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Abstract

Since their inception in 1996, the select agent regulations have shaped the direction of research on high-risk biological agents in the United States. Implemented in response to an increased concern about nefarious use of biological agents, the overarching aim of the regulations is to protect the public health of the United States through both security and safety infrastructure. However, while there does exist an evident need for effective regulations surrounding certain pathogens and toxins, the bureaucratic and inordinate nature of the existing regulations has created significant regulatory and financial burdens in conducting select agent research. Specifically, impediments to this research have arisen from complicated bureaucratic procedures, the impractical financial burden associated with adhering to facility standards, and confusion about research surrounding species-level designation of listed microorganisms. While intended to protect public health, the ineffectual and overly stringent nature of these regulatory policies continues to hinder essential scientific research and, in turn, may paradoxically lead to safety and security vulnerabilities now and in the future.

Keywords: Select Agent, Pathogen, Regulation, Policy, Biosecurity, Biowarfare, Bioterrorism

1. Regulating Access to Agents in Response to Domestic Threats

The necessity of regulation for certain select agents was brought to the forefront of the public's minds in 1995, when microbiologist Larry Wayne Harris successfully ordered and received a sample of *Yersinia pestis*, the causative agent of bubonic plague, from a laboratory in Rockville, Maryland. The laboratory mailed the sample to Harris under the impression that it would be delivered to the company for which he was working. However, the laboratory, growing suspicious after Harris repeatedly pestered them about the sample, ultimately alerted authorities. Harris, who had, in fact, intended to spread the *Yersinia pestis* in the New York City subway,[1] was found with three vials of the bacteria in his car's glove compartment.[2] However, due to the lack of existing laws governing high-risk biological agent possession, Harris was only charged with fraud for lying about his intended use of the pathogen.[2] This case prompted Congress to pass the Antiterrorism and Effective Death Penalty Act of 1996. The legislation required the Department of Health and Human Services (DHHS) to draft regulation of biological select agents and toxins (BSAT) deemed most capable of posing a severe threat to public health and safety.[3] In response, DHHS published the first version of the select agent regulations (SARs), which regulated the possession, use, and transfer of 47 pathogens and toxins.[4]

Public concern surrounding bioterrorism was exacerbated further in 2001, when letters containing

anthrax spores were anonymously mailed to news offices and senators just one week after the attack on the World Trade Center, killing five and infecting seventeen others. Congress was thus compelled to move swiftly to strengthen the SARs, developing a strict set of laws surrounding these agents.[5] The USA PATRIOT Act was the first Congressional response to this end, restricting access to select agents by "restricted persons". These persons are defined as those guilty of a crime punishable by imprisonment for over one year, fugitives, illegal "aliens", prior patients of mental institutions, or those who received dishonorable discharges from the United States Armed Services.[6] In accordance with the USA PATRIOT Act, institutions are required to document and submit the names of employees who require access to select agents. These individuals must then comply with a security risk assessment conducted by the attorney general to ensure they meet the criteria to possess, use, or transfer agents. Once an individual has passed the security risk assessment, they are subjected to intensive training provided by the laboratory's designated responsible official (RO) before they are granted access to the select agents. Detailed records of these trainings must be kept by the RO, including the identity of the individuals trained, the date of training, and the specific means used to verify that the individual understood the training. Even upon successful completion of this risk assessment and training, approval for an individual to work with select agents is only valid for 5 years, after which it must be renewed.[7] Furthermore, access to select agents is only valid at the specific laboratory wherein an individual is currently employed.[8]

2. Refining the Regulations

The form of the SARs as they appear today was initiated by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. This act built upon the infrastructure of the Antiterrorism and Effective Death Penalty Act of 1996, requiring the Department of Health and Human Services (DHHS) to regulate BSAT concerning human health and the U.S. Department of Agriculture (USDA) to regulate those concerning plant and animal health.[6] Under the authority of this legislation, the SARs were to be updated within one year; DHHS and USDA also published their own lists of "overlap agents" that pose risks to both human and animal health. The resultant SARs[9–11] delegated authority to regulate select agents dangerous to human and agricultural health to the Centers for Disease Control and Prevention (CDC) Division of Select Agents and Toxins (DSAT) and the Animal and Plant Health Inspection Service (APHIS), respectively.[12] These regulations are reviewed biennially, so it is the responsibility of institutions and researchers to work in accordance with the most up-to-date legislation. Failure to comply with these regulations can yield criminal penalties including fines and up to ten years of imprisonment.[8]

