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Biosecurity risks and governance in the age of synthetic biology

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HIGHLIGHTS

- Recent advances in synthetic biology have dramatically changed the biosecurity landscape in terms of potential agents and parties involved
- Biological threat attribution technology is developing and has seen relative success, but is limited by its enforceability
- International efforts have provided a source of threat mitigation, but gaps in compliance verification along with the rapid pace of technological development, pose ongoing issues to these agreements

The COVID-19 pandemic demonstrated the susceptibility of the United States and the world to biological threats. These threats can be unintentional, such as the result of zoonotic spillover or laboratory accidents, or deliberate, such as the release of a pathogen intended to be used as a biological weapon (or, bioweapons). While unintentional outbreaks are difficult to prevent, much effort has been spent to prevent the spread and use of bioweapons in the modern era. However, advances in technology threaten to outpace efforts to control bioweapon proliferation. This article reviews the changing nature of bioweapons, the governance structures established to prevent their spread, and the advances in technology that could deter and mitigate their use.

According to the World Health Organization, bioweapons are defined as microorganisms (e.g. virus, bacteria, fungi, or other toxins) that are created and released deliberately to cause disease and death in humans, animals, or plants [1]. Throughout history, states and organizations attempted the use of pathogenic organisms as a means of achieving military ends. Prominent examples include the deliberate deployment of smallpox containing blankets to Native American populations or the use of a wide number of biological agents by Imperial Japan during the Second World War. A more recent example is the use of anthrax by terrorist groups and individuals, such as Amerithrax in the United States (U.S.) and unsucessfully by Aum Shimrikyo in Tokyo [2].

The national and global responses to bioweapons threats were primarily driven as responses to known threats, including agents previously developed as biological weapons (e.g. smallpox). In the U.S., efforts to regulate pathogens that could be used as bioweapons led to the creation of the Federal Select Agents Program, administered by the Centers for Disease Control and Prevention and the U.S. Department of Agriculture [3]. This program regulates the use of a defined list of animal and plant pathogens, which have the potential to pose a severe threat to public, animal, or plant health [4]. The Federal Select Agents Program is designed to regulate the use and distribution of high consequence pathogens, with a particular focus on preventing their distribution outside of authorized users.

The identification of specific pathogens that may be used as bioweapons also defines the effort of the U.S. to generate medical countermeasures (MCMs). The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) is primarily responsible for developing, commercializing, and stockpiling MCMs against biological agents deemed to be biological threats [5]. The PHEMCE process led to the stockpiling of non-pharmaceutical countermeasures, such as respirators, that could be used in the event of bioweapons use, as well as specific pharmaceutical countermeasures, such as anthrax vaccines, that could be deployed following the deliberate use of a specific pathogen.

Both the Federal Select Agents Program and PHEMCE focus on known threats, limiting access to specific pathogens or developing countermeasures against Department of Homeland Security-classified threats, respectively. For example, while SARS-CoV is recognized as a Select Agent, SARS-CoV-2 currently is not, despite fitting the traditional criteria for a Select Agent. Likewise, the Federal Select

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Agents Program's focus on specific pathogens allows research on related pathogens, limiting the effectiveness of the regulations [6]. For example, while research on smallpox is almost completely prohibited (only two sites in the world are allowed to store smallpox samples), similar research on related viruses (e.g. horsepox or monkeypox) is not. This allows for research on related viruses, generating knowledge that may be applicable to a regulated pathogen. As an example, the development of methods to synthesize the horsepox genome could create the know-how necessary to synthesize the smallpox genome [7]. This is a gap in the regulation of potential bioweapons threats.

Likewise, the PHEMCE focus on threat-based MCM development does not necessarily prepare the U.S. government to respond to yet unknown or evolving bioweapons threats. Despite a history of developing and purchasing countermeasures for threats such as anthrax, the PHEMCE was largely sidelined during the response to SARS-CoV-2, as it was not prepared to develop a novel vaccine rapidly [5]. However, advances in vaccine and therapeutic technology offer the potential to better respond to unknown bioweapons threats by enabling rapidly adaptable countermeasures. This is particularly important with the advent of synthetic biology (SynBio), a scientific discipline that seeks to design and engineer biological systems, and which has the potential to both facilitate the development of new MCMs and alter the traditional biothreat landscape [8, 9].

