Multiple experts contributed to the ideas presented in this paper with support from NTI | bio to inform the NTI Biosecurity Innovation and Risk Reduction Initiative. The paper was informed by discussions held under Chatham House Rule at a meeting organized by NTI | bio, Wellcome Trust, and the World Economic Forum.

INCENTIVIZING TECHNICAL INNOVATION TO BUILD SAFER AND MORE SECURE TECHNOLOGIES

The Challenge

With each major biotechnology breakthrough – such as the discovery and widespread use of advanced gene editing technology (*e.g.*, CRISPR)[1,2,3,4] or the development of gene drives[5] – there are new calls for national policies and governance to mitigate risk[6]. On the one hand, there are growing public and private concerns regarding emerging biological risks that need to be addressed. On the other hand, new standards – or even norms – that are only adopted in one country or region could drive risk (and technical advances) to emerging leaders and markets and away from countries that implement and enforce stringent oversight policies. These dynamics argue for stakeholder-driven risk reduction approaches that can cross borders.

Current Situation

One way to mitigate risk associated with advances in technology is to develop and incentivize technical solutions that decrease the likelihood that the technology could cause societal harm. In today's world, technical innovation targeted at improving security is a major business. However, unlike some other fields (such as cybersecurity) the field of biosecurity remains largely confined to discussions about policies and best practices – not technical solutions. Experts working with agents that are immediately hazardous to human or animal health are trained to implement safe and secure practices to protect materials and the people working with them. But, there is no real technical profession surrounding biosecurity, which would aim to develop safer and more secure technologies. Hacking competitions in the life sciences are generally designed to develop new modes of solving societal challenges – not safer and more secure ways of achieving those goals.

A recent positive step forward has been the advent of the Defense Advanced Research Projects Agency (DARPA) Safe Genes Program[7], which was launched to address risks posed by gene editing technologies, including by developing ways to, "…restrict or reverse propagation of engineered genetic constructs." Safe Genes has created a

[1] Gasiunas, G. et al. (2012). Cas9–crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. *Proceedings of the National Academy of Sciences* 109, E2579–E2586.
[2] Jinek, M. et al. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 337, 816–821.
[3] Cong, L. et al. (2013). Multiplex genome engineering using CRISPR/Cas systems. *Science* 339, 819–823.
[4] Mali, P., Yang, L., Esvelt, K.M., Aach, J., Guell, M., DiCarlo, J.E., Norville, J.E., and Church, G.M. (2013). RNA-guided human genome engineering via Cas9. *Science* 339, 823–826.
[5] Kyrou K. et al. (2018). A CRISPR-Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitos. *Nature Biotechnology*, Advance Online Publication, https://doi.org/10.1038/nbt.4245.
[6] National Academies of Sciences, Engineering, and Medicine, "Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies," *The National Academies Press*, 2017, https://doi.org/10.17226/24761.
[7] "Setting a Safe Course for Gene Editing Research," Defense Advanced Research Projects Agency (DARPA), September 7, 2016, https://www.darpa.mil/news-events/2016-09-07.

mechanism – and hopefully someday a market – for leading researchers to consider innovative mechanisms to reduce or counter biological risks associated with technologies that they (or other researchers) create.

The annual International Genetically Engineered Machine Competition (iGEM)[8] also provides an opportunity to engage broader and next generation community in best practices that can be propagated. The iGEM competition seeks to not only bolster safe and secure practices among competitors in its annual competition, but also could serve as a test-bed for developing new technical approaches to countering biotechnology risks. In 2018, iGEM included over 320 teams from around the world[9].

Potential Way Ahead
Academic challenges focused on designing safe and secure biotechnologies could serve as one way to incentivize scientists and engineers to pursue risk mitigation as an integral piece of the discovery process. There are some risks associated with incentivizing experts to consider all the ways in which specific biotechnologies could be misused – even for the purpose of mitigating those risks. However, incentivizing a cadre of scientists and engineers who are focused on countering negative outcomes associated with new biotechnologies might also dissuade or deter those with harmful intent.

