Breakout B (three concurrent), Session 8.** (*open to all participants, indicate choice*)
	1. *Sustainability of surveillance laboratories: Cutting costs without compromising safety. Chair*: **Rakesh Bhatnagar** *Rapporteur*: **H.K. Prasad** (Convention Centre)
	2. *Diagnostic and field laboratories: Safety considerations for transportation of diagnostic samples and in emergencies situations. Chair*: **S.K. Tripathy**, *Rapporteur:* **U.D. Gupta** (Lecture Hall, Convention Centre)
	3. *Laboratory accidents and Laboratory-Acquired Infections (LAIs): Response, reporting, and planning. Chair:* **Karen Byers** (Multipurpose Hall, Jubilee Building)

6:00pm	Key Note Speaker, **Raghavendra Gadagkar**, President, INSA, On War and Peace at INSA Auditorium followed by **Dinner at INSA hosted by President INSA**.

November 20, Day 3

9:00-10:00am	**Plenary, Session 9. Six Reports from Breakout Group Rapporteurs**
	Discussion
10:00-10:30am	Tea Break
10:30-11:30am	**Plenary, Session 10. Management of Natural Disasters**
	Chair: **Indira Nath** Speaker 1, **Muzzafar Ahmad**, Infections in Disaster Management.
	Discussion
11:30am-1:00pm	**Plenary Session 11 Collaboration and Going Forward in Partnership**
	Co-Chair, **T.S. Rao** Co-Chair, **Diane Griffin** Speaker 1, **N.K. Ganguly**, *Biaosafety needs and partnerships* Speaker 2, **Norman Neureiter**, *The Indo-U.S. Science and Technology Forum: Going Forward in Partnership* Speaker 3, **S.R. Rao**, *Opportunities in Regulatory Sciences*
1:00-2:00pm	Lunch
2:00-2:30pm	Closing Discussion *Final thoughts from the co-chairs and participants*.
	Co-Chair, **Indira Nath** Co-Chair, **James LeDuc**
	2:30-3:00pm Formal Adjournment of Workshop
	Dinakar Salunke, Vice-President, International Affairs, INSA **Diane Griffin**, Vice President, USNAS
3:00pm	Tea

D

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety Co-Chairs' Statement

The Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety, held November 18-20, 2014 on the campus of the Indian National Science Academy, encouraged scientists from both countries to examine global issues related to emerging and existing infections and global health safety, to share experience and approaches, and to identify opportunities for cooperation to improve practice and research in these areas. The workshop was the culmination of a multi-year joint effort by the Indian National Science Academy (INSA) and the U.S. National Academy of Sciences (NAS) to enhance partnership among the scientific and technical communities of the two countries on urgent and relevant areas of global health and biological safety.

The primary goal of the workshop was to jointly share challenges and lessons learned regarding biological safety, laboratory management, and the general efficient and sustainable operation of laboratories for public and animal health research, and clinical applications for improving global health safety. A secondary goal was to encourage collaborative partnerships between Indian and American scientists in areas identified by both groups during the workshop keeping in mind the existing multilateral agreements between the two countries.

Workshop speakers outlined the burden of infectious diseases and the importance of antimicrobial resistance; food security, pathogen identification, infectious disease control (including the global challenges of influenza and Ebola) and provided an overview of laboratory diagnostics for virulent and drug resistant pathogens. The inclusion of biotechnology and modern biology, such as synthetic biology, was also raised as absolutely essential to incorporate since the rate of scientific advancement is only increasing, posing both potential benefits and

hazards to global health safety. Throughout the plenary sessions and breakout groups, speakers and participants discussed the importance of:

- assessment of risk associated with particular types of research and the appropriate biosafety levels for such research;
- inter-sectoral needs and coordination when dealing with emerging diseases of humans and animals;
- development and approval of guidelines, regulations, and best practices;
- training at all levels, from management to maintenance personnel;
- developing and retaining leaders, including biosafety officers, building engineers and scientists, basic and applied professionals with scientific and technical depth who are globally connected and able to work with international colleagues;
- addressing advances in biotechnology and their effects on the management and maintenance of laboratories;
- issues related to data sharing, planning, construction and operation of biosafety laboratories;
- effective laboratory leadership to building trust and to instill a culture of safety and responsibility among all laboratory personnel; and,
- importance of communication with the public to promote community engagement to address and alleviate concerns and build confidence.

Each of these topics could serve as a point of departure for the joint cooperation between INSA and NAS to formulate joint findings and recommendations for consideration by the governments of India and the United States. The unique capabilities of the science academies of India and the United States were cited as holding exceptional ability to provide guidance to their governments, and the cooperation between INSA and NAS exemplified in this workshop underscores the opportunities for relevant, realistic, long-term, and sustainable partnership.

Several speakers representing the government of India stated the urgency and importance of the multiple critical issues covered during the 2 ½ day workshop. Specifically, multiple Indian government participants indicated that advice regarding biosafety guidelines for laboratories, effective training for researchers and clinicians dealing with infectious

and zoonotic diseases, and enhanced public engagement and outreach on the importance of safe and secure laboratories would be particularly welcomed.

Beyond India and the United States, the needs of the broader South Asian region for more robust laboratory capacity to address diagnostics, response and research regarding public health challenges were discussed by multiple speakers and participants. Given India's existing and planned laboratory capacity, capabilities in global health research, and expanding international partnerships, it is well situated to become a leader in global health safety.

As a direct follow-on to this workshop, INSA and NAS agreed to partner together to conduct a regional workshop in 2015 focusing on building the capacity of laboratories and affiliated researchers to tackle the region's most difficult public health challenges safely and securely. The workshop will provide an opportunity to convene life science, biological safety and disease surveillance experts from academia, industry, and government to address a set of issues, which may include:

- development of guidelines;
- laboratory training, certification and leadership development;
- mechanisms for reporting laboratory-associated infections;
- right-sizing the regulatory environment and collaboration in regulatory sciences;
- regional transport of samples and specimens;
- matching precautions to risks; and,
- responsible research practices in pursuit of the benefits of life science research.

At the opening and closing sessions of the Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety, leaders of INSA and NAS underscored their support for the workshop, for the India-U.S. partnership that it embodies, and for future cooperative efforts to strengthen global health safety and security in their two countries, in the region, and around the world. The two countries are uniquely suited to carry this cooperation forward to address existing and emerging infectious diseases of humans, animals, and plants, and to thereby improve the health and welfare of people and the environment globally.

