Leveraging Advances in Biotechnology to Strengthen Biological Weapons Convention Verification Protocols

June 2022

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This paper was produced for the 2022 Next Generation for Biosecurity Competition. Visit nti.org/nextgenbio for more information.

The 2022 Next Generation for Biosecurity Competition was sponsored by the Nuclear Threat Initiative, the Next Generation for Global Health Security Network, the iGEM Foundation, SynBio Africa, and the Global Health Security Network.

The authors wish to thank the following experts for taking the time to contribute to insightful discussions and provide thoughtful comments over the course of our research—

Dr. Antony Schwartz, PhD. Director of the Biological Safety Division for Duke University's Select Agent Program; formerly ran the U.S. National BSL4 Training Center's BSL4 laboratories.
Dr. Lalitha Sundaram, PhD. Research Associate at Cambridge University's Center for the Study of Existential Risk.
Ms. Lane Warmbrod, MS, MPH. Senior Analyst at the Johns Hopkins Center for Health Security.

The views expressed in this publication are those of the authors alone, and do not necessarily reflect those of the sponsoring organizations, members of their Board of Directors or institutions with which they are associated, or any external experts involved with judging the competition.

Executive Summary

In the wake of the Biological and Toxin Weapons Convention (BWC)'s 50th anniversary, growing geopolitical tensions and global vulnerability to biological threats heighten the risk of continuing without mechanisms to maintain and assess States Parties' compliance. Though increasingly powerful and accessible biotechnologies increase the risks posed by biological weapons, they can also be harnessed to strengthen BWC verification mechanisms.

No single verification mechanism will serve to completely foster trust or transparency, let alone assess compliance or hinder the development of bioweapons. However, we argue that an incremental, multi-layered verification mechanism could raise the activation energy required for State and non-State actors to violate BWC obligations clandestinely. Following our review of primary literature regarding emerging technologies, case studies and former verification proposals, and interviews with leading experts in biosecurity and biotechnology, we make three key recommendations:

(i) Implementation of machine learning to detect anomalies in purchasing of nucleic acid sequences and therapeutics such as antivirals
(ii) Use of portable next-generation sequencers and multiplex immunoassays for sampling declared facilities with dual-use capabilities
(iii) Use of community wastewater surveillance for biological threat agent detection

By simultaneously targeting several aspects of bioweapons development, this approach increases the likelihood of non-compliance detection. The three applications of modern biotechnologies to strategically monitor BWC compliance should be accompanied by bolstering existing confidence building measure reporting requirements and the implementation of routine, non-challenge visits to declared biological sites. We recommend these approaches are coordinated by a newly established independent agency composed of experts in relevant scientific, technological, legal and security domains, which would be responsible for coordinating and implementing verification mechanisms, in addition to identifying potential breaches of BWC obligations.

Background

The BWC is an international treaty that aims to effectively prohibit the development, production, stockpiling, and use of bioweapons.[1] Definition of the term "verification" varies widely in its context, though it broadly refers to the process of ensuring States Parties are compliant.

The BWC is unique in its lack of a verification system relative to other disarmament and nonproliferation treaties. The most significant progress toward a verification regime involved the formation of a group of "verification experts", VEREX, who were tasked with evaluating verification measures and the degree of confidence each measure would provide on whether States Parties were compliant with the treaty. Based on the VEREX report, a special conference of BWC States Parties

assembled an Ad-Hoc Group (AHG) to draft a legally-binding and comprehensive verification regime.[2] Negotiations collapsed in 2001 following US withdrawal due to intellectual property concerns and perceived difficulties with verifying compliance.[3] Subsequent verification efforts have been futile.[4] In 2019, a Meeting of Experts revealed some Parties wished to resume AHG protocol negotiations, whilst several countries had "no desire to do so".[5]

Several technical barriers have impeded verification negotiations. The dual-use potential of biological agents and research facilities makes distinguishing offensive and defensive research difficult; experiments involving biological threat agents can be central to legitimate defensive research, and novel biotechnologies can be misappropriated to engineer more virulent pathogens. Small volumes of biological agents can be sufficient for bioweapon use but are difficult to detect. Furthermore, pathogens' self-replicating nature means they can be rapidly scaled, making them poorly suited to material accountancy. Finally, laboratory decontamination procedures facilitate concealment.