Synthetic biology

In recent years, the convergence of advances in fields such as genetics, molecular biology, chemistry, and computer science has led to the development of an arsenal of highly efficient SynBio tools, opening a myriad of applications in medicine and agriculture. However, these biotechnological advances have also facilitated the precise manipulation of potentially harmful organisms by state and non-state actors, thereby altering the conventional biothreat landscape both in terms of agents and parties involved.

For example, early progress in recombinant DNA technology enabled the manipulation of DNA segments to modify genes and edit organisms [10]. In 2012, two controversial studies showed that genetic modifications of avian influenza could make the virus more transmissible, demonstrating that genome editing approaches can be used to modify the pathogenicity of known pathogens [11]–[13]. Additionally, the discovery and development of clustered regularly interspaced short palindromic repeats (CRISPR) into a powerful biotechnological tool have been a critical breakthrough for precise genome manipulation [14, 15]. Today, CRISPR technology allows the deletion or insertion of virtually any DNA sequence inside an organism of interest with high efficiency and simplicity. Low-cost and easy-to-use CRISPR kits are now commercially available to any consumer in the U.S., significantly lowering the bar for modifying biological agents outside of traditional laboratory settings [16].

Moreover, owing to the development of next-generation sequencing (NGS) technologies, we are now able to "read" the genetic information of virtually any organism, including novel biological agents. The techniques, chemistries, and instruments used for NGS have rapidly improved, greatly increasing their throughput and driving down the costs [17]. These advances have facilitated the adoption of NGS technologies by numerous laboratories around the world, creating vast amounts of genomic data readily-available for systematic exploration [18]. Using publicly-available data, a recent study leveraged cloud computing resources to identify over 100,000 novel RNA viruses, highlighting the accessibility and scale at which novel pathogens can be discovered [19].

These recent advances in genome editing and sequencing have been followed by novel improvements to DNA synthesis. State-of-the-art methods for nucleic acid synthesis have enabled the synthesis of large pieces of custom DNA sequences, allowing the assembly of genes or even entire viruses [20, 21]. Under high-containment laboratory conditions, scientists have recreated previously extinct pathogens (e.g., horsepox and 1918 pandemic influenza) from commercial DNA fragments, demonstrating the possibility of recreating any virus from genomic information alone [7, 22].

Even though several technical barriers remain, the growing simplicity and availability of SynBio tools coupled with increased access to genomic information have lowered the cost, time, equipment, and education needed to engineer organisms, thereby increasing the likelihood of an accidental or intentional release of biothreats [23].

Attribution of bioweapons threats

Biotech's barrier to entry has lowered not only for lab environments, but for the public as well—and with it has come the rise in the potential for serious biological threat events to occur. However, the ability to attribute biological threat events to the actor or actors that instigated them may help to deter an increase in bioterrorism [24].

When attempting to attribute threat events to a plausible cause, there are roughly three classifications of evidence that can help to inform a conclusion: contextual clues, such as the victim or location of the event; intelligence, like whistleblowers or other informants; and technical forensics, in which the characteristics of the event may be scientifically analyzed to determine a likely causative agent [24]. For biological threats, the former two classes are comparable to any other threat attribution; however, advances in technical forensics have begun to allow biological threat events to be tracked back to approximate labs of origin.

Early attempts at this tracking process paralleled how one might identify a famous author—rarely is it an individual, standout phrase that gives it away, so much as a collection of little, stylistic choices that collectively constitute the author's writing style. It may not be evident in specific parts, but it shines through the article as a whole. In similar fashion, recent attempts at DNA attribution to research lab-of-origin have looked for both minor stylistic choices within the DNA's construction—the use of a specific backbone or genetic part

instead of the several thousand others that perform the same task—as well as larger side effects of the DNA's function in live cells. Scientists have trained machine learning algorithms to pick up on these subtleties, and identify a probable lab of origin—the most recent algorithm to this end has seen up to a 70% attribution accuracy rate in distinguishing amongst 1300 different labs, and an 84% accuracy in identifying the nation of origin [25, 26]. Provided a DNA sequence, then, this technology has the potential to assist in lending context to the scene of a biological incident.