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E

Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety Biographical Sketches of the U.S. National Research Council Planning Committee Members

James LeDuc directs the Program on Global Health within the Institute for Human Infections and Immunity at the University of Texas Medical Branch where he is also a professor of Microbiology and Immunology. He also serves as director of the Galveston National Laboratory. Previously he served as the coordinator for Influenza for the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia and was the director of the Division of Viral and Rickettsial Diseases in the National Center for Infectious Diseases (NCID), CDC. His professional career began as a field biologist working with the Smithsonian Institution's African Mammal Project in West Africa. Following that he served for 23 years as an officer with the United States Army Medical Research and Development Command. He joined CDC in 1992 and was assigned to the World Health Organization as a medical officer, later becoming the associate drector for Global Health at NCID. His research interests include the epidemiology of arboviruses and viral hemorrhagic fevers, and global health. He has participated in a number of NRC studies.

Indira Nath received MBBS from the All India Institute of Medical Sciences (AIIMS), New Delhi. After the mandatory hospital training undertaken in UK, she returned to AIIMS for MD (Pathology). She was prompted to specialize in immunology due to her exposure to the new discipline while in UK availing the Nuffield Fellowship (1970). She decided to work in the area of infectious diseases, particularly leprosy which was a major concern in India at that time. She worked with Professor John Turk at the Royal College of Surgeons and Dr RJW Rees at the National Institute for Medical Research, London and then joined faculty in AIIMS. She first joined Professor GP Talwar's Department of

Biochemistry which had just initiated immunology research in India; then moved back to the Department of Pathology (1980), became head of the new Department of Biotechnology (1986) at AIIMS, and continued to work there as INSA-SN Bose Research Professor even after her retirement (1998). She was invited as dean of School of Medicine in Asian Institute of Medicine, Engineering and Technology in Malaysia and subsequently as director of Blue Peter Research Centre (Lepra Research Centre), Hyderabad. She also received DSc (hc) from Pierre and Marie Curie University, Paris (2002). Academic and Research Dr. Nath made pioneering contributions to immunology research by her seminal work on cellular immune responses in human leprosy. Throughout her career, her research contributions centered on mechanisms underlying immune unresponsiveness in man, reactions and nerve damage in leprosy and a search for markers for viability of the leprosy bacillus which is not cultivable. She has over 120 publications, invited reviews, opinion an/comments on recent developments in prestigious international journals. She also mentored many MBiotech, M.D. and Ph.D. students.

David R. Franz is an independent consultant, he served as deputy commander and commander of the U.S. Army Medical Research Institute of Infectious Diseases and as chief inspector on three United Nations Special Commission biological warfare inspection missions to Iraq. Prior to joining the command, he served as group veterinarian for the 10th Special Forces Group (Airborne). He also served as a member of the first two U.S.-UK teams that visited Russia in support of the Trilateral Joint Statement on Biological Weapons and as a member of the Trilateral Experts' Committee for biological weapons negotiations. In addition to being a member of the NAS Committee on International Security and Arms Control (CISAC), he has served as chair of the National Research Council (NRC) Committee to Review Proposals from the Former Soviet Union Biological Weapons Personnel and Institutes, and co-chaired the NRC committee on Protecting Occupants of DOD Buildings from Chemical or Biological Release. He serves on the boards of the Federation of American Scientists and the Kansas Bioscience Authority. Dr. Franz was technical editor for the Textbook of Military Medicine volume on Medical Aspects of Chemical and Biological Warfare released in 1997. Dr. Franz holds an adjunct appointment as professor for the Department of Diagnostic Medicine and Pathobiology at the College of Veterinary Medicine at Kansas State University. His

current focus is on the role of international engagement in the life sciences as a component of national security policy. Dr. Franz holds a D.V.M. from Kansas State University and a Ph.D. in physiology from Baylor College of Medicine.

Diane E. Griffin (NAS/NAM), at the Johns Hopkins Bloomberg School of Public Health, is the Alfred and Jill Sommer Professor and chair of the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health. She holds joint appointments in the departments of Neurology and Medicine. In 2004, Dr. Griffin was elected to the United States National Academy of Sciences (NAS) in the discipline of microbial biology. After earning her undergraduate degree from Augustana College in Rock Island, Illinois, she joined a joint M.D./Ph.D. graduate program at Stanford University, where she pursued research on immunoglobulins. Griffin received her Ph.D. and M.D. in 1968 and remained at Stanford Hospital for her internship and residency. Dr. Griffin performed postdoctoral research in virology at the Johns Hopkins University School of Medicine. Along with Janice E. Clements and others, Griffin is a notable trainee of neurovirology specialist Richard T. Johnson. Dr. Griffin became a faculty member at Johns Hopkins in 1973 in the Department of Neurology. She attained the rank of full professor in 1986. In 1994, Dr.Griffin became the chair of the Department of Molecular Microbiology and Immunology at the Johns Hopkins School of Hygiene and Public Health, now known as the Bloomberg School of Public Health. Virology has been her specialty since her postdoctoral work. Her research examines how the body responds to viral infection. Dr. Griffin has placed particular emphasis on the central nervous system, researching the effects of Sindbis virus and the measles virus on the brain. In 2013, she was elected vice president of the National Academy of Sciences.

Joseph Kanabrocki, of the University of Chicago, Ph.D., C.B.S.P., is currently the assistant dean for biosafety and associate professor of microbiology in the Biological Sciences Division of the University of Chicago. In this capacity, he serves as Select Agent Responsible Official, University Biosafety Officer and director of the Biosafety programs at the University of Chicago's Ricketts Regional Biocontainment Laboratory and the Great Lakes Regional Center for Excellence in Biodefense and Emerging Infectious Diseases Research. Dr. Kanabrocki

received a B.S. degree in biology from the University of Notre Dame and his Ph.D. in microbiology from the University of South Dakota School of Medicine. He was trained as a post-doctoral fellow in the Section of Genetics and Development at Cornell University, Ithaca, N.Y. and in the Laboratory of Molecular Biology at the University of Wisconsin-Madison. He obtained his professional certifications as a Certified Biological Safety Professional from the American Biological Safety Association, where he has been a member since 1992, and from the American (ABSA) Society for Microbiology National Registry of Microbiologists-Specialty Biological Safety. He served for 7 years as the director of biological safety/biological safety officer, assistant director of Environmental Health and Safety and Assistant Research Professor in the Department of Molecular Microbiology at Washington University in St. Louis. He served as the administrative officer for the Washington University Institutional Biological and Chemical Safety Committee as well as the institution's responsible official for the select agent program. Prior to this appointment, Dr. Kanabrocki served for 8 years as the responsible official and as biosafety officer at the University of Wisconsin-Madison. he is currently a member of the National Institutes of Health Recombinant DNA Advisory Committee (NIH-RAC) and the National Science Advisory Board on Biosecurity. He is an active member of ABSA and just completed a three year term as ABSA councilor. He also serves as chair of the Examination Board for the American Society for Microbiology National Registry of Certified Microbiologists and is a member of the Scientific Advisory Board for the National Institutes of Health National Biosafety and Biocontainment Training Program.