Going forward, we define verification as a series of continuous measures designed to maintain and assess States Parties' compliance with BWC Articles, particularly the non-proliferation Articles. We argue the value of verification is fourfold: it serves to (i) foster trust by increasing transparency and confidence; (ii) incrementally build norms and progress without a comprehensive, legally binding regime; (iii) allow countries to credibly deny culpability following significant biological events; and (iv) deter "by denial"[1], as well as by making it harder to conceal prohibited activities.

We recommend multi-layered verification mechanisms that leverage modern biotechnologies to inform passive and active monitoring (Figure 1). These mechanisms—in addition to bolstering existing confidence building measure (CBM) reporting requirements and routine, non-challenge visits—improve our ability to maintain and assess States Parties' compliance. An overview of these mechanisms follows:

- **Increase compliance with CBM and Declaration reporting requirements** by providing funding to strengthen countries' biosecurity capacities to facilitate reporting; limiting non-reporting countries' access to compliant countries' CBM and Declaration information; or escalating to revoke veto ability for countries failing to meet reporting requirements.
- **Expand screening of nucleic acid synthesis orders** for potentially dangerous pathogens.
- **Leverage machine learning to screen transactions and purchases** of compounds like antivirals.
- **Implement routine, non-challenge visits** to potential dual-use facilities identified in countries' CBM reports (frequency and location determined randomly). These should be led by core experts in virology, synthetic biology, biosecurity, HVAC systems, bioweapons, etc., and experts tailored to the facilities' research.
- **Sample "high-value" areas in facilities** using next generation sequencing and multiplex immunoassay tools.

[1] Deterrence by denial refers to strategies which "seek to deter an action by making it infeasible or unlikely to succeed, thus denying potential actors' confidence in satisfying their objectives" (i.e., deterring the use of biological weapons by emphasizing state's capacity to defend against, and respond to, such acts).

- **Establish community wastewater surveillance** to monitor biological threat agents.
- **Install an independent, international organization** to implement the mechanisms described incrementally

