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Establishing a National Biological Laboratory Safety and Security Monitoring Program

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The growing concern over the potential use of biological agents as weapons and the continuing work of the Biological Weapons Convention has promoted an interest in establishing national biological laboratory biosafety and biosecurity monitoring programs. The challenges and issues that should be considered by governments, or organizations, embarking on the creation of a biological laboratory biosafety and biosecurity monitoring program are discussed in this article. The discussion focuses on the following questions: Is there critical infrastructure support available? What should be the program focus? Who should be monitored? Who should do the monitoring? How extensive should the monitoring be? What standards and requirements should be used? What are the consequences if a laboratory does not meet the requirements or is not willing to comply? Would the program achieve the results intended? What are the program costs? The success of a monitoring program can depend on how the government, or organization, responds to these questions.

This article discusses the challenges that can be encountered when embarking on establishing a biological laboratory monitoring program. The discussion is intended to provoke a sharing of experiences by those countries that have established, or have already embarked on establishing, such a program. The issues and challenges described here are the result of the author's experience in implementing the US Federal Select Agent Program, which involves evaluating and monitoring biosafety and biosecurity programs in more than 400 biological laboratories. It is not intended to be a complete list addressing every possible issue or challenge that a nation might encounter, as the US experience may be different from the experience in another country. Nor is it suggested that the US program is the ideal program. The US program works in the American legal system, but it would be unwise to try to implement a similar program without regard for a nation's culture and political environment. Each country will encounter issues and challenges unique to its particular situation and will need to develop the solutions that work best in that environment. Not all issues and challenges can be anticipated, but without careful planning and preparation the chances of success are significantly at risk.

Events in the late 20th century in the US, culminating in the 2001 anthrax attacks, resulted in an awareness of the need for improved laws to control the possession, use, and transfer of biological agents and toxins that have the potential to be used as biological weapons. Prior to 2001, the Antiterrorism and Effective Death Penalty Act of 1996 required the Secretary of Health and Human Services (HHS) to promulgate regulations identifying biological agents that have the potential to pose a severe threat to public health and safety and to regulate their transfer. Development and implementation of the regulations (Additional Requirements for Facilities Transferring or Receiving Select Agents: Final Rule, 42 C.F.R Part 72.6) was the responsibility of the Centers for Disease Control and Prevention (CDC).

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The passage of the USA PATRIOT Act in 2001(Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001) and the Public Health Security and Bioterrorism Preparedness and Response Act in 2002 (Bioterrorism Response Act) established the legal framework to allow the US government to regulate the safety and security practices of individuals and institutions in possession of dangerous biological agents and biological toxins. This significantly expanded the regulation of biological agents and toxins, as defined in the Rule, resulting in the expansion of the CDC Select Agent Program oversight and creating specific US Department of Agriculture (USDA) authority over select agents that present a hazard to animals and plants or animal and plant products.

In 2002, the CDC's Division of Select Agents and Toxins and the USDA's Animal and Plant Health Inspection Service (APHIS) jointly established the Federal Select Agent Program (FSAP), an interagency cooperative activity to coordinate the regulation of select agents and toxins that are hazardous to humans and to animals and plants and animal products. FSAP is assigned responsibility for carrying out the provisions of the USA PATRIOT Act, the Bioterrorism Response Act, and the Agricultural Bioterrorism Protection Act of 2002 through 3 select agent regulations (42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121).

There are currently 400 laboratories in the US registered with FSAP. FSAP inspectors have conducted more than 1,200 onsite laboratory inspections in the US since 2003. FSAP promotes laboratory safety and security by developing and promulgating regulations, registering laboratories, conducting onsite inspections, and providing guidance to the regulated community. FSAP approves and tracks shipments of biological select agents and toxins (BSAT); investigates reports of theft, loss, and release of BSAT; collects information on BSAT identified by diagnostic laboratories; and provides select agent facility status information to federal decision makers during responses to natural and intentional disasters.

FSAP and US select agent regulations are consistent with the broad international framework of agreements developed to prevent the development and proliferation of biological weapons. The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, commonly known as the Biological Weapons Convention (BWC) or Biological and Toxin Weapons Convention (BTWC), was opened for signature in 1972 and entered into force in 1975. It prohibits the development, production, acquisition, transfer, retention, stockpiling, and use of biological and toxin weapons and is a key element in the international community's efforts to address the proliferation of weapons of mass destruction.