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Indo-U.S. Workshop on Challenges of Emerging Infections and Global Health Safety Biographical Sketches of Workshop Speakers and Session Chairs

Rakesh Bhatnagar is a professor in the School of Biotechnology at JNU, New Delhi. He has been working in the field of anthrax for the past 20 years. He has to his credit the development of genetically engineered vaccine against anthrax. The technology of recombinant anthrax vaccine has been transferred to Panacea Biotec Ltd. and the vaccine has successfully undergone Phase I and Phase II human clinical trials. Also, his research group pioneered the expression of Protective Antigen gene in a plant system, which marks the first milestone towards developing edible vaccine against anthrax. DNA vaccine against rabies has been developed in his laboratory and is ready for technology transfer. Further research is being done to develop DNA vaccine against anthrax. His laboratory is also engaged in study of programmed cell death in prokaryotes. His research group has recently initiated research in other important infectious disease systems like Mycobacterium, Brucella; aiming to open avenues for their control. He received his Ph. D. (Biochemistry) from the National Sugar Institute, Kanpur.

Karen Byers is an assistant professor of medicine in the Division of Infectious Diseases and Clinical Director for the Division and director of the Surgical Infectious Diseases Unit. Dr. Byers completed her internal medicine training at Temple University Hospital and completed a 3-year fellowship in infectious diseases at the University of Virginia, where she received a masters degree in epidemiology. She was recruited to join the UPMC staff in February 2001. Dr. Byers' research interests include influenza and surgical infections. Her previous work has focused on infection control, nosocomial pathogens, and HIV. Dr. Byers is involved in the UPMC Health Systems planning for bioterrorism, SARS and pandemic influenza.

Christopher Todd Davis is an associate editor of virology reports at the Centers for Disease Control and Prevention (CDC), Influenza Division. Dr. Davis joined the Influenza Division at the Centers for Disease Control and Prevention as a postdoctoral researcher in 2005. His research interests include studies to characterize the evolution and antigenicity of avian, swine and human influenza viruses. As lead of the Zoonotic Virus Team, Dr. Davis directs molecular epidemiologic research activities for animal influenza viruses and conducts small animal studies to determine, among other things, the consequences of influenza virus evolution on antigenic properties and the pandemic potential of these viruses. As part of the Influenza Divisions' pandemic planning/response, this team utilizes molecular and virologic approaches to characterize and select vaccine candidates for potential use in influenza vaccine manufacturing. In addition, Dr. Davis's research aims to designs novel molecular assays for the detection and quantification of various influenza virus subtypes and continues to work towards improving international surveillance and laboratory capacity by training collaborators in various laboratory techniques, viral sequencing, and phylogenetics. Dr. Davis earned his Ph.D. from the University of Texas Medical Branch.

Pawan K. Dhar is a professor and head of the Synthetic Biology Group at Shiv Nadar University and director of the Centre of Systems and Synthetic Biology, University of Kerala. He has over 15 years of experience in systems and synthetic biology. Previously, he held senior scientific positions at RIKEN Genomics Sciences Centre, Japan, Bioinformatics Institute, Singapore, Keio University in Japan and Manipal University. Professor Dhar has published 75 peer-reviewed scientific papers and has represented India at key global synthetic biology meetings. His work on making functional proteins from naturally non-expressed DNA sequences has shown a new way of doing biology and generated socially useful applications. Dr. Dhar is the founding editor-in-chief of the Springer's System and Synthetic Biology journal. He serves on the Department of Biotechnology (Government of India) review panel of bioenergy and marine synthetic biology. He also serves on the external board of referees for European Science Foundation.

Shiv Chandra Dubey is a veterinary microbiologist having specialization in animal health and production, biosafety, biosecurity and animal welfare. After his initial years at COVS, JNKVV, Jabalpur and a

year in MP State Veterinary Services, he joined ICAR as a scientist in 1976. He served in various groups including Head Animal Health at CSWRI, Avikanagar, Raj. He retired from the post of Joint Director HSADL (now NIHSAD), Bhopal, MP. His significant contributions include development and implementation of a Bimodal Disease Data Information System for small ruminants along with Flock Health Approach and Annual Health Calendar leading to reasonable reduction in morbidity and mortality in all age groups of SRs under farm and field conditions. Dr. Dubey is considered a reference expert for his handling of the AIV by OIE. During his research life he authored four books and 108 research papers in national (81) and international research journals (27) along with 124 scientific presentations. He is recipient of four national awards, two fellowships, and a number of society awards.

Amy DuBois was posted as the HHS Health Attaché in New Delhi, India on October 10, 2013. Dr. DuBois previously held the role of acting director for the Office of Research and Science with the Office of the U.S. Global AIDS Coordinator. She also served as the deputy director Global AIDS Program for U.S. Centers for Disease Control and Prevention (CDC) in Guyana, as the Branch Chief for Strategic Information for the CDC Office in Mozambique, and as an Epidemic Intelligence Service Officer with the CDC where she worked in food-born and diarrheal diseases. A native of Michigan, Dr. DuBois completed her medical school and residency in general surgery at Wayne State University. She holds an M.P.H. from Johns Hopkins University and a B.S. from Calvin College. She practiced general surgery in a community teaching hospital in Massachusetts for several years and still maintains her board certification in surgery.

David R. Franz (See biography on page 180.)