However, this is not to say that biotechnological forensics are always critical in threat attribution—there are many instances in which this sort of advanced technology is unnecessary to diagnose a situation accurately. For example, Foot-and-mouth disease (FMD) is a highly contagious virally-transmitted disease which infects common livestock like cows, pigs, or sheep. While not highly lethal, FMD is still a biological threat by way of its effect on the economic value of the infected animals [27]. So, when a breakout was identified in 2007 in Pirbright, England, attribution of this biothreat event became immensely helpful to determine that this was not the result of a malicious actor. Fortunately, this was the case: various contextual clues led investigators to identify that a nearby viral research lab had leaked the causative virus into the nearby drainage system [27]. Thus while the aforementioned algorithms may have been useful in this investigation, they were by no means necessary for attribution.

That said, the act of simply having this advanced attribution technology may help to deter malicious agents from placing serious consideration into bioweaponry. While biological weapons are formally outlawed at the international level, it may be difficult to enforce these rulings over non-state agents. However, having a firm, explicit stance regarding how to track and punish wielders of bioweaponry—in the form of an international framework for bioweapon attribution—is a necessary first step that can potentially integrate with existing international efforts.

Global governance of biological threats

As a means for controlling the development and deployment of biological weapons, international efforts that formulate a mutually agreed upon set of restrictions have great potential. The modern era of international restrictions on biological weapons use largely begins with the Geneva Protocol, which was signed by 38 states in June 1925 and entered into effect in February 1928. In particular, the text of this treaty sought that member states agree to ban the use of chemical and biological agents in war [28]. In practice, the Protocol became viewed as direct opposition to the offensive use, but not the development and stockpiling, of these biological weapons in preparation for potential retaliatory attacks [29]. As a result, the U.S., the United Kingdom (U.K.), the Union of Soviet Socialist Republics (U.S.S.R.), and others, sought to begin or continue such development programs even in the aftermath of the Protocol's introduction [29].

While the Geneva Protocol was credited for the absence of chemical and biological agent deployment on the battlefields of Europe throughout the Second World War, it did not prevent the use of chemical and biological weapons in other contexts in the intervening years [30]. Of note, though they had not signed on to the treaty, Japanese military's infamous Unit 731 was noted to extensively use biological agents such as *Vibrio cholerae* (cholera) and *Yersina pestis* (plague) during the Second World War against China. Further, the Mussolini regime in Italy was found to deploy chemical weapons in their invasion of Ethiopia between 1935-1937, though they had been an original signatory of the Geneva Protocol [29, 31].

International efforts to address the development and production of biological weapons gained little traction until the early 1970s. Starting as a series of discussions and negotiations in the United Nations (UN) in 1969 to further address biological weapon proliferation, the Biological Weapons Convention (BWC) emerged as an answer to the perceived gaps in the Geneva Protocol. Among other terms, the 15 articles included in the BWC bind joined states to not develop or stockpile biological weapons, including destroying any previously produced agents that can be used as toxins and weapons [32]. Further, the BWC provided for a means of addressing future breaches through mechanisms of the UN, and also provided for a review conference of the BWC to be held every five years.

The treaty, initially deposited jointly by the U.S., U.S.S.R., and the U.K., gained the ratification of 22 states in total at the time it went into effect in March 1975 [33]. As of the writing of this review, 183 states have ratified or acceded to the BWC [32] (Fig. 1).

Though viewed as a clear improvement to the Geneva Protocol in terms of preventing the development and proliferation of biological weapons, skeptics of the BWC's true usefulness and power have identified weaknesses that continue to pervade today. The two main concerns of the BWC are its (1) absence of delineated and enforced verification steps to ensure member states are adhering to the BWC's articles and (2) relevance in the face of rapidly evolving technologies.