United Nations Security Council resolution 1540 was unanimously adopted by the United Nations Security Council on April 28, 2004. The resolution established the obligations under Chapter VII of the United Nations Charter for all member states to develop and enforce appropriate legal and regulatory measures against the proliferation of chemical, biological, radiological, and nuclear weapons. The resolution calls on member states to report to the 1540 Committee on the steps they have taken, or intend to take, to implement the provisions of the resolution. Subsequent BWC conferences have promoted efforts to control biological agents that have the potential to be used as weapons. The BWC and the conferences and resolutions that have followed since 1975 have resulted in the implementation of programs by some countries to prevent the use of biological agents for harmful purposes.

National, regional, and international associations and organizations have been established to promote general laboratory safety, not specifically limited to biological weapons concerns. In some countries, there are regulatory programs that establish standards and requirements for laboratory safety, or laboratory research, and to some extent requirements for the security of biological agents that can be used as bioweapons. While progress has been made, there are still some countries that have limited or no programs to address the requirements of Resolution 1540. There is no international laboratory biosafety and biosecurity monitoring program to which all nations belong. Creating national laboratory monitoring programs and linking national programs into an international network may be the way to accomplish this. The first step is creating national programs, and this article describes some of the challenges that nations should expect if they embark on doing this.

The Challenges

Nations that are in the process of establishing, or considering establishing, a national biological laboratory monitoring program for the purpose of regulating biological agents that have the potential to be used for purposes other than the public good face a number of challenges. These challenges are brought into focus by asking the following questions: Is there critical infrastructure support for a monitoring program? What should be the program focus? Who should be monitored? Who should do the monitoring? How extensive should the monitoring be? What standards and requirements should be used? What are the consequences if a laboratory does not meet the requirements or is not willing to comply? Would the program achieve the results intended? What are the program costs? These challenges and possible options to meet the challenges are discussed below.

Is There Critical Infrastructure Support?

FSAP was created by law after events that were regarded as a threat to US national security. It has the statutory and

regulatory authority necessary to require laboratory compliance. A nation must have the legislative mechanisms to develop the laws and establish the regulatory oversight agencies necessary to support a monitoring program. It is also important to enlist political leadership, using the available legislative mechanisms, to promote the development and enactment of laws necessary to require the enrollment and compliance of the country's laboratories. It is outside the scope of this article to provide model legislation, but it is important in the development of legislation to consider, in addition to national requirements, international treaty requirements. It is also important that the scientific community be engaged in the process.

The enactment of laws and regulations establishing a biological laboratory monitoring program requires adequate funding to implement and sustain it. The funding may be through government resources or registration fees or both. There are governments and private foundations that provide funding to develop laboratories and support health programs, and they may be a resource for initial startup costs, but this is not a sustainable funding solution.

The alternative to government regulation is a volunteer program built on an interest by the scientific, medical, research, and commercial laboratory community in improving laboratory biosafety and biosecurity. Some countries have national associations, or participate in regional associations, that promote laboratory safety but do not have regulatory authority. A few examples are the African Biological Association, the European Biosafety Association, and the Association of Biosafety for Australia and New Zealand. These associations are part of the International Federation of Biosafety Associates, which currently has 22 association members. The volunteer approach is not ideal because consensus can be difficult to achieve, resulting in less than full participation. This approach does not meet the obligation of states to take and enforce effective measures to establish domestic controls to prevent biological weapons and their means of delivery as specified in the United Nations Security Council Resolution 1540. Nevertheless, the voluntary approach may provide the foundation on which a more robust and sustainable program can be developed.

An additional consideration is the availability of professionals with a combination of biological laboratory expertise and scientific facility security expertise. Individuals with biological laboratory experience can be trained in biosafety and biosecurity, but it is more difficult to develop laboratory evaluation competence if the individual has never worked in a laboratory. This is not to diminish, however, the importance of a solid understanding of laboratory biosafety and biosecurity. It can be difficult to recruit individuals who have extensive biosafety or biosecurity expertise. There are organizations that have active training programs in biosafety, such as the American Biological Safety Association, and there are international conferences and workshops on biosafety and biosecurity.

What Should Be the Program Focus?