Raghavendra Gadagkar is the president of the Indian National Science Academy, New Delhi, and a JC Bose National Fellow at the Centre for Ecological Sciences, Indian Institute of Science. His research interests are in understanding the diverse research methodologies of different disciplines and create opportunities to rethink the foundations of his own disciplines. He obtained his B.Sc (Hons) and M.Sc. in zoology from Bangalore University and Ph.D. in molecular biology from the Indian Institute of Science, Bangalore, India. He is also chairman at the Centre for Contemporary Studies and an Honorary Professor at the Jawaharlal

Nehru Centre for Advanced Scientific Research, Indian Institute of Science Education and Research, Kolkata. He has published over 250 research papers and articles and two books. His research work has been recognized by a number of awards including the Shanthi Swarup Bhatnagar Prize, B.M.Birla Science Prize, Homi Bhabha Fellowship, B.P. Pal National Environment Fellowship on Biodiversity, the Third World Academy of Sciences award in biology and H. K.Firodia award. He is an elected fellow of the Indian Academy of Sciences, the Indian National Science Academy, the National Academy of Sciences, India, the Academy of Sciences for the Developing World, Foreign Associate of the National Academy of Sciences, and the German National Science Academy Leopoldina. He received his Ph.D. from the Indian Institute of Science, Bangalore.

Nirmal Kumar Ganguly, M.D was formerly a distinguished biotechnology research professor with the department of biotechnology in the government of India. He was formerly president of the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), as well as that of the Asian Institute of Public Health, Bhubaneswar, Odisha. He is the former director general of the Indian Council of Medical Research (ICMR), New Delhi. He is also the former director, PGIMER (Chandigarh) and former director of the National Institute of Biologicals (Noida). Dr. Ganguly has published 773 research papers and has supervised 130 Ph.D. theses as supervisor/co-supervisor. His major areas of research have been tropical diseases, cardiovascular diseases and diarrhoeal diseases. His interest encompasses the disciplines of immunology, biotechnology, and public health. He is president of The Asian Conference on Diarrhoeal Diseases and Nutrition, Yogyakarta, Indonesia. He is an honorary global health research fellow and adjunct professor at Boston University, U.S. He is also an adjunct professor of environmental health in the School of Public Health at the University of Minnesota, U.S. He is also a member of the Scientific Board, Grand Challenges, Bill and Melinda Gates Foundation. He has received 117 awards, including 6 international and 111 national awards. He has been honored with the prestigious Padma Bhushan award by Her Excellency, the president of India on January 26, 2008 in the field of medicine.

B. M. Gandhi was formerly an adviser to the government of India in the Ministry of Science and Technology, Department of Biotechnology. He is CEO (Founder, Partner) of Neo BioMed Services, New Delhi, and a

consultant (Biotechnology) to the Federation of Indian Chambers of Commerce and Industries, New Delhi. His fields of interest in research and development include immunology of parasitic, bacterial and viral infections, especially amoebic diseases; viral diseases including hepatitis; liver diseases; and diagnostics, food and nutritional health problems. He has been published in 60 international journals, and 65 national journals. He is also an adviser to the Centre for Drug Development Sciences, PSG Institute of Medical Sciences and Research, Coimbatore and a consultant in the Department of Biotechnology at the National Institute of Immunology. He is the director of the Biotech Consortium India, Limited as well as director of EmProCell Clinical Research Private Limited, Mumbai. Dr. Gandhi received his Ph.D. in experimental medicine at the University of Bergen, Bergen, Norway, and his M.Sc. in biochemistry at Punjab Agricultural University, Hissar, Haryana, India.

Ashley M. Grant, Ph.D., MPH, is senior biological scientist at the Government Accountability Office. Her primary areas of interest include pathogens, science policy and biosafety. She is a graduate of the University of Texas Medical Branch.

Diane Griffin (See biorgraphy on page 181.)

Umesh Datta Gupta heads the laboratory for Animal Experiments at JALMA. He received a Ph.D. from N.D.R.I., Karnal University and has 22 years of experience in this area. During this time he has contributed to 40 papers on related subject matter. He is currently engaged in studies on testing of viability for M.leprae in the mouse footpad, drug resistance in leprosy as a part of multicentric study and is initiating studies on testing of drugs on Mycobacterium tuberculosis in animals. During his career he has worked as faculty at GBPUA&T, Pantnagar, as Senior Research Officer (Animal House), National JALMA Research Institute for Leprosy & Other Mycobacterial Diseases, Tajganj and is presently deputy director (SG)/Scientist F cum Head, at the Experimental Animals Facility. He has attended more than 100 national and international conferences in India and abroad. He has published 80 papers in national and international journals and contributed chapters in several books. Dr. Gupta is vice president of the Society of Immunology and Immuno-pathology and a recipient of ICMR Senior Scientist International Fellowship (2006) as well as ICMR's JALMA oration award in 2008 for work in Mycobacterial research.

F. Gray Handley, M.S.P.H., is the NIAID associate director for International Research Affairs. Mr. Handley coordinates and facilitates international research activities for NIAID, ensuring that the Institute has a well-integrated, scientifically productive program of international research cooperation. He is involved in integrating NIAID global activities with those of other National Institutes of Health (NIH) Institutes and Centers, the agencies of the U.S. Department of Health and Human Services (HHS) (including the Centers for Disease Control and Prevention and the Food and Drug Administration), and other U.S. federal agencies (including the U.S. Department of State, U.S. Agency for International Development, and U.S. Department of Defense). Mr. Handley has had a long career in the U.S. government as a global health and biomedical research program manager, senior advisor, and health diplomat. From 2001 to 2006, he served as Health Attaché and HHS Regional Representative in Southern Africa, at the U.S. Embassy Pretoria, South Africa; and, from 1992 to 1998 he was assigned as U.S. Science Attaché and HHS Representative in South Asia at the U.S. Embassy New Delhi. Mr. Handley also served as associate director for Prevention Research and International Programs at the NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development; associate director for International Relations at the NIH Fogarty International Center; and global public health advisor for the U.S. Department of State. He has had other assignments at the NIH National Institute of Environmental Health Sciences, the World Health Organization, the White House Office of Management and Budget, the U.S. Department of Defense, and the U.S. Agency for International Development. Mr. Handley has received many awards in recognition of his service and accomplishments. He received his master's degree in the Science of Public Health from the University of North Carolina, Chapel Hill.

Joseph Kanabrocki (See biography on page 181.)