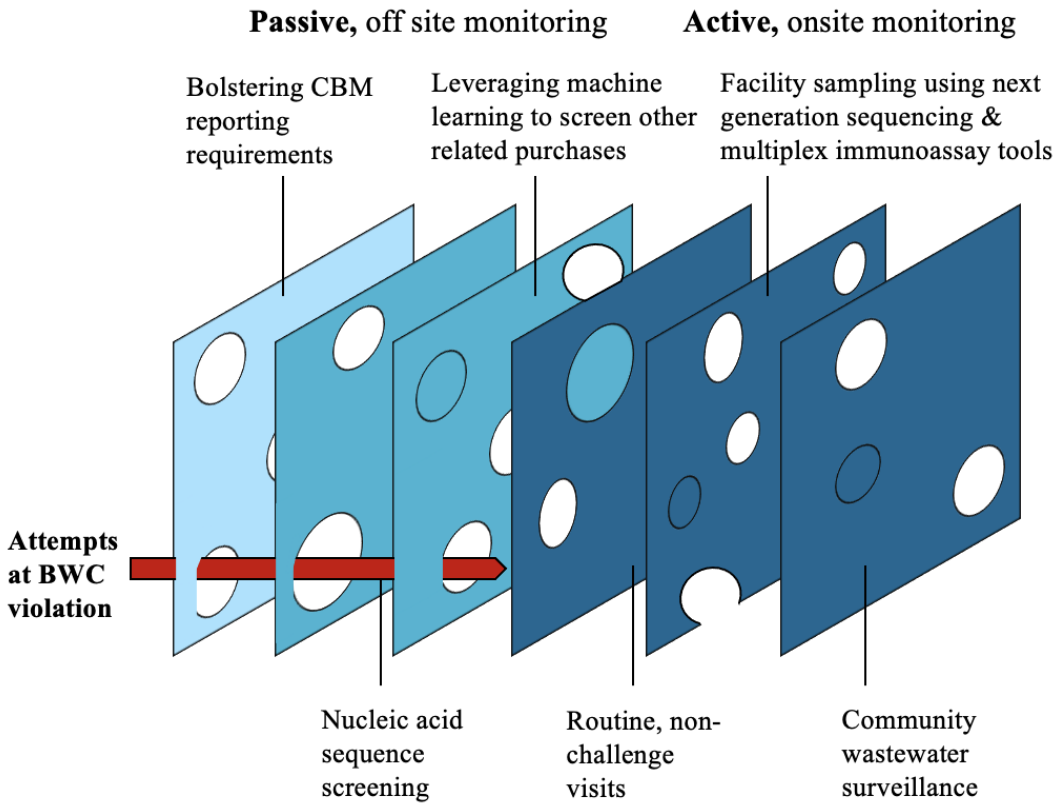

Figure 1: Schematic depicting the multi-layered approach recommended to assess BWC compliance and hinder development of bioweapons. Visualization adapted from Mackay, Ian M "The Swiss Cheese Respiratory Virus Defense." Virology Down Under, 26 Dec. 2020, https://virologydownunder.com/wpcontent/uploads/2020/12/SwissCheese-Respiratory-Virus Interventions-ver4.0.png#main.

Disturbing trends in global biosecurity, biotechnology and geopolitical landscapes contribute to the increased risk of bioweapons development and use. The 2021 Global Health Security (GHS) Index found 92% of countries score below 50/100 for biosecurity, with only 10% of countries demonstrating a record of facilities storing or processing dangerous pathogens and their inventory.[6] Similarly, less than 50% of Statess Parties on average submit CBMs annually[7], with submissions often inconsistent or incomplete (Figure 2).[8]

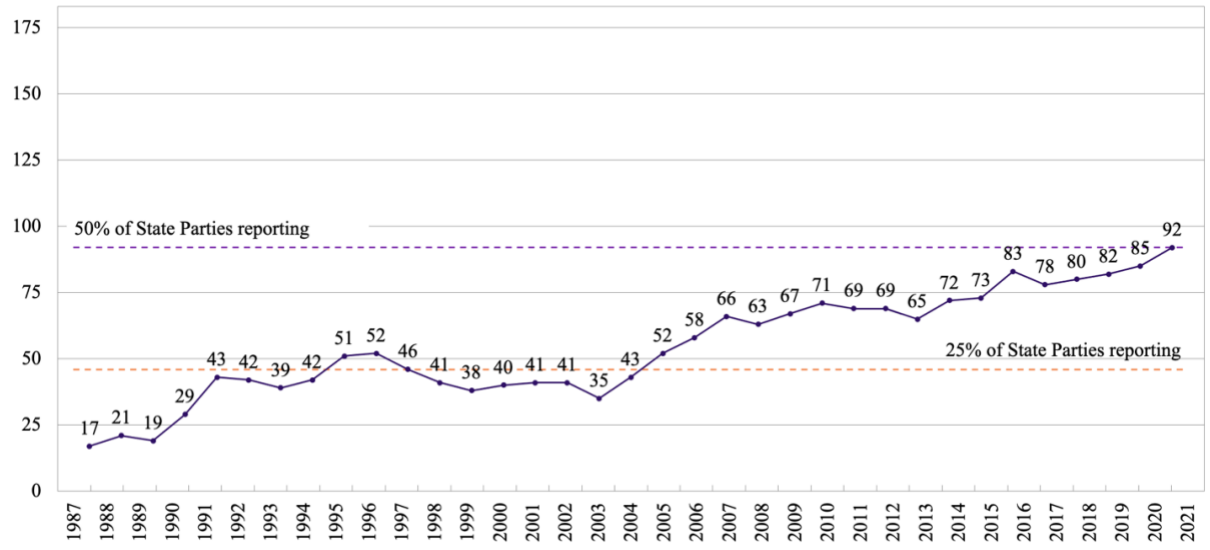

Figure 2: Confidence Building Measures (CBM) report submissions by year. As of 2022, the BWC has 183 States Parties.

Growing geopolitical tensions also threaten norms and increase bioweapons risk. In 2021, 52 countries were estimated to have a high or very high threat of "international tensions with negative repercussions"—including all countries accused of historical BWC violations (Table 1).[9] Such risks are further exacerbated by recent international conflicts.

Global trends in these areas are compounded by risks associated with emerging technologies: increasingly powerful—and accessible—biotechnologies enable State-led bioweapons development and use and lower the barrier to entry for non-State actors.