To ensure and track abidance, entities possessing listed select agents must legally register by applying to either the CDC or the USDA for each select agent it uses, transfers, or possesses. This registration requires the designation of an RO who must maintain extensive records about every activity involving select agents. Specifically, these ROs must provide a list of all select agents in or intended for laboratory use, possession, or transfer, detailing the specific location within buildings the select agents will be stored. In this inventory, the RO must include the characteristics, source, date of acquisition, and vial quantity of select agents, as well as an explanation for any inventory discrepancies.[7] Additionally, each laboratory must develop a safety plan in accordance with the CDC and NIH guidelines for work with recombinant DNA.[7] To this end, laboratories must implement and

document a site-specific security plan that addresses: inventory control procedures; education and experience criteria for those with access to agents; rules regarding cleaning, maintenance, and repair; provisions for training employees in security procedures; provisions for securing select agent areas; provisions for loss of means to enter to select agent areas (i.e.: keys, passwords, etc.); inspection of all packages that enter and exit the area; and protocol for select agent transfers between entities. [7]

The RO is responsible for inspecting facilities and procedures to ensure compliance with these regulations, the results of which must be documented, and any deficiencies corrected.[7] Laboratories working with select agents are also subjected to outside inspections, with 15% of select agent laboratories enduring inspections from multiple federal agencies within the same two-year period. These federal agencies include the Department of Transportation (DOT), the CDC, the APHIS, the Department of Homeland Security (DHS) and Department of Defense (DOD).[13]

3. Ramifications of the Regulations

The bureaucratic and uncompromising nature of the SARs has presented excessive and significant challenges for researchers, leading to sample destruction, abandoning of research programs on select agents, increased facility maintenance costs, and ambiguity about species-level designation of some agents. Here, we will survey accounts of each of these hurdles and review certain challenges associated with specific aspects of the SARs.

After the enactment of the SARs, in response to the strict legal and regulatory framework governing select agent research, many institutions decided to discontinue their research on these agents. While some investigators worked to save their collections by transferring them to a registered entity, when confronted with the complicated and time-consuming transport procedures, many elected to simply eliminate the samples rather than comply with the extensive process.[14] One of the logistical aspects that makes transfer especially difficult is that non-registered institutions are allotted only a short time period to transfer select agents; however, the SARs require all BSAT transfers to be approved prior to shipment, a time consuming process meant to ensure that the receiving entity and principal investigator are registered appropriately.[12] Consequently, unregistered institutions which are unwilling or unable to transfer agents continue to destroy collections of select agent isolates to date. In some of the collections destroyed thus far, there were unusual samples indicating potential new strains or species. Further, given that these are often field samples, the libraries of which are made by isolating and maintaining specimens from wild animals or infected humans, these collections can contain unique and unusual isolates -- the analysis of which can be invaluable in assessing the genetic diversity in a strain. Additionally, the historical isolates of certain microbes with rapid genetic variation can develop distinct genomics over time, the study of which is invaluable in understanding the spread and evolution of disease.[14] Thus, the potentially irretrievable loss of biodiversity from the destructions of these unique and invaluable collections will undoubtedly have an impact on scientific advancement, with the depletion of these samples likely hindering future investigations on pathogenesis and epidemiology, forensic investigations, and therapeutic development. Given the critical role of microbial collections in these endeavors, the lamentable and avoidable loss of these collections represents a potential decline in future public health security.[14] Furthermore, because of the severity of the SARs, talented researchers may be more inclined to enter fields where they will not be

faced with such cumbersome regulatory requirements, causing institutions to in turn continue to abstain from select agent research.[15] Thus, it is plausible that the SARs could potentially drive select agent research out of US academia, making US citizens vulnerable to these agents and posing a risk to public health.[6]

Institutions that have chosen to proceed with select agent research continue to endure significant regulatory burdens. The strict regulations surrounding those who can work with select agents also make it difficult for foreign nationals to work with these agents.[8] Restricting access to this demographic is intended to protect public health security. However, given that, as of a 2010 report, foreign nationals constituted 60% of postdocs employed in US federally funded research and development centers, restricting access of these agents to such a substantial proportion of researchers significantly limits the breadth of skill set and qualifications in this field.[16]