Vishwa Mohan Katoch is known for his experience with microbiology and for managing the high containment research enterprise for the government in India. He joined the Indian Council of Medical Research (ICMR) as a Talent Search Schemes Fellow and was posted at JALMA (Japanese Leprosy Mission for Asia) Agra and became Director of this Institute. He was selected as First Secretary to the Government of India,

Department of Health Research, Ministry of Health and Family Welfare and is presently the Director-General, ICMR, New Delhi. Katoch developed the molecular methods of rapid diagnosis of TB, leprosy and DNA chips; DNA fingerprinting methods; and viability determination methods like ATP bioluminescence. Studies carried out by his group in collaboration with others have led to important new findings and new technologies such as enzyme based methods in the 1980s, molecular biology based techniques in the 1990s and genomics based methods in the recent past. He is a fellow of the National Academy of Sciences, Allahabad; the National Academy of Medical Sciences; and the Indian Academy of Sciences, Bangalore. Dr. Katoch received his MBBS from Shimla and M.D. from the All India Institute of Medical Sciences, New Delhi. He obtained specialized training at the VA Medical Center, Long Beach, and the National Institute for Medical Research, U.K.

John Kenneth is the head of the Infectious Disease Unit and Molecular Diagnostics, dean and vice dean of St. Johns Research Institute and associate professor in microbiology of infectious disease. He completed a MBBS from Christian Medical College (CMC) Vellore and graduate training at MGR Medical University. His research interests include molecular methods for rapid diagnostics and point of care testing, bacterial resistance, viral exanthems, and mycobacterial disease and prevention. He has a lead assessor for NABL certification.

Thomas G. Ksiazek is currently a director of high containment laboratory operations for the Galveston National Laboratory at the University of Texas Medical Branch. He is also director of the National Biodefense Training Center and a world-renowned virus expert with 40 years of experience on the front lines of some of the worst outbreaks the world has ever seen. In August 2014, he led the U.S. Centers for Disease Control and Prevention Ebola outbreak control operations, assisting the government of Sierra Leone in Africa. Prior to that, Dr. Ksiazek was the chief of the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control, in Atlanta, Georgia. He had been in the Special Pathogens Branch at the CDC since 1991 after retiring from the U.S. Army as Lieutenant Colonel with 20 years of active duty service. Dr. Ksiazek earned his DVM in 1970, and then spent a year as associate veterinarian, at the Adirondack Animal Hospital in Glensfalls, New York. He started his military career when he joined the U. S. Air force in

1971, holding a position that year as base veterinarian at Sheppard Air Force Base, Texas. He then worked as chief of Veterinary Services, Royal Air Force Chicksands, UK.

Jens H. Kuhn, M.D./Ph.D., Ph.D., M.S., is a principal at Tunnell Government Services (TGS), Inc., Bethesda, Maryland, tasked as the lead virologist (contractor) at the IRF. He is also TGS team leader for all IRF-Frederick TGS contractors. Dr. Kuhn specializes in highly virulent viral pathogens. He is the author of *Filoviruses: A Compendium of 40 Years of Epidemiological, Clinical, and Laboratory Studies* (Vienna: Springer, 2008) and co-author of *The Soviet Biological Weapons Program – A History* (Cambridge: Harvard University Press, 2012) and has studied and worked in Germany, Italy, Malta, Russia, South Africa, and South Korea. In the United States, he rotated through or worked at Harvard Medical School, Boston, Massachusetts; the Arthropod-Borne Infectious Disease Laboratory in Fort Collins, Colorado; the Centers for Disease Control and Prevention in Atlanta, Georgia; and the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, Maryland. Dr. Kuhn was the first western scientist with permission to work in the former Soviet biological warfare facility SRCVB "Vector" in Siberia, Russia, within the U.S. Department of Defense Cooperative Threat Reduction Program. Dr. Kuhn was a contributor to the Center for International and Security Studies at Maryland's Controlling Dangerous Pathogens Project and a member of the Center for Arms Control and Nonproliferation's CBW Scientist Working Group. He is currently chairing the International Committee on Taxonomy of Viruses Study Groups and is a subject-matter expert for the National Center for Biotechnology Information for all mononegaviruses; is a member of the editorial boards of *Applied Biosafety–Journal of the American Biological Safety Association*, *Archives of Virology*, *BioMed Research International*, *Journal of Bioterrorism and Biodefense*, *PLoS One*, *PLoS Pathogens, Viruses*, *Virologica Sinica, Voprosy Virusologii*, and *World Journal of Virology*; was a member of the U.S. National Academy of Sciences' committee on animal models for assessing countermeasures to bioterrorism agents; and is continuously involved with the American Association for the Advancement of Science and the U.S. Department of State bioengagement efforts in the Broader Middle East and North Africa region, Turkey, and the Newly Independent States.

D. D. Kulkarni is a principal scientist at ICAR, the national Institute of High Security Animal Diseases. He is a fellow of National Academy of Veterinary Science (India). He is the recipient of a number of awards including the Dr. C.M. Singh Award for the best research paper published in Indian Journal of Comparative Microbiology, the Dr. Ganty A. Sastry Award for the best article published in the field of pathology in *Indian Veterinary Journal* and the Intas-Polyvet Award for the best review article published in *Intas-Polyvet Journal* among others. He has published eight books and 56 research papers. He has earned a Ph.D. in veterinary microbiology.

Krishan Lal is an honorary professor at IIT, Kanpur. Dr. Lal established and led an active research group on crystal growth and study of crystal defects by high-resolution X-ray diffraction techniques. He has made important contributions in the area of lattice imperfections in nearly perfect crystals and crystal growth. His research work has led to breakthroughs in understanding the nature of real materials and their interaction with radiation and external fields. His basic research has helped in establishing the origin of diffuse X-ray scattering from crystals; made it possible to directly observe and characterize the effect of external electric fields on real structure of semiconductors and insulators; enabled characterization of effect of processing steps for solid state devices fabrication on substrate materials; and enabled growth of single crystals of unprecedented perfection level. He has edited eight books and published more than one hundred research papers in refereed journals. He has seven patents to his credit. He was elected as the President of ICSU's (International Council for Science) Committee on Data for Science and Technology (2006). He was editor of Zeitschrift fur Kristallographie (1996-2003) and is presently editor-in-chief of the proceedings of the Indian National Science Academy. He obtained his Ph. D. (1969) from Delhi University in solid-state physics. He obtained his B.Sc. (1959) and M.Sc. (1961) degrees from Meerut College, (Agra University).