The absence of verification and implementation have been considered as major weaknesses to the BWC since its ratification. Verification measures describe procedures that allow for the confirmation of adherence to an agreement, such as through inspections [36]. Though not defined within the text of the BWC, efforts to address verification have been attempted. The Third Review Conference of the BWC, held in 1993, saw the formation of a multilateral group of government officials charged with identifying and examining options for verification measures, as well as their scientific and technical feasibility [37]. In the group's final report, 21 potential options for verification measures were laid out, including remote sensing (such as through satellites) and surveillance of publications and legislation [37]. While there is general support for verification measures, none have been enacted

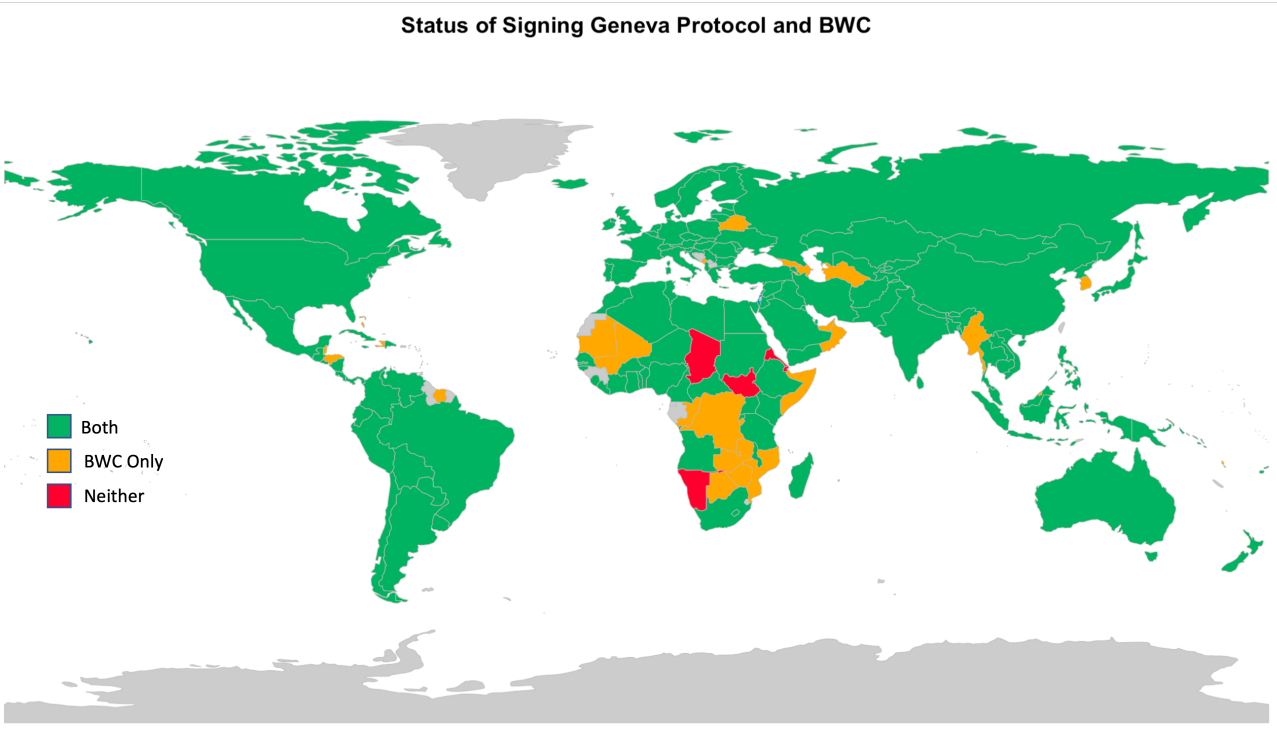

Figure 1: Map showing signatories to the Geneva Protocol and Biological Weapons Convention [34, 35].

for the BWC, leaving many to question the effectiveness of the resolution [38, 39]. Of note, multiple countries have indeed broken the articles of the BWC, including the U.S.S.R which continued their biological weapons programs far after being an initial signer of the BWC, Iraq (which signed but did not ratify the BWC) in the era of Saddam Hussein, and South Africa during the era of Apartheid [40]–[42]. Further, experts have considered the continued development of bioweapons within other countries to be likely. Many point to the need for national implementation, or countries using the BWC to incorporate national legislation, instead of multilateral efforts, but even these actions have not been widely adopted [43].