Additionally, to meet the requirements of the SARs, many laboratories must increase administrative and laboratory staffing. The costs of the security and safety installments necessary for a lab to be authorized to conduct select agent research often exceed the federal funding received by institutions to cover facility, maintenance, and operational costs.[5] As an example, two laboratories have stated that the cost to employ armed guards in accordance with the SARs is over 3 million dollars per year, a cost that composes over 10% of the operating budget for one lab, and around 25% for the other.[17] Ultimately, as a direct result of SARs, there has been an estimated 2 to 5-fold increase in the cost of researching select agents.[15] Provided regulations were less fiscally demanding, laboratories could instead use a fraction of the funds currently required for SAR compliance to advance their research.[5] Furthermore, there exists significant criticism regarding the extent to which these expensive administrative security and safety requirements actually provide genuine security. The requirement to track individual vials is particularly problematic, given that select agents are living and reproducing organisms and thus can easily be removed from a vial without a noticeable change. Consequently, this documentation does not necessarily prevent the removal of material for malicious purposes.[18] It is also more likely that a knowledgeable insider would simply take a sample from intrinsically unaccountable sources for infectious materials, such as discarded pipette tips.[17] Thus, the meticulous documentation required to account for select agent vials, while putting significant stressors on time and laboratory efficiency (one lab reports hiring 2 full-time employees solely to account for the vials), provides only "the illusion of security." [17] Additionally, the multiplicity of agencies conducting laboratory SAR compliance inspections can often lead to discrepancies in standards. The varied interpretations of inspection results make it difficult for laboratories to be compliant with these conflicting standards. Further, this abundance of inspections requires copious amounts of time, effort, and funds, detracting from what could otherwise be spent on research.[18] Thus, the overly administrative and counterproductive oversight surrounding BSATs is at the preventable expense of essential scientific progress.

Taxonomic semantics have also proven challenging for researchers, as there are instances of significant confusion surrounding what constitutes a select agent. Microorganisms that are added to the select agents list are codified by standards of taxonomy, which is a problematic approach given the uncertainty surrounding what constitutes a microbial species.[19] Consequently, the boundaries between a select agent pathogen and a similar sequence from a related species are often equivocal and unclear. For instance, criminal penalties apply to unlawful possession of biological matter "that

contains more than 85 percent of the gene sequence of the variola…virus," [6] defining the agent on the sole basis of genome sequence similarity. However, there does not yet exist a clear and objective definition of an agent based on sequence homology. Thus, the sequence homology stipulation is subjective, failing to account for differences in virulence and allowing for multiple interpretations of what is covered within this 85%. For example, many regions of the variola major and minor virus genomes are over 85% similar to sequences found in harmless naturally occurring viruses, such as the vaccinia virus. Given that the vaccinia virus is vital for research surrounding the development and production of smallpox vaccine, the problematic and arbitrary definition surrounding the variola virus could inadvertently restrict and criminalize this essential vaccine research.[20] In one case, because researchers were unsure if samples qualified as select agents, an entire collection of Newcastle disease virus was destroyed. In another, stocks of attenuated acapsular strains of *Bacillus anthracis* were lost to the ambiguity surrounding whether or not they qualified as select agents. In fact, there have been thirteen documented cases (almost undoubtedly an underestimate) wherein microbial collections were destroyed due to confusion about whether they fell within the regulatory scope of the SARs, impeding scientific advances meant to promote public health.[14]

4. Review of Recommendations Made by the Scientific Community

Ultimately, while scientists recognize the incumbent role of the SARs in addressing United States biosecurity and bioterrorism concerns, there exists an evident need to significantly reform the current regulations so that they do not unnecessarily hinder laboratory efficiency and scientific progress. We will review recommendations made by others, based on both general and specific observations from the regulations and the literature. To this end, we will focus on five topics: sample accounting, inspection standardization, transport requirements, dedicated central funding for select agent research, and nomenclature concerns.