Table 1: Trends within political and security risk indicators for countries historically accused of violating the Biological Weapons Convention (BWC) compared to the global average as measured by the 2021 Global Health Security Index. Red indicates a greater political and security risk relative to the global average. (Source: 2021 GHS Index)

Country	**Political and security risk score** (100.0 = best conditions, lowest risk)	**Likelihood of international conflict with significant repercussions**	**Likelihood of perpetuating human rights infringement**	**Likelihood of domestic or foreign terrorist attacks with high disruption**
Iran	32.3	Very high	Very high	High
Iraq	9.1	Very high	Very high	Very high
Libya	9.0	Very high	Very high	Very high
North Korea	35.4	Very high	Very high	Low
Russia	22.2	Very high	High	Low
Sudan	9.0	Very high	Very high	Moderate
Syria	0.3	Very high	Very high	Very high
United States	69.1	Moderate	Low	Moderate
Global average	58.1	Moderate	High	Low

Worst conditions	Poor conditions	Moderate conditions	Good conditions	Best conditions

These trends are especially salient given all countries are ill-equipped to detect and respond to biological threats, irrespective of income (Table 2)[10]—further emphasized by the COVID-19 pandemic. These trends, and a global lack of preparedness for biological threats, make strengthening BWC verification critical.

Table 2: Trends in global health security capacities for countries stratified by income classification and region as measured by the 2021 Global Health Security Index. Each category is scored from 0-100, where 100 reflects an optimal health security environment. (Source: 2021 GHS Index)

Country Group	Overall 2021 GHS Index Score	Biosecurity Capacity	Prevention Capacity	Detection Capacity	Response Capacity
Global Average	38.9	18.7	28.4	32.3	37.6
Income classification					
Low	26.4	3.6	14.0	21.0	27.1
Low-middle	32.5	8.6	20.0	26.6	32.2
Upper-middle	39.2	19.2	29.7	32.7	38.8
High	50.2	34.2	41.7	42.2	46.2
Region					
East Asia and Pacific	37.6	14.0	24.0	33.9	39.5
Europe and Central Asia	50.8	41.7	45.4	42.3	43.8
Latin America and Caribbean	37.7	12.1	27.4	28.1	38.8
Middle East and North Africa	33.6	8.8	24.9	26.3	33.3
North America	72.9	88.0	74.9	75.5	57.5
South Asia	34.7	11.5	22.8	31.9	29.7
Sub-Saharan Africa	29.2	3.8	14.3	23.8	31.0

Discussion

No single verification mechanism is sufficient to increase trust or transparency, let alone assess compliance or hinder the development of bioweapons. However, a combination of several mechanisms increases the likelihood of these outcomes in addition to increasing both the risk of detection and activation energy required for States Parties to clandestinely violate their obligations. Therefore, we favor a model composed of several mechanisms—each of which targets different phases in the development of biological weapons, originally described by Frinking et al. (Figure 3). We firmly believe that making progress via an incremental approach that effectively utilizes international cooperation is superior to continuing to endure stagnated negotiations of a comprehensive, legally binding verification protocol.