Another major issue for the BWC to contend with is the rapid pace of technology development, and the rate that such technologies appear to be becoming democratized. The growth and adoption of technologies such as gene editing and SynBio, both in and out of the conventional lab environments, amplifies the risk of accidental or deliberate misuse [44]. Other efforts to address the export and deliberate misuse of related technologies have been instituted. The Australia Group is one such coordinated effort, functioning to harmonize export controls across its 42 member states to ensure exports are not put towards the construction of chemical or biological weapons [45]. Even with these efforts, it is clear that the tacit knowledge to produce risky biological products is decreasing, or at least becoming harder to define [46, 47]. Though the BWC does take efforts to keep states abreast of relevant developments, such as through the review conferences and other ad-hoc meetings, critics have voiced concerns that the effectiveness of such steps is truly preventing deployment of these technologies. Additionally, and in the context of a growing democratization of many biological technologies, though the BWC has acknowledged the growing risk of non-state actors, many believe it places too little functional focus on these groups [48, 49].

Policy options

Several strategies have been proposed to respond to the evolving biosecurity landscape. One suggested approach has been to regulate the synthesis and distribution of nucleic acid fragments. State-of-the-art DNA editing, sequencing and synthesis technologies rely on custom-made nucleic acid fragments (e.g., primers or guide RNAs), which (for now) are exclusively produced by gene synthesis companies. Many large gene synthesis providers have voluntarily joined the International Gene Synthesis Consortium [50], which screens every order for sequences that alter the pathogenicity of a wider range of select organisms, as indicated by the Australia Group. This constitutes a simple and cost-effective approach for overseeing nucleic acid synthesis and distribution. However, screening and cataloging any other DNA sequence is not legally required for gene synthesis providers within the U.S. Moreover, additional advances in nucleic acid synthesis technologies could enable on-demand and low-cost gene synthesis outside of laboratory settings, and in doing so, these advances could enable the construction and manipulation of biological agents without governmental oversight.

As an alternative strategy, one can enhance the preexisting measures within the BWC. During the Second Review Conference of the BWC, it was established that member parties must submit a set of six confidence-building measures (CBMs) [51]. These measures took the form of reports that

would help to ensure the compliance of member states, often by providing information about regulation, prior activities, and a listing of current research centers doing work in biological defense. The addition of a seventh CBM is a possible policy implementation that would serve to enable the aforementioned attribution technologies—by requesting that members provide sequence information on the natural and engineered strains used in their labs' research, one would potentially acquire immense amounts of training data with which to improve these algorithms to the point of legal legitimacy. This is not guaranteed, however, as many countries currently fail to fulfill the current set of CBMs, despite a move to electronic CBMs for ease of access [52].

Finally, the Nucleic Acid Observatory (NAO) coalition has recently proposed to build nation-wide surveillance infrastructure to monitor wastewater, waterways, and ports of entry in search of viruses and other organisms undergoing exponential growth (i.e., causing an outbreak) [53]. This proposal relies on metagenomic sequencing. Derived from NGS technologies, metagenomic sequencing allows the sensitive and all-inclusive characterization of genomic material from environmental samples. As such, metagenomic sequencing has enabled the detection and monitoring of virtually any organism—including novel pandemic-class agents—in a timely manner. This NAO could offer a decentralized, robust and comprehensive solution to the problem but its deployment would be more costly and presents substantial infrastructure and deployment challenges.