GLOBAL OVERSIGHT FOR RESEARCH THAT ENHANCES THE TRANSMISSIBILITY OR VIRULENCE OF POTENTIALLY PANDEMIC PATHOGENS

The Challenge
Stakeholders struggle to define both risks and merits associated with research that creates, modifies, or enhances transmissibility or virulence of infectious agents – particularly those with pandemic potential. While this debate continues, international experts have been stymied in their ability to define concrete, globally applicable norms and actions to reduce risks associated with this type of research.

The advent of faster and cheaper technologies for DNA synthesis led to the synthetic construction of poliovirus in 2002[10] and the 1918 H1N1 influenza pandemic virus in 2005[11]. In 2012, research in the Netherlands and the United States to enhance the function of H5N1 avian influenza[12,13] ignited fears over accidental or intentional release of a pandemic agent. And, in 2018, privately funded Canadian research to recreate the horsepox virus[14] – a near neighbor of the virus causing smallpox – sparked new calls for

[8] "Safety & Security at IGEM," International Genetically Engineered Machine Competition, accessed 09 May 2018, http://igem.org/Safety.
[9] "Team List For iGEM 2018 Championship," iGEM, accessed 03 October 2018, http://igem.org/Team_List?year=2018.
[10] Rosengard A.M. et al. (2002). Variola virus immune evasion design: Expression of a highly efficient inhibitor of human complement. *Proceedings of the National Academy of Sciences* 99(13): 8808-8813.
[11] Tumpey T.M. et al. (2005). Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. *Science* 310(5745): 77-80.
[12] Enserink M. (2011). Scientists Brace for Media Storm Around Controversial Flu Studies. *Science*, 23 November 2011, www.sciencemag.org/news/2011/11/scientists-brace-media-storm-around-controversial-flu-studies.
[13] Imai M. et al. (2012). Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* 486: 420–428.
[14] Noyce R.S., Lederman S., Evans D.H. (2018). Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. PLoS ONE 13(1): e0188453. https://doi.org/10.1371/journal.pone.0188453.

research norms and public discussion about biological risk associated with advances in technology.

Each controversial experiment has ignited public interest in risk reduction, and some progress has been made. The U.S. has been particularly active in launching federal and institutional oversight requirements for federally funded Dual Use Research of Concern[15] and recently enacting the first guidelines[16] for research that enhances the transmissibility and/or virulence of a pandemic agent.

Current Situation

However, existing national guidelines to oversee research or businesses that create and modify pathogens are fragmented, generally do not apply to research that is funded by the private sector, and do not adequately take into account the global and changing nature of life sciences research collaborations. Many countries place safety and security controls on dangerous infectious agents but do not provide guidelines for assessing the aims, outcomes, or risks of research experiments conducted to make, modify, or enhance transmissibility or virulence of them. Others recommend self-governance or provide guidance, but do not have laws or regulations in place[17]. And others, like the United States, use the Fink Report's[18] seven specific classes of experiments as a guide and then apply oversight requirements when those experiments are conducted with specific agents. But, there is no oversight mechanism that would require specific guidelines for facilities, including World Health Organization (WHO) collaborating centers, that create, modify, or enhance the transmissibility or virulence of infectious agents.

As DNA synthesis has become common-place, more focus has been placed on screening orders and customers. DNA synthesis screening guidelines in the United States[19] and voluntary guidelines through the International Gene Synthesis Consortium (IGSC)[20] have been developed to guard against the creation of dangerous pathogens by nefarious actors. However, most countries do not require companies that operate within their territory to screen orders or customers[21].