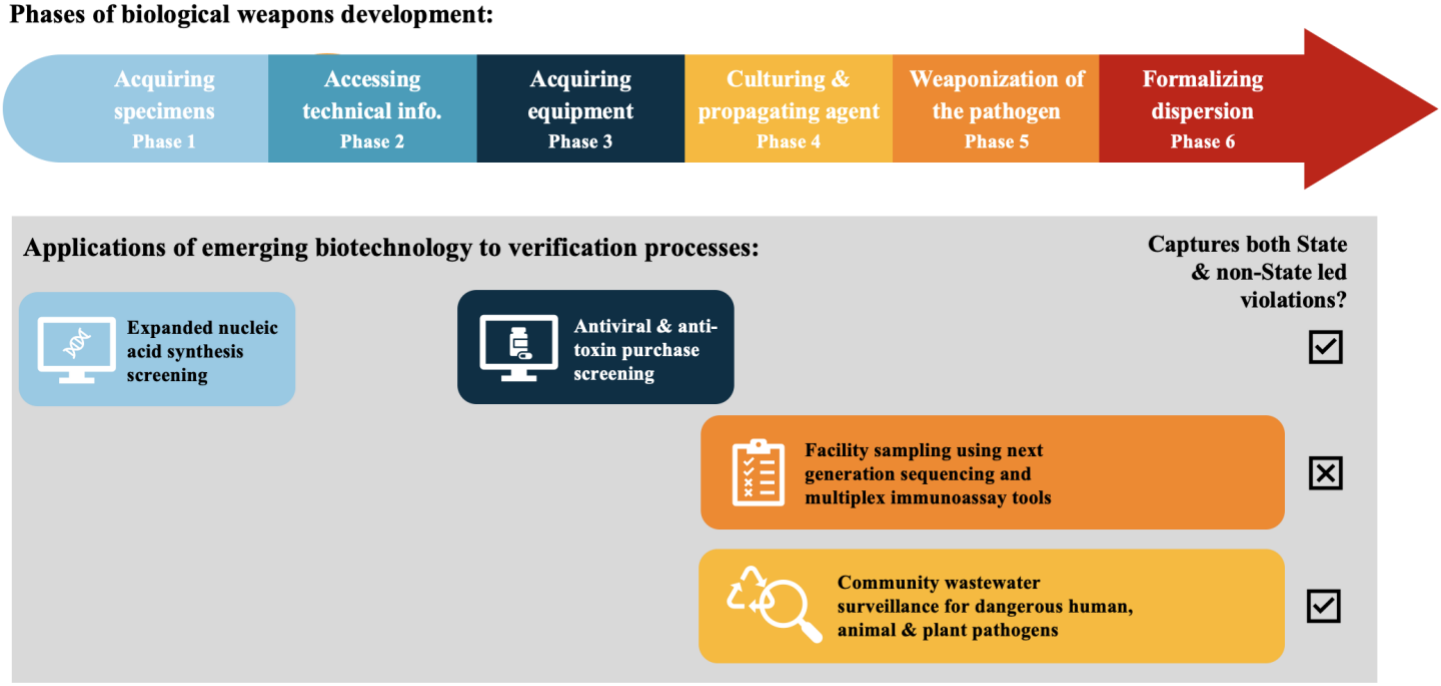

Figure 3: The general stages of biological weapons development and the applications of emerging biotechnologies to verification at each stage. Stages adapted from Frinking, Erik et al. "The Increasing Threat of Biological Weapons: Handle with Sufficient and Proportionate Care." The Hague Centre for Strategic Studies, 2016, p. 8.

Implementation of machine learning to detect anomalies in laboratory purchasing and activity

One barrier to BWC enforcement is that illegitimate biological agent research can require purchasing the same pathogens and therapeutics as legitimate research. Determining legitimacy, therefore, requires simultaneous analysis of numerous variables. Advances in artificial intelligence can help unravel these complex problems using machine learning (ML) technology. ML uses inputted sample/data to build a model that can make predictions or classifications.[11] We propose using ML to identify purchases that may be for illegitimate purposes.

Advances in synthetic biology have afforded manipulation of existing pathogens and even generation of pathogens directly in laboratories.[12] In response, synthetic biology companies have implemented safeguards, including screening orders for sequence homology to regulated pathogens.[13] However, screening against regulated pathogens means detecting only those currently defined as pathogenic and those we have previously encountered. To close this gap, we propose an expanded screening process using ML to evaluate whether ordered sequences could be related to biological agents predicted to threaten human, animal, or plant health. Such algorithms are used in several contexts, including predicting host tropism[14], transmission potential[15], or host adaptation[16] based on genome sequence alone. The proposed expanded screening process will look for pathogen signatures beyond standard homology, which includes codon usage, elements with predicted relevant secondary structure (e.g., IRES), etc.

Building on the success of basic screening of synthetic DNA orders, we propose using ML to monitor purchases of therapeutics from pharmaceutical companies. These algorithms could cross-reference purchases to methods sections of published works or declared research. For example, this could flag a laboratory performing legitimate research on influenza that purchases diphtheria antitoxin. Although ML will miss some illegitimate purchases, there is utility in establishing a baseline of normal laboratory purchases to identify irregularities and inform future models.

To establish these algorithms, models will be trained to flag purchases of therapeutics related to pathogens (non-standard antibiotics, antitoxins, and antivirals) using databases of pharmaceutical purchase orders. Information related to the purchase, such as delivery address, payment information, and customer identification should be used to scan public databases of primary literature and funding reports (e.g., NIH RePORTER) for terms related to legitimate use of such purchases. Flagged purchasers with no identifiable related work should be contacted by private companies to verify orders are for legitimate purchases. Implementation of this process will require significant cooperation from private companies. However, policies that hold private companies accountable for the distribution of these compounds could be enacted – and would ensure that the prevention of pharmaceutical acquisition by bad actors would be in the company's best interest.