Conclusion

Biosecurity emergencies can arise with little notice and have devastating consequences for humans, livestock, crops, and the economy. In the U.S., more lives have been lost to COVID-19 than to all military conflicts in the past century combined [54]. Recent advances in biotechnologies have enabled us to edit, read and write whole genomes with increasing ease, simplifying the discovery, adaptation, and co-option of biological organisms with benign or belligerent intentions. Attribution technologies have improved significantly, and—with enough time—may be sufficiently accurate to determine region of origin of a biological threat. While international efforts to ensure the non-proliferation of bioweapons have been broadly accepted, limitations in their ability to verify compliance have created potential gaps to ensure biosecurity. Further, a decreasing barrier to entry for the materials and methods needed to create and potentially deploy hazardous agents continues to raise the risk of deliberate misuse. To address this, efforts to monitor the synthesis of DNA and increased surveillance methods may help to bolster biosecurity.

Citation

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References

[1] Biological weapons. Online: https://www.who.int/health-topics/biological-weapons#tab=tab_1.

[2] Croddy, E., Perez-Armendariz, C. & Hart, J. Biological warfare: A brief history. In Croddy, E., Perez-Armendariz, C. & Hart, J. (eds.) *Chemical and Biological Warfare: A Comprehensive Survey for the Concerned Citizen*, 219–236 (Springer New York, New York, NY, 2002).

[3] National Research Council (US) Committee on Scientific Milestones for the Development of a Gene Sequence-Based Classification System for the Oversight of Select Agents. *The Select Agent Regulations* (National Academies Press (US), 2010).

[4] Federal Select Agent Program. Online: https://www.selectagents.gov/.

[5] National Academies of Sciences, Engineering, and Medicine, National Academies Of Sciences Engineeri, Health and Medicine Division, Board on Health Sciences Policy & Committee on Reviewing the Public Health Emergency Medical Countermeasures Enterprise. *Ensuring an Effective Public Health Emergency Medical Countermeasures Enterprise* (National Academies Press, 2022).

[6] Rambhia, K. J., Ribner, A. S. & Gronvall, G. K. Everywhere you look: Select Agent pathogens. *Biosecurity and Bioterrorism* **9**, 69–71 (2011). https://doi.org/10.1089/bsp.2011.0321.

[7] Noyce, R. S., Lederman, S. & Evans, D. H. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One* **13**, e0188453 (2018). https://doi.org/10.1371/journal.pone.0188453.

[8] Cubillos-Ruiz, A. *et al.* Engineering living therapeutics with synthetic biology. *Nature Reviews Drug Discovery* **20**, 941–960 (2021). https://doi.org/10.1038/s41573-021-00285-3.

[9] Cameron, D. E., Bashor, C. J. & Collins, J. J. A brief history of synthetic biology. *Nature Reviews Microbiology* **12**, 381–390 (2014). https://doi.org/10.1038/nrmicro3239.

[10] Cohen, S. N., Chang, A. C., Boyer, H. W. & Helling, R. B. Construction of biologically functional bacterial plasmids in vitro. *PNAS* **70**, 3240–3244 (1973). https://doi.org/10.1073/pnas.70.11.3240.

[11] Imai, M. *et al.* Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* **486**, 420–428 (2012). https://doi.org/10.1038/nature10831.

[12] Herfst, S. *et al.* Airborne transmission of influenza A/H5N1 virus between ferrets. *Science* **336**, 1534–1541 (2012). https://doi.org/10.1126/science.1213362.

[13] Gronvall, G. K. H5N1: A case study for dual-use research. Tech. Rep. (2013). Online: https://cdn.cfr.org/sites/default/files/pdf/2013/05/WP_Dual_Use_Research.pdf?_ga=2.47606244.2142736497.1575382530-1043326905.1575382530.

[14] Jinek, M. *et al.* A programmable Dual-RNA–Guided DNA endonuclease in adaptive bacterial immunity. *Science* **337**, 816–821 (2012). https://doi.org/10.1126/science.1225829.