Significant discord also remains among experts regarding the need for researchers to conduct certain types of experiments[22], including those that could create new and more harmful agents. For example, some experts have argued that research that enhances the transmissibility or virulence of pandemic influenza virus is not necessary to make gains in countermeasure development, does not justify the potential risk[23], or should

[15] "Dual Use Research of Concern," *Science, Safety, Security*, accessed May 9, 2018, https://www.phe.gov/s3/dualuse/Pages/default.aspx.
[16] U.S. Department of Health and Human Services, "Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens," 2017, https://www.phe.gov/s3/dualuse/Documents/p3co.pdf.
[17] Millett P.D. (2017). Gaps in the International Governance of Dual-Use Research of Concern. *National Academies*, 17 January 2017, accessed 03 October 2018, https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_176434.pdf.
[18] U.S. National Academies National Research Council, "Biotechnology Research in an Age of Terrorism."
[19] U.S. Department of Health and Human Services, "Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA," Public Health Emergency, accessed May 9, 2018, https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx.
[20] "International Gene Synthesis Consortium," International Gene Synthesis Consortium, accessed May 09, 2018, https://genesynthesisconsortium.org/.
[21] Gronvall G. (2016). *Synthetic Biology: Safety, Security, and Promise*. CreateSpace Independent Publishing Platform.
[22] Lipsitch M. and Inglesby T.V. (2014). Moratorium on Research Intended To Create Novel Potential Pandemic Pathogens. *MBio* 5(6):e02366-14.
[23] Rozell D.J. (2015). Assessing and Managing the Risks of Potential Pandemic Pathogen Research. *MBio* 6(4):e01075-15.

require oversight from an international (*e.g.*, UN) body. Others have argued against limitations on peaceful life sciences research or its publication, whatever the potential involved risks.

Potential Way Ahead

Existing oversight models – such as prequalification of certain types of laboratories or the existing structure for oversight for smallpox research – could serve as a guide for research that would enhance virulence or transmissibility of other potentially pandemic agents[24]. Insurance models to incentivize norms and actions related to the synthesis or modification of infectious agents with pandemic potential could also be considered[25]. Reinsurers that focus on terrorism risk, including CBRN risk[26,27], as well as pandemic risk[28], should be involved in developing these options.

ESTABLISHING PUBLISHING STANDARDS FOR POTENTIALLY RISKY RESEARCH

The Challenge

Managing the tension between freedom of openness and biosecurity concerns in journal publishing is inherently difficult. Some journal publishers have processes for assessing research with a potential biosecurity risk and have established systems for making decisions on whether these papers should be published. However, these processes, systems and standards are not common or agreed between different publishers around the world.

Current Situation

Previous efforts to align, such as the publication in 2003 of a statement by a group of editors, were helpful steps but were not consistently implemented in the policies of publishers.[29] The US National Science Advisory Board for Biosecurity (NSABB) convened an editors' roundtable in 2011 to discuss dual-use publication and strategies to improve biosecurity review[30]. Despite these efforts, the current system relies on the practices of individual journals and may have a minimal impact on the goal of biosecurity as authors could resubmit to different journals or choose alternative routes for making their work public[31].

[24] National Academies of Sciences, Engineering, and Medicine, "Gain-of-Function Research: Summary of the Second Symposium, March 10-11, 2016," *The National Academies Press*, (2016): 59, https://www.nap.edu/read/23484/chapter/5.
[25] Sebastian Farquhar, Owen Cotton-Barratt, and Andrew Snyder-Beattie. "Pricing Externalities to Balance Public Risks and Benefits of Research." *Health Security* 15, no. 4 (2017): 401-08, https://www.liebertpub.com/doi/pdfplus/10.1089/hs.2016.0118.
[26] "Pool Re Hails Government Action to Close the Terrorism Insurance Gap," Pool Re insurance, March 22, 2018, , accessed May 09, 2018, https://www.poolre.co.uk/pool-re-hails-government-action-close-terrorism-insurance-gap/.
[27] "Pool Re and the Nuclear Threat Initiative Highlight Radiological Material Security Efforts," Nuclear Threat Initiative, April 5, 2017, http://www.nti.org/newsroom/news/pool-re-and-nuclear-threat-initiative-highlight-radiological-material-security-efforts/.
[28] "Swiss Re Helps Establish the Pandemic Emergency Financing Facility," Swiss Re, accessed May 09, 2018, http://www.swissre.com/global_partnerships/swiss_Re_helps_establish_the_pandemic_emergency_financing_facility.html.
[29] Patrone, Resnik and Chin 2012 'Biosecurity and the Review and Publication of Dual-Use Research of Concern', Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, 10 (3)
[30] Patrone, Resnik and Chin 2012 'Biosecurity and the Review and Publication of Dual-Use Research of Concern', Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, 10 (3)
[31] Patrone, Resnik and Chin 2012 'Biosecurity and the Review and Publication of Dual-Use Research of Concern', Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, 10 (3)