In the US, FSAP monitors laboratories that possess specific biological agents and toxins that have the potential to be misdirected for use as bioweapons. The emphasis of the US select agent regulations is on laboratory security. However, one of the benefits of the regulatory program, in addition to enhanced security, has been an enhancement in laboratory safety awareness. In developing a biological laboratory monitoring program, it is important to determine the focus or purpose of the program. Will it be limited to laboratory security, or will it incorporate both security and biosafety? The 2 are closely related. While the focus of the program may be limited to regulatory compliance, there are programs that also include education, guidance, laboratory training, and advising. The Public Health Agency of Canada, which for many years conducted a laboratory certification program under their importation regulations, monitors laboratories from construction to operation. This adds expense to the program but can serve to improve compliance. Implementation of a program without focus will result in wasted time and effort and duplication of efforts and will significantly risk success of the program.

Who Should Be Monitored?

In the US, FSAP developed a list of biological agents and toxins, and these agents and toxins are monitored through a program of registration and inspection of the laboratories that possess, use, and transfer them. The list consists of agents and toxins that have been determined to have potential for use as bioweapons. Laboratories working with infectious disease agents that may have significant public health consequences but do not have the potential for misuse as bioweapons—for example, human immunodeficiency virus, *Mycobacterium tuberculosis*, *Plasmodium,* or rabies virus—are not on the list. This may be viewed as a missed opportunity to promote general biological laboratory safety. The more extensive the list of agents included for regulatory oversight, the more complex and expensive the program will be. However, a more comprehensive list would theoretically decrease opportunities for misuse.

Another approach is to combine a laboratory monitoring program into a program that provides permits for the import of infectious disease agents. In this kind of program, only those laboratories that request an import permit would be evaluated and monitored. This kind of program could be less expensive and present less management challenges if there is little import activity and if the list of agents requiring permits is limited.

There is also the approach of monitoring laboratories that conduct a particular type of work regardless of agents. Laboratories that conduct research using animals or engage in genetic engineering are examples.

Finally, there is the approach of only monitoring those laboratories that are of a particular containment level, such

as monitoring only maximum containment laboratories. The advantage of limiting the program to a type of laboratory, a particular type of activity, or a short list of agents is that it may be less expensive and easier to operate. However, if the monitoring program is too specific, it may not meet the objectives intended, and if it is too broad in scope, it may not be adequately subscribed to, resulting in its not meeting risk reduction objectives. It is also important to appreciate that a program that is too intrusive may inhibit essential scientific productivity.

Who Should Do the Monitoring?

If the initiative for the biological laboratory monitoring program is from a centralized government, the simple course may be to use an already existing agency or government unit. The decision should consider the government unit that has the necessary expertise and a vested interest, such as the health or agriculture agencies.

In the US FSAP, there are 2 separate agencies that share responsibilities for the program. In a decentralized government environment, the monitoring units may be the country's province or regional governments, but this is more likely to introduce standardization problems. The monitoring may also be by a private firm contracted by the government to conduct laboratory evaluation and monitoring activities in accordance with government specifications. This can avoid startup expense to the government, but the government must retain program oversight and compliance action authority.

If the program is initiated and operated by an association of laboratories, the members of the association may be involved in the monitoring, with association dues covering part of the expense of the monitoring. Using this approach, members of one laboratory participate in an inspection of one of the member laboratories, with any administrative functions supported by association dues or fees. This approach is similar to the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), which uses ad hoc consultants and specialists to supplement a regular staff of inspectors. It may also be possible for countries within a region to enter into an agreement to evaluate a member country's laboratories, but this is not an approach currently being used.

How Extensive Should the Monitoring Be?

The answer depends on the objective of the program and the funding available. A program that involves extensive monitoring will be a greater burden and expense on the participating laboratories and on the program but has the advantage of potentially reducing risk of an incident or misuse of biological agents. A program could be established to only evaluate documentation submitted by the participating laboratory about safety and security practices. This approach assumes trust that the laboratory will provide accurate information, since there is no onsite verification. A more extensive program involves an evaluation of documentation accompanied by an onsite verification inspection. Requiring laboratories to address deviations from established standards adds additional complexity to the program. Additional requirements such as notification of laboratory changes, notification of biological agents transfer, reporting of biological agent detection, and incident reporting adds more complexity and thus expense, but the value is greater oversight of the possession and use of the biological agents of interest.

What Standards and Requirements Should Be Established?

FSAP uses 3 primary resources: *Biosafety in Microbiology and Biomedical Laboratories* (BMBL, 5th Edition); the NIH Guidelines on Recombinant DNA Molecules (NIH Guidelines), which are biosafety guidelines; and the federal regulations (42 CFR 73, 9 CFR 121, 7 CFR 331) that specify security requirements. The BMBL and NIH Guidelines are used as standards to measure biosafety practices of registered laboratories, and the regulations are used as requirements for both safety and security.