[15] Barrangou, R. & Doudna, J. A. Applications of CRISPR technologies in research and beyond. *Nature Biotechnology* **34**, 933–941 (2016). https://doi.org/10.1038/nbt.3659.

[16] Sneed, A. Mail-order CRISPR kits allow absolutely anyone to hack DNA. *Scientific American* (2017). Online: https://www.scientificamerican.com/article/mail-order-crispr-kits-allow-absolutely-anyone-to-hack-dna/.

[17] Levy, S. E. & Myers, R. M. Advancements in next-generation sequencing. *Annual Review of Genomics and Human Genetics* **17**, 95–115 (2016). https://doi.org/10.1146/annurev-genom-083115-022413.

[18] Borry, P. *et al.* The challenges of the expanded availability of genomic information: an agenda-setting paper. *Journal of Community Genetics* **9**, 103–116 (2018). https://doi.org/10.1007/s12687-017-0331-7.

[19] Edgar, R. C. *et al.* Petabase-scale sequence alignment catalyses viral discovery. *Nature* **602**, 142–147 (2022). https://doi.org/10.1038/s41586-021-04332-2.

[20] DNA script announces world's first enzymatic synthesis of a high-purity 150-nucleotide strand of DNA. Online: https://www.businesswire.com/news/home/20181002005389/en/DNA-Script-Announces-World%E2%80%99s-Enzymatic-Synthesis-High-Purity.

[21] Kosuri, S. & Church, G. M. Large-scale de novo DNA synthesis: technologies and applications. *Nature Methods* **11**, 499–507 (2014). https://doi.org/10.1038/nmeth.2918.

[22] Tumpey, T. M. *et al.* Characterization of the reconstructed 1918 spanish influenza pandemic virus. *Science* **310**, 77–80 (2005). https://doi.org/10.1126/science.1119392.

[23] Esvelt, K. M. Inoculating science against potential pandemics and information hazards. *PLoS Pathogens* **14**, e1007286 (2018). https://doi.org/10.1371/journal.ppat.1007286.

[24] Lewis, G. *et al.* The biosecurity benefits of genetic engineering attribution. *Nature Communications* **11**, 6294 (2020). https://doi.org/10.1038/s41467-020-19149-2.

[25] Nielsen, A. & Voigt, C. Deep learning to predict the lab-of-origin of engineered DNA. *Nature Communications* **9**, 3135 (2018). https://doi.org/10.1038/s41467-018-05378-z.

[26] Alley, E. C. *et al.* A machine learning toolkit for genetic engineering attribution to facilitate biosecurity (2020). https://doi.org/10.1038/s41467-020-19612-0.

[27] Ozturk, N., Kocak, O. & Vosough Ahmadi, B. Economic analysis of increasing Foot-and-mouth disease vaccination frequency: The case of the biannual mass vaccination strategy. *Frontiers in Veterinay Science* **7**, 557190 (2020). https://doi.org/10.3389/fvets.2020.557190.

[28] Protocol for the prohibition of the use in war of asphyxiating, poisonous or other gases, and of bacteriological methods of warfare, 1925 (Geneva Protocol of 1925) (2015). Online: https://www.un.org/disarmament/wmd/bio/1925-geneva-protocol/.

[29] Seth Carus, W., National Defense University (U S) & National Defense University. Center for the Study of Weapons of Mass Destruction. *A Short History of Biological Warfare: From Pre-history to the 21st Century* (Government Printing Office, 2017).

[30] Bunn, G. Banning poison gas and germ warfare: should the United States agree. *Wisconsin Law Review* **1969**, 375–420 (1969).

[31] Cunliffe, W. H. *Select Documents on Japanese War Crimes and Japanese Biological Warfare, 1934-2006* (National Archives and Records Administration, 2007).

[32] United Nations Office for Disarmament Affairs. Convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction. Online: https://treaties.unoda.org/t/bwc.

[33] United Nations Office for Disarmament Affairs. The Biological Weapons Convention: An introduction (2017). Online: https://s3.amazonaws.com/unoda-web/wp-content/uploads/2017/07/BWS-brochure.pdf.