Potential Way Ahead

Consistent policies for biosecurity across journals would provide standardized levels of scrutiny and review for all researchers. Standards, expectations and requirements for editors, reviewers, and authors would be uniform and would promote both the legitimacy of, and compliance with, biosecurity publication policies. Convening journal publishers to develop a list of 'red flag' topics or triggers, discuss best practices, and gain consensus on the 'no undercut' principle could bring the sector together and move it towards achieving a consistent approach to biosecurity. Establishing an independent review body, rather than ad-hoc use of NSABB or WHO, could provide greater consistency, legitimacy and expertise but would need evaluation to determine the benefits, challenges and most appropriate governance for such a body.

Pre-prints:

A desire to make research findings accessible faster has led to the rise of pre-print and post-publication peer review platforms that complement traditional journal publication. A pre-print is a version of a paper that is shared ahead of formal publication in a peer-reviewed scholarly or scientific journal. Making papers available prior to peer review allows the faster dissemination of findings, which will hopefully speed scientific discovery. However, this process makes papers openly available before the biosecurity measures used by many journal publishers would take effect. Understanding the current biosecurity review practices of pre-print servers would help establish the landscape for thinking about what actions could be taken either individually or collectively. Measures such as providing transparency around what processes are currently occurring, or mechanisms for removing pre-prints that may pose a concern, would begin to establish biosecurity policies as a consideration for the sector and set the norms for future pre-print servers that emerge[32].

DEVELOPING ONE OR MORE MULTILATERAL GOVERNANCE MODELS FOR MITIGATING BIOLOGICAL RISKS ASSOCIATED WITH ADVANCES IN TECHNOLOGY[33]

Individual national policies and mechanisms will not be sufficient to ensure biosecurity and biosafety. It will also be necessary to develop larger scale, potentially global, approaches to continuously monitor the field, identify gaps, and rapidly establish effective tools for addressing those gaps.

We propose consideration of a comprehensive, adaptive and creative approach to the governance and oversight of biotechnologies. There exists a mismatch between traditional governmental approaches to legal/ethical oversight and the speed of scientific discovery and technological innovation and deployment. This mismatch is commonly referred to as a pacing problem. A responsive regime for biosecurity and biosafety will need to rely on more adaptive soft law (industry standards, laboratory practices and procedures, insurance policies, etc.), industry self-governance, and technical means to mitigate potential harms.

A global oversight committee that functions as a good-faith broker mediating between stakeholders, monitors advances in biotechnologies, and draws upon the research and

[32] COPE Council, COPE Discussion document: Preprints. March 2018.
[33] Original concepts shared by Wendell Wallach via personal communication. NTI | bio added to and modified based on discussions held under Chatham House Rule at a meeting organized by NTI | bio, Wellcome Trust, and the World Economic Forum.

best-practices developed by other individuals and institutions, might be able to facilitate quick and adaptive responses to biosecurity challenges as they arise. To develop such a group, it will be essential to engage a cross-section of representative stakeholders to acquire relevant biorisk-related information and work through competing concerns. It will also be essential for such a committee to establish its credibility as an honest and trustworthy broker facilitating cooperation between stakeholders. If that challenge can be met, such an oversight committee might also serve as a communications vehicle sharing analyses and recommendations with responsible press and directly with the public.

Of course, any new body established to comprehensively monitor developments in biotechnology and to facilitate cooperation among stakeholders will confront an array of implementation challenges. For example, how will it establish authority, legitimacy, and adequate influence? How will it be funded, and to whom will it be accountable? Nevertheless, the need is serious, and such implementation challenges, while difficult, should be avidly debated.