Notably, ML algorithms identifying dangerous sequences or purchases have dual-use potential. To prevent potentially highlighting dangerous information to bad actors, these algorithms could remain "black-boxed".[2]

Use of portable next-generation sequencers and multiplex immunoassays for sampling declared facilities

A barrier to verification of BWC compliance is that bioweapons can be easily hidden within research facilities. Not only would it be impossible to sample every stock during an inspection, but until recently there were no methods to validate the legitimacy of biological specimens quickly, easily, reliably, and specifically. Additionally, handling BSL3/4 pathogens requires adherence to strict biosafety protocols, meaning sampling equipment cannot be brought into labs without undergoing time-consuming decontamination processes to remove the sampling equipment.

Advances in the speed, sensitivity, and cost of next generation sequencing (NGS) have enabled detection of genetic material for any pathogen.[17] Unlike PCR or qRT-PCR, which amplify a specific identifying sequence that could be mutated to prevent identification, NGS can determine the sequence of millions of pieces of nucleic acid at once. Importantly, these sequences can be assembled to generate the full genome of a pathogen, which could indicate whether a pathogen was engineered to enhance its virulence (e.g., addition of a polybasic cleavage site to "low" pathogenic avian influenza strains, rendering them highly pathogenic). Nanopore's MinION sequencer can sequence inputs as low as one molecule of DNA or RNA directly (no preamplification or cDNA library generation required), fits in a backpack, and provides real-time sequencing results.[18, 19,20] States Parties may be more amenable to sampling

[2] Black-boxing refers to the ability to see both inputs and outputs whilst limiting the ability to see the internal workings—this can be achieved through implementation of user interface restrictions.

if sample preparation and sequencing is observable and performed on-site by inspectors, rather than sending samples for analysis off-site. Furthermore, sequencing data could be erased upon inspection completion to protect intellectual property.

Toxin-derived bioweapons cannot be detected using NGS as they lack nucleic acids. However, improvements to immunological assay sensitivity, including ELISAs and lateral flow rapid strip tests, have yielded several multiplexed tests that can be performed, analyzed, and, importantly, disposed of directly in BSL3/4 laboratories.[21, 22]

A significant complication with sampling, regardless of technological advances, is that there are practical limitations regarding sampling volume and what could reasonably be expected to contain pathogen signatures, given the constant surface decontamination during routine lab work—and potential efforts to obscure bioweapons development.[23] However, we believe active sampling of the following three locations during inspections may circumvent these issues: (i) HEPA filters in biological safety cabinets (BSCs) and building air systems, (ii) biohazard waste (not yet autoclaved), and (iii) animal feces. A range of microorganisms are recoverable for days to months following aerosolization experiments in BSCs under normal operating conditions.[24] Furthermore, the absence of specimens in HEPA filters, for example, could be interpreted as a red flag itself, as it could suggest extensive cleaning prior to inspection.

Use of community wastewater surveillance for biological threat agent detection

Wastewater surveillance is an established method of biological and chemical agent detection previously used to detect polio outbreaks, levels of drug use, and community transmission of SARS-CoV-2 variants.[25] Current approaches require sampling wastewater from sewage systems and applying nucleic acid detection methods, such as RT-qPCR, to detect specific pathogens.[26] Given its previous uses—and interest from policymakers following COVID-19 applications[27]— we propose leveraging this technology as a verification mechanism by detecting community infections caused by accidental or deliberate bioweapon release. Specially, this approach would focus on sampling community sewage and agricultural run-off. This would allow wastewater surveillance to serve as an early warning system for accidental or deliberate release of bioweapons that threaten human, animal, or plant health.[28, 29, 30]

Extensive decontamination procedures and clean-in-place waste removal systems make it difficult to detect the presence of biological agents using wastewater surveillance within research environments. As an alternative, our proposal applies multiplex nucleic acid detection to community wastewater that focuses on Select Agents[31], with particular emphasis on agents unexpected in each area. While this mechanism does not hinder bioweapons development, it confers value by: (i) providing scientific evidence of potential BWC violation and (ii) serving as an attractive, low-cost early warning system—particularly valuable when over 100 countries have little to no zoonotic disease surveillance capabilities.[32]

Implementation of BWC verification mechanisms

We propose an independent, international organization be responsible for

implementing and executing BWC verification mechanisms. Such an entity should be:

(i) composed of—or partnered with—non-governmental experts across relevant scientific, security, technological, legal, and public health communities
(ii) free to engage with a range of industry, academia, and government stakeholders and
(iii) designed to work closely with relevant groups within the United Nations system, including the BWC.