James LeDuc (See biography on page 179.)

Robert Martin, MPH, Ph.D., has an extensive background in laboratory practice in both clinical and public health settings, including: directing and managing laboratories, addressing state and national policies governing the practice of laboratory medicine, and supporting laboratory

capacity development in resource-limited countries. While at the Centers for Disease Control and Prevention (CDC) he served as executive director of CLIAC; the Federal Advisory Committee that, together with FDA and CMS, governs the practice of laboratory medicine in the United States. While at CDC, Dr. Martin also held the positions of acting director of the National Center for Public Health Informatics and director of the Division of Laboratory Systems (DLS). As director of DLS, he developed the laboratory systems branch to strengthen laboratory capacity both domestically and internationally. In this capacity Dr. Martin worked with the CDC Global AIDS Program, Department of Defense, World Bank, and World Health Organization in Africa, Southeast Asia and Central Asia to address strengthening of laboratory systems. Dr. Martin joined the International Training and Education Center for Health in 2009 as director of laboratory systems development. In this role, he provides technical assistance in laboratory capacity development in countries in Central Asia, the Southern Caucuses, Southeast Asia and sub-Saharan Africa, including Namibia.

Arabinda Mitra was confirmed by the Indian and United States governments as the first executive director of the bi-national Indo-U.S. Science and Technology Forum. Dr. Mitra has had an extensive career with varied positions in the fields of geology and ocean research and development. Dr. Mitra was the Director in the International Division of the Department of Science and Technology for the Government of India. He was a member of the 12th Indian Expedition to Antarctica and has undertaken several scientific cruises to the Indian, Atlantic and Pacific Oceans. Dr. Mitra has won several academic awards like the ORS Award of UK; Bursary Award of St. Edmund's College; UK and JSPS Award of Japan and was also elected as a Fellow of Geological Society, London. In 1988, he was awarded the prestigious Cambridge Nehru Fellowship to pursue his doctoral research at the University of Cambridge, UK. His Ph.D. project was jointly carried out with MIT, USA in the area of mid oceanic ridge hydrothermal systems. His research work was published in journals like *Nature*, *Marine Chemistry and Geochimica Cosmo-chimica Acta*, and *International Journal of Remote Sensing*.

Vasantha Muthuswamy is currently president of FERCI (Forum for Ethics Review Committees in India) and advisor for clinical research and ethics at PSGIMS&R, Coimbatore. She retired as senior deputy

director general (Scientist G) and chief of Division of Basic Medical Sciences, Traditional Medicine and Bioethics and Division of Reproductive Health and Nutrition from the Indian Council of Medical Research (ICMR) after three decades of service in different capacities. She has played a major role in the area of drug development including traditional medicine, genetics and genomics, haematological disorders, ethics of animal and human experimentation, and promotion of research by medical students. She is well recognised for bringing out the ICMR's "Ethical guidelines for biomedical research on human subjects" in 2000 and the revised version "Ethical guidelines for research on human participants" in 2006. Dr. Muthuswamy received the Lifetime Achievement Award from the Indian Society for Clinical Research (ISCR), National Bioethics Conference (NBC) and FERCAP. She is a medical graduate from R.G. Kar Medical College, Kolkata and received an M.D. from the Institute of Obstetrics and Gynaecology, Madras.

G. Balakrish Nair works at the Translational Health Science Technology Institute, a newly founded autonomous institute of the Department of Biotechnology in Gurgaon, Harayana, India. He took up this position in October 2011. He was formerly the director of the National Institute of Cholera and Enteric Diseases (NICED), Kolkata, India. He joined NICED in 1981 and worked there until April 2000 after which he took up a 7-year assignment at the International Centre for Diarrhoeal Diseases in Dhaka, Bangladesh as the Director of Laboratory Sciences Division. Dr. Nair's research is on enteric pathogens with particular emphasis on *Vibrio cholerae,* the causative agent of the disease cholera. For the past five years, his research interests have expanded into the human microbiome especially on the gut and vaginal microbiota in relation to malnutrition and diarrhoea. He is a fellow of the National Academy of Sciences, India, fellow of the Indian National Academy of Sciences, Foreign Associate of the U.S. National Academy of Sciences, fellow of the Academy of Sciences for the Developing Nations (Italy), fellow of the American Academy of Microbiology and fellow of the German Academy of Sciences (Leopoldina). Among other awards, Dr. Nair received the prestigious Shanti Swarup Bhatnagar award for Medical Sciences in 1998 for his contributions to the discovery of *Vibrio cholerae* O139 Bengal. Under his supervision, 29 students have obtained doctoral degrees. He is the author of over 500 research papers and several book chapters and has edited several books on enteric diseases.

Indira Nath (See biography on page 179.)

Norman P. Neureiter was born in Illinois and grew up near Rochester, New York. He received a B.A. in chemistry from the University of Rochester and a Ph.D. in organic chemistry from Northwestern University.. He spent a year as a Fulbright Fellow in the Institute of Organic Chemistry at the University of Munich. In 1957, he joined Humble Oil and Refining (now part of Exxon) in Baytown, Texas as a research chemist, also teaching German and Russian at the University of Houston. On leave from Humble in 1959, he served as a guide at the U.S. National Exhibition in Moscow, subsequently qualifying as an escort interpreter for the Department of State. In 1963, he joined the International Affairs Office of the U.S. National Science Foundation in Washington and managed the newly established U.S.-Japan Cooperative Science Program. Entering the U.S. Foreign Service in 1965, he was named Deputy Scientific Attache at the U.S. Embassy in Bonn. In 1967, he was transferred to Warsaw as the first U.S. Scientific Attache in Eastern Europe with responsibility for Poland, Hungary and Czechoslovakia. Dr. Neureiter returned to Washington in 1969 as an assistant for international affairs to the President's Science Advisor in the White House Office of Science and Technology. He left the government in 1973 and joined Texas Instruments (TI), where he held a number of staff and management positions including manager, East-West Business Development; manager, TI Europe Division; vice president, Corporate Staff; and Vice President of TI Asia, resident in Tokyo from 1989-94. After retirement from TI in 1996, he worked as a consultant until being appointed in September 2000 as the first Science and Technology Adviser to the U.S. Secretary of State. Finishing the 3-year assignment in 2003, he was made a Distinguished Presidential Fellow for International Affairs at the U.S. National Academy of Sciences. In May 2004, he joined the American Association for the Advancement of Science (AAAS) as the first director of the new AAAS Center for Science, Technology and Security Policy (CSTSP), funded by the MacArthur Foundation.