[34] United Nations Treaty Collection. Geneva Convention relative to the protection of civilian persons in time of war. Online: https://treaties.un.org/pages/showdetails.aspx?objid=0800000280158b1a.

[35] Arms Control Association. Biological Weapons Convention signatories and states-parties. Online: https://www.armscontrol.org/factsheets/bwcsig.

[36] Zilinskas, R. A. Verifying compliance to the biological and toxin weapons convention. *Critical Reviews in Microbiology* **24**, 195–218 (1998). https://doi.org/10.1080/10408419891294262.

[37] United Nations. Ad Hoc Group of governmental experts to identify and examine potential verification measures from a scientific and technical standpoint: Report. Tech. Rep. (1993).

[38] Drobysz, S. Verification and implementation of the Biological and Toxin Weapons Convention. *The Nonproliferation Review* **27**, 487–497 (2020). https://doi.org/10.1080/10736700.2020.1823102.

[39] Shearer, M., Potter, C., Vahey, R., Connell, N. & Gronvall, G. BWC assurance: Increasing certainty in BWC compliance. *Preprints* 2022040051 (2022). https://doi.org/10.20944/preprints202204.0051.v1.

[40] Moodie, M. The Soviet Union, Russia, and the biological and toxin weapons convention. *The Nonproliferation Review* **8**, 59–69 (2001). https://doi.org/10.1080/10736700108436838.

[41] Pearson, G. S. *The UNSCOM Saga: Chemical and Biological Weapons Non-Proliferation* (Springer, 2000).

[42] Gould, C. & Folb, P. Project Coast: Apartheid's chemical and biological biological warfare programme. Tech. Rep. (1990). Online: https://unidir.org/sites/default/files/publication/pdfs//project-coast-apartheid-s-chemical-and-biological-warfare-programme-296.pdf.

[43] United Nations Office of Disarmament Affairs. National implementation of the Biological Weapons Convention. Online: https://www.un.org/disarmament/biological-weapons/national-implementation/.

[44] Novossiolova, T., Whitby, S. M., Dando, M. R. & Pearson, G. S. Strengthening the Biological and Toxin Weapons Convention: The vital importance of a web of prevention for effective biosafety and biosecurity in the 21st century (2019). Online: https://bradscholars.brad.ac.uk/handle/10454/17580.

[45] The Australia Group. Online: https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/index.html.

[46] Vogel, K. Bioweapons proliferation: Where science studies and public policy collide. *Social Studies of Science* **36**, 659–690 (2006). https://doi.org/10.1177/0306312706059460.

[47] Dunlap, G. & Pauwels, E. The intelligent and connected bio-labs of the future. *The Wilson Center* (2017). Online: https://www.wilsoncenter.org/sites/default/files/media/documents/publication/dunlap_pauwels_intelligent_connected_biolabs_of_future.pdf.

[48] United Nations official document. Online: https://www.un.org/ga/search/view_doc.asp?symbol=S%2FRES%2F1540+%282004%29.

[49] Lentzos, F. Biology's misuse potential. *Connect.* **15**, 48–64 (2016). https://doi.org/10.11610/Connections.15.2.04.

[50] International Gene Synthesis Consortium (2022). Online: https://genesynthesisconsortium.org/.

[51] Second Review Conference of the parties to the Convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction. Online: https://docs-library.unoda.org/Biological_Weapons_Convention_-_Second_Review_Conference_(1986)/BWC_CONF.II_13.pdf.

[52] Electronic confidence building measures portal. Online: https://bwc-ecbm.unog.ch/.

[53] The Nucleic Acid Observatory Consortium. A global nucleic acid observatory for biodefense and planetary health. *arXiv e-prints* arXiv–2108 (2021). https://doi.org/10.48550/arXiv.2108.02678.

[54] McCarthy, N. Infographic: U.S. deaths from covid-19 match toll of three major wars (2021). Online: https://www.statista.com/chart/amp/24252/us-covid-19-deaths-compared-to-deaths-in-major-wars/.