4.1 Sample Accounting

As discussed, there are a myriad of ways that select agents can be stolen, given that only trace amounts of these replicating agents are required to grow and establish new stocks. Thus, the current time-intensive and bureaucratic procedure of "vial counting" fails to functionally inhibit this nefarious activity, instead providing only an outward appearance of security. To address the ineffective procedure of vial counting, it is the recommendation of the National Center for Biotechnology Information (NCBI) that the Federal Select Agents Program (FSAP) implements a more rational inventory system that accounts for the living and self-replicating nature of BSAT.[18] Suggestions from the scientific community in this vein include an accountability system, which rather than attempting to count the amount of select agents in a laboratory, would instead account for those who have access to the agents–documenting when and which individuals access agents, as well as their intended use with these BSATs. Accountability of the individuals working with select agents would effectively combat and reduce nefarious opportunity.[21] Although this solution still requires documentation, the implementation of this method would ensure that the valuable laboratory time dedicated towards security measures is being used efficiently and efficaciously.

4.2 Inspection Standardization

Substantial laboratory time, effort, and money is also spent reconciling the inconsistent inspection results that arise from being subjected to multiple laboratory inspections by varying agencies. This bureaucratic burden could be significantly alleviated by converging the standards and interpretations of the SARs, centralizing control and responsibility for

select agent laboratory inspections to a single agency.[18] In ensuring consistent regulations, this solution could preserve laboratory resources and efficiency without compromising the protection offered by the SARs.

4.3 Transport Requirements

Provided the implementation of effective policy promoting feasible transport of select agents, it is likely that many microbial collections destroyed because they contained (or might have contained) select agents could have been saved. Specifically, lengthening the grace period allotted to store and secure recently regulated BSATs outside of SAR approved labs would ensure that there is sufficient time for these laboratories to transfer the collections.[14] As a result of this increased time and flexibility laboratories would have in the transfer of select agents, a longer grace period would necessarily promote the likelihood of successful transfer. Laboratories could still take measures to further secure select agents on-site until a time they could transfer them, necessarily ensuring the agents remain safe from theft or tampering during this grace period. It would also be beneficial to catalogue microbial collections of agents being considered for inclusion within the SARs prior to listing, as this would allow government agencies to preemptively work to ensure the preservation of these collections.[14] These solutions, all of which could be implemented with relative ease, would be invaluable in ensuring the preservation of irreplaceable and indispensable microbial collections.

4.4 Dedicated Central Funding for Select Agent Research

The copious cost required to meet the safety and security requirements of the regulations is arguably one of the most consequential barriers to select agent research. To ensure that laboratories do not have to use their research funding to meet these regulatory demands, it is the recommendation of the National Research Council that entities conducting select agent research are granted a separate and stable federal fund to finance the security subsidization, facility upgrades, and other administrative demands of the SAR. Given the important role of central infrastructure in conducting select agent research, this added and distinct form of financial support would be imperative in ensuring that operational costs do not compete directly with scientific funding.[21] With this funding addressing the added financial burden of select agent research, which has disincentivized countless laboratories, it is likely that many more institutions would be willing to engage in this research, creating unprecedented opportunities for scientific advancement in this field.

4.5 Nomenclature Concerns

Grouping microbial strains by species in the designation of select agents can also unnecessarily hinder essential scientific research, as this method fails to consider differences in virulence within the specific strains of a species. As recommended by the NCBI, excluding strains with a lower virulence when designating select agents would facilitate innocuous research and allow investigators to carry out critical work on low-virulence strains outside of the confines of the SARs.[18] In ensuring that harmless strains are not subject to these restricting regulations, this solution would address needless administrative burdens endured by researchers while preserving the intent of the SARs.

5. Conclusion

The SARs, while intended to protect public safety against bioterrorism and biowarfare threats, have created significant barriers to scientific research conducted in the best interest of public health. Specifically, the time consuming and costly requirements have deterred countless researchers and laboratory entities from working with select agents, hindering scientific advancements in a crucial field. In working to reform administrative

regulations that do little to provide safety or security, we can ensure that scientific research meant to protect public health is necessarily robust and streamlined. Balancing the obligation for oversight surrounding BSATs while recognizing the necessity of facilitating scientific progress and freedom, reformed regulations can promote the complementary goals of scientific research and federal aims, ensuring the best outcome for the public health of our nation now and for generations to come.

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