These characteristics are embodied by a recent proposal for an International Biosecurity and Biosafety Initiative for Science (IBBIS)[33]—which aims to promote stronger norms and develop governance tools that mitigate risks posed by emerging biotechnologies. The proposal recommends IBBIS manage an international Common Mechanism[34] for nucleic acid synthesis screening. Their remit could be expanded to include the mechanisms we propose if initial implementation is successful. Outsourcing these responsibilities circumvents the BWC's current lack of authority and capacity to conduct monitoring activities. The establishment of an agency to facilitate verification was recently found to have widespread support amongst States Parties and key stakeholders.[35]

To facilitate the implementation of the described verification mechanisms, we recommend related policies are drafted by the independent, international organization and carried out in a stepwise fashion. An incremental adoption, starting with passive monitoring and working up to active monitoring, will serve to build trust and confidence in both the independent organization and the verification mechanisms. Importantly, implementation of these mechanisms should go hand-in-hand with providing lower- and middle-income countries the assistance and support required to help them build and sustain their own biotechnology and public health programs.

Limitations

This proposal is subject to several limitations. List-based approaches to identifying potentially dangerous pathogens, such as wastewater surveillance, by definition, capture a limited number of known pathogens. A wide variety of human and animal pathogens pose a threat to health security: beyond what is captured by the Select Agent list. Moreover, this approach does not account for novel pathogens, including those that may be engineered.[36]

Mechanisms such as bolstering CBM reporting and conducting routine, non-challenge visits to potential dual-use facilities are focused on identifying State-led (as opposed to non-State actor) bioweapons violations. This shortcoming may be particularly concerning given increasing accessibility of powerful biotechnologies and a growing "DIY-bio" movement that encourages amateur scientists to conduct experiments outside of regulated scientific institutions.[37]

Finally, caution ought to be taken where verification mechanisms that serve national security or surveillance purposes overlap with public health functions (e.g., the ability of wastewater surveillance to serve as an early warning system for accidental or deliberate bioweapon dispersion, or naturally occurring pandemics). Trust in public health and government underlie successful responses to biological health threats and must be preserved.[38]

Conclusion

We advocate for multi-layered verification mechanisms that use biotechnology to facilitate both passive and active monitoring. We recommend using ML to monitor laboratory-related purchases, in combination with NGS, improved immunoassays, and multiplex nucleic acid detection techniques to sample both in and around declared dual-use facilities to verify BWC compliance. Despite limitations, we provide a reasonable approach that increases the activation energy required of both State and non-State actors to develop or use bioweapons clandestinely.

Since the collapse of VEREX negotiations, a multitude of practical barriers have rendered efforts to establish verification mechanisms unsuccessful. Firstly, differentiating between offensive and defensive biological weapons research is extremely difficult. Furthermore, the ability of pathogens to self-replicate negates the necessity of maintaining large stocks, making them easier to conceal and more difficult to inventory. However, advances in the sensitivity of molecular and immunoassays renders pathogen detection easier. Advances in technology portability facilitate more manageable facility sampling, and "in-house" sequencing safeguards intellectual property.

Additionally, States Parties have not previously felt it was in their best interest to participate in verification mechanisms. However, full participation in these mechanisms could provide plausible deniability for culpability should any unexpected outbreak occur; allowing them to avoid the intense scrutiny that China (particularly, The Wuhan Institute of Virology) has faced over SARS-CoV-2 origins.

Finally, it is crucial that discussions—and incremental implementation—of proposed verification mechanisms occur in parallel with (not as a substitute for) discussions regarding a comprehensive, legally binding verification protocol. Though historical discussions of verification have been fraught, the April 2022 Preparatory Committee meeting highlighted some States Parties continue to suggest addition of a legally binding verification system would strengthen the Convention[39], indicating the upcoming 9th Annual Review Conference and subsequent intersessional processes should be embraced as opportunities to discuss issues of verification.

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