H. K. Prasad is a professor in the Department of Biotechnology at the All India Institute of Medical Sciences (AIIMS). He teaches immunology for masters candidates in biotechnology. In his research he is currently trying to establish the complex web of mycobacterial transmission that could potentially occur between humans and

domesticated animals; and the reservoirs of infection that maintain the pathogens in the environment. In order to establish transmission of pathogens from humans to cattle and cattle to humans, efforts are on to identify and trace the origin of strains of mycobacterial pathogens isolated from clinical samples. He is a member of several scientific societies including the Indian Immunology Society, the Molecular Immunology Forum, the Society of Biological Chemists, the Society for Scientific Values, the American Society for Microbiology and the Guha Research Conference. He has published 53 research papers and three chapters in books. He has five patents outstanding. In his future research plans he would like to attempt to understand the basis of tissue predilection of mycobacterial pathogens in a clinical context as well as work on a collaborative project for development of bovine vaccines for prevention of tuberculosis.

Vijay Raghavan is currently distinguished professor and director of The National Centre for Biological Sciences. He was awarded the Infosys Prize in the life sciences category. He completed his doctoral work in the field of molecular biology and holds a Ph.D. from the Tata Institute of Fundamental Research. During his post-doctoral work, he was a research fellow and, a senior research fellow at the California Institute of Technology. In 1988, he joined the Tata Institute of Fundamental Research as a Reader and, then National Centre for Biological Sciences (NCBS), which is under the aegis of Tata Institute of Fundamental Research that joined NCBS. He moved to Bangalore and was instrumental in the establishment of NCBS in Bangalore. His fields of specialization are developmental biology, genetics and neurogenetics. His research primarily focuses on the important principles and mechanisms that control nervous system and muscles during development and how these neuromuscular systems direct specific locomotor behaviours. Dr. Raghavan is also a director of the Centre for Cellular and Molecular Platforms. He is a member of the Board of Governors of the Okinawa Institute of Science and Technology, the Advisory Committee of the Janelia Farm Research Centre of the HHMI and a senior editor of the new journal *eLife*. Professor Raghavan has received numerous awards such as British Council Fellowship, Procter & Gamble Fellowship (Caltech), Lucile P Markey Fellowship (Caltech) and Biotechnology Career Development Award of Rockefeller Foundation. He was elected fellow of the Indian Academy of Sciences. K. Vijay Raghavan was conferred with the Shanti Swarup Bhatnagar Prize for

Science and Technology award by the Council of Scientific and Industrial Research. In January 1999, he became an associate faculty member of the Jawaharlal Nehru Centre for Advanced Scientific Research. He became a fellow of the Indian National Science Academy, a member of the editorial board of *Journal of Genetics* and a member of the Asia-Pacific International Molecular Biology Network.

Ch. Mohan Rao is presently the director of Centre for Cellular and Molecular Biology, Hyderabad. He combines biophysical, molecular biological, and cell biological approaches to address problems of biomedical importance. His research interests include protein folding, molecular chaperones and heat shock proteins, molecular basis for lens transparency, cataract and keratitis, biosensors, DNA based diagnostics, Nanobiology, Photoacoustic spectroscopy and its application to biomedical problems. His recent research addresses the role of small heat shock proteins in gene expression, cell division, differentiation and apoptosis. Mohan Rao is a member of the program advisory committees and task force committees of major government funding agencies, a member of editorial boards of scientific journals and a section editor for *BBA-Proteins and Proteomics*. He is a fellow of the World Academy of Science, Trieste, Italy, a fellow of the Indian National Science Academy, the National Academy of Sciences, India the Indian Academy of Science, and Andhra Pradesh Akademi of Sciences. He is the president of the Andhra Pradesh Akademi of Sciences, Honorary President of the Jana Vigyana Vedika (Andhra Pradesh), and president of the Society of Biological Chemists (India). He is also a member of the Council of International Union for Pure and Applied Biophysics, Asia Pacific Protein Association, and the Federation of Asian and Oceanian Biochemists and Molecular Biologists. He is recipient of several awards including Ranbaxy Award for Basic Medical Sciences (2000) and the Shanthi Swarup Bhatnagar Prize (1999). He is a "J C Bose National Fellow." He is the recipient of Eminent Educationist Award, The Indus Foundation; Visishta Puraskaram, Ramineni Foundation-USA, Doctor of Science (Honoris Causa), Kakatiya University, and Bires Chandra Guha Memorial Lecture Award (INSA). He has obtained his Ph.D. from the University of Hyderabad in Chemistry.

S. R. Rao is director in the department of biotechnology, for the government of India and is responsible for international cooperation especially in the Asian region and the establishment of biotech facilities

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T. S. Rao is working as adviser in the department of biotechnology in the Ministry of Science and Technology, for the government of India. He has coordinated programs related to medical biotechnology, human genetics and genome analysis, National Bioethics Committees, and vaccine research and development since 1988-1989. This includes the Jai Vigyan Mission program on S&T for new and improved vaccines, Vaccine Grand Challenge Programme, glue grant, rapid grant for young investigators and also the two human vaccine production units established under Technology Mission on Immunization, namely Bharat Immunologicals and Biologicals Corporation Limited and Indian Vaccines Corporation Limited, Gurgaon. In addition, he has established the National Brain Research Centre, Manesar, Translational Health Science and Technology Institute, Faridabad, and Institute for Stem Cell and Regenerative Medicine, Bangalore, as autonomous institutions of the Department of Biotechnology, including its niches centers and extramural units. Before joining the department of biotechnology in 1988, Dr. Rao worked at the National Institute of Communicable Diseases, Ministry of Health and FW for the government of India in the area of development of Malaria vaccine by using molecular biology methods and developed monoclonal antibodies for blood stages of P. falciparum. Dr. Rao has 18 scientific publications to his credit in national and international peer-reviewed journals. He is also one of the co-author's of a comprehensive book entitled An Introduction to

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David A. Relman, M.D. is the Thomas C. and Joan M. Merigan Professor in Medicine, and Microbiology and Immunology, and Co-Director of the Center for International Security and Cooperation at Stanford University. He is also Chief of Infectious Diseases at the Veterans Affairs Palo Alto Health Care System in Palo Alto, California. Dr. Relman's research focus is the human indigenous microbiota, and the identification of previously-unrecognized microbial agents of disease. He has advised the U.S. government on emerging infectious diseases, human-microbe interactions, and future biological threats. He is Chair of the Forum on Microbial Threats at the Institute of Medicine (National Academies of Science) and past president of the Infectious Diseases Society of America. He is a fellow of the American Academy of Microbiology, and a member of the Institute of Medicine.