Internationally the following guidelines are commonly used: *Laboratory Biosafety Manual* (3rd edition, WHO), Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens (WHO), the *Laboratory Biosafety Guidelines* (3rd edition, Canada), and International Biosafety Working Group (European Biosafety Association at http://www.ebsaweb.eu/). This is not a complete list, and a country may elect to create its own standards. If a country decides to develop its own guidelines or regulations for biosafety and security, it should do so using experts in those areas. Guidelines are primarily recommendations on practices, while regulations are enforceable requirements. A country should determine whether it will use guidelines or regulations or a combination of both and whether it will adopt international guidelines or develop its own. The objectives of the program should be considered in the decision.

What Are the Consequences of Noncompliance?

If a participating laboratory has agreed to a code of practice, or set of standards, but does not adhere to the agreement, or chooses not to participate in the program, the biological laboratory monitoring program must clearly state the consequences. This is a critical question, and the answer depends on the type of program. If the program is strictly voluntary, the consequences to a member that does not

comply with the program could be exclusion from the program. Exclusion can have greater value if the failure to adhere to the program requirements comes at a loss of opportunity for the laboratory. Opportunity loss might include loss of research grants, accreditation, services contracts, or authority to import or export. A program established by laws and regulations should clearly describe the penalties for noncompliance, which can vary from loss of opportunity to civil and criminal consequences.

Would the Program Achieve the Results Intended?

Measuring the effectiveness of a biological laboratory monitoring program is difficult without criteria for measuring effectiveness and the ability to obtain appropriate data. Data supporting the conclusion that a laboratory security program has an impact on preventing bioterrorism may be difficult to acquire or quantify. A reduction in incidents of theft at biological laboratories may be an indication of better security. A reduction in laboratory accidents may be an indication of better safety practices. In developing a biological laboratory monitoring program, consideration should be given to establishing criteria and methods for collecting data necessary to evaluate the effectiveness of the program. The ability to establish program effectiveness has implications for funding sustainability.

What Are the Costs of the Program?

Any biological laboratory monitoring program will require a means for covering the costs of the program regardless of how the program is structured. If the funding is to be provided by the government, it must be sufficient to cover the startup costs of the program, and there must be some assurances of sustainable funding if the initial investment is to be protected. In determining what is sufficient funding, consideration must be given to the education and experience of the individuals who are expected to carry out the program as this will determine personnel costs. Travel costs must be considered for a program where the monitoring staff is located in a centralized location and must travel to other parts of the country for onsite inspections. Additional considerations are the number of laboratories to be monitored, how often they are monitored, and to what degree. There are administrative costs, such as information technology system development and maintenance, accounting, personnel management, and clerical support functions.

There are also costs to those who are subject to regulation by the biological laboratory monitoring program. These costs include administrative costs (eg, personnel, management, communication, record maintenance, and training) and may include facility modifications, equipment maintenance, and security enhancements. While these are not direct costs to the regulatory entity, they should be considered in determining if the biological laboratory monitoring program places an unsupportable burden on the laboratories to be regulated.

Promoting Safety and Security

The questions asked and discussed here have focused on the challenges of establishing a program of monitoring the security and safety of biological laboratories. The approach that has not been considered is providing services to laboratories that do not include any evaluation or monitoring of the laboratory's operations. FSAP has a regulatory role, but it also provides security and safety information at scientific conferences, training workshops, guidance documents, and advisory services. A country may determine that a softer approach is appropriate and create a program that offers only advisory and training services. The advisory services approach requires creating and maintaining a sustainable resource of subject matter experts. This approach can result in improved biological laboratories and can also be used as the foundation on which a regulatory program can eventually develop.

Conclusion

This article has described the challenges that countries may encounter in establishing a program to enhance the security and safety of biological laboratories in their country. Countries with an established biological laboratory monitoring program may find the discussion helpful in evaluating their programs. There are undoubtedly challenges that have not been discussed, and it is hoped that the third purpose of this article will be to encourage conversations on the challenges other countries encounter and how they are being met.

The implementation and management of an effective biological laboratory monitoring program can serve to meet the requirements of the BTWC, but it can also serve to foster a culture of biosafety and biosecurity awareness and responsibility in the laboratory community. This has public health implications because of the protection that can result for the laboratory worker and the public from exposure to agents possessed by laboratories.

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