Ratnakar Sahoo is a professor at the RML Hospital in New Delhi. Professor Sahoo is an active member of the Association of Physician of India (API) and regularly attends API conferences. He has presented several scholarly papers on various aspects of internal medicine in API conferences. He organized the annual conference of the Indian Society of Hematology and Transfusion Medicine as Treasurer (ISHTM-2008) at JIPMER, Pondicherry. He has guided 14 PG students for their thesis and has been the co-guide for many others. He has to his credit 35 publications in various national and international journals and contributed chapters in seven different medical books. He has received an FIACM award in 2012 and an FICP award. Professor Sahoo has conducted 38 MBBS, M.D., and DNB examinations as external examiner. He has been invited to deliver lectures for DNB student at IGONU periodically. He participated in the Indo-U.S. workshop and delivered a talk on ebola giving an Indian perspective at the Indian National Science Academy in November 2014.

Dinakar Salunke is the director of ICGEB New Delhi. Prior to joining ICGEB, Dr. Salunke was the executive director at the Regional Centre for Biotechnology (RCB), India. His research has focused on understanding the physiological processes of self-nonself discrimination in terms of physicochemical principles of molecular interactions. He has analyzed how the immune system reacts when encountered with the

antigens that keep changing shape and showed that the restricted paratope conformational repertoire on binding of an antigen to multiple independent antibodies may be relevant for minimizing possibility of self-reactive antibodies. He is a fellow at the Indian National Science Academy, the National Academy of Sciences (India), and the Indian Academy of Sciences. He is a member of the Molecular Immunology Forum and the Guha Research Conference. He has received numerous awards during his career including the Professor R.C. Shah Memorial Award, the Dr. C. R. Krishnamurthi Oration Award, Dr. A.T. Varute Oration Award, the JC Bose National Fellowship Award the Professor G. N. Ramachandran 60th Birthday Commemoration Medal and the S. K. Mitra Birth Centenary gold medal. He obtained his Ph.D. from the India Institute of Science, Bangalore, and went on to join the National Institute of Immunology in 1988.

Sudhir Kumar Sopory is the Vice Chancellor at the Jawaharlal Nehru University, New Delhi. He is one of India's most distinguished scientists. An eminent plant molecular biologist of International repute, Prof. Sopory began his academic career in 1973 as a faculty at the School of Life Sciences, Jawaharlal Nehru University. His teaching and research career spans over 37 years. Professor Sopory has been awarded various national and international awards for his pioneering contributions to scientific research and teaching. Notable among them are: the prestigious Bhatnagar Award of CSIR; Chakravorty Award; Birbal Sahni Medal of the Botanical Society; Birbal Sahni Birth Centenary Award of Indian Science Congress; Godnev Award Lecture of Belarus Academy of Sciences and Padma Shri, Government of India. He is an elected Fellow of the Indian National Science Academy (New Delhi); Indian Academy of Sciences (Bangalore); National Academy of Sciences (Allahabad); National Academy of Agricultural Sciences (New Delhi) and The World Academy of Sciences (Trieste, Italy). Recently he has also been awarded Corresponding Membership Award of American Society for Plant Biology, 2010, the first time to an Indian. He has to his credit 200 research publications in refereed journals; 13 edited books and 50 chapters in books. He received his BSc and MSc from Jammu and Kashmir University and completed his Doctorate at the University of Delhi in the field of plant molecular biology.

David Swayne, D.V.M., M.Sc., Ph.D., is a research veterinarian in avian influenza. Since 1987, his personal research has focused on pathobiology

and control of high pathogenicity avian influenza with more than 262 peer-reviewed publications and more than 237 invited presentations. He is a former faculty member at Ohio State University and for the past 20 years has been the Director of the U.S. Department of Agriculture's in-house high-biocontainment laboratory for research on exotic, emerging, and endemic viral diseases of poultry and is subject-matter expert on avian influenza. In 2011, he completed a 16-month sabbatical to the World Organization for Animal Health (OIE), conducting a global assessment of avian influenza control programs, especially the role of vaccines. He is the editor of the international text Avian Influenza, editor-in-chief of the 13th edition of Diseases of Poultry, and associate editor for two journals: Veterinary Pathology and Influenza and Other Respiratory Pathogens. Dr. Swayne has served on OIE international committees to update the avian influenza chapters in Terrestrial Animal Health Code and Manual of Standards for Diagnostic Tests and Vaccines. He has participated in missions or conferences on avian influenza control and biosafety/biosecurity in 44 countries in the past 15 years.

Srikanth Tripathy is the Director of the National JALMA Institute of Leprosy and Other Mycobacterial Diseases (ICMR). Dr. Tripathy's areas of research specialization include tuberculosis, HIV-TB, HIV drug resistance, drug resistance TB and drug resistance in leprosy. He has published 84 research papers and studies. He received a Fogarty Fellowship from Harvard School of Public Health where he worked on HIV and molecular epidemology. He obtaind his M.D. from Madras Medical College.

Jaya Sivaswami Tyagi is a professor in the Department of Biotechnology at the All India Institute of Medical Sciences, Ansari Nagar, New Delhi. She has 39 years of teaching experience including 35 years of experience in molecular biology molecular genetics and recombinant DNA technology. She has published over 78 research papers and has written 6 chapters in medical books. Dr. Tyagi has five patents in India and six in the international arena. She has been awarded the Dr. Kona Sampath Kumar Memorial Prize at the University of Delhi, the P.S. Sarma Memorial Award and the National Women Bioscientist Award as well as the New Millennium Science Medal. She has contributed significantly to the discovery and elucidating mechanism of action of DevR-DevS two component system of Mycobacterium

tuberculosis using RNA subtractive hybridization, development of TB diagnostic tool box, the development of novel dormancy cell infection model for Mycobacterium tuberculosis and the development of inhibitors against DevR dormancy regulator. She received her Ph.D. from the University of Delhi.