Working Group on the Strengthening of the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction

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Advancements in Science and Technology Relevant to the Biological and Toxin Weapons Convention: Examples of developments relevant to a new structured science and technology review process

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Summary

Science & Technology (S&T) is a cross cutting and integral theme across BTWC provisions and as such, State Parties have stressed its importance to the BTWC for decades. Not least by recognising the importance of S&T at the Ninth Review Conference by agreeing 'To develop with a view to establish a mechanism to review and assess scientific and technological developments relevant to the Convention and to provide States Parties with relevant advice…' Captured herein are S&T advancements that could be assessed in a new systematic and structured S&T review process under the BTWC. Illustrative examples of beneficial applications of S&T include advances in the development of novel therapies, exploiting Artificial Intelligence (AI) to treat infectious diseases and how small interfering RNAs (siRNAs) can be harnessed to improve plant resistance to crop diseases. This working paper also outlines risks associated with antimicrobial resistance (AMR) across the human, animal and plant health landscape.

I. Introduction

1. This working paper collates advances in the life sciences of relevance to the operation and implementation of the BTWC. This paper draws particular attention to the emergence of Artificial Intelligence (AI) and draws on science and technology (S&T) developments where AI has been applied to, or co-developed with bioscience technologies for beneficial purposes. This paper also draws particular attention to risks posed by the spread of antimicrobial resistance across human, animal and plant health sectors.

II. Science and Technology is a Cross Cutting Theme

2. S&T is a cross cutting and integral theme across BTWC provisions and as such, State Parties have stressed its importance to the BTWC for decades. With S&T at the Convention's core, it is clear that S&T review does not stand alone, rather it has implementation and operational impact for key themes across the BTWC, particularly those identified by States Parties at the 9th Review Conference. These include:

- International cooperation and assistance under Article X;
- Scientific and technological developments relevant to the Convention;
- Confidence-building and transparency;
- Compliance and verification;
- National implementation of the Convention;
- Assistance, response and preparedness under Article VII and
- Organizational, institutional and financial arrangements.

The UK sets out key elements for the S&T review process in Working Paper BWC/WG/2/WP.9. It has also been recently emphasised to BTWC States Parties that S&T will be essential to any international cooperation and assistance mechanism and that S&T is relevant to Article X and other provisions of the Convention.

3. The UK describes below illustrative examples of S&T themes and advancements that could be discussed in a future structured and systematic S&T review process under the BTWC. The Ninth Review Conference, in paragraph 19 of Section III of the Final Report agreed, "To develop with a view to establish a mechanism to review and assess scientific and technological developments relevant to the Convention and to provide States Parties with relevant advice. In order for this mechanism to be established, the Working Group on the strengthening of the Convention will make appropriate recommendations". This working paper also highlights the cross cutting and integral nature of S&T and its relevance to the BTWC; as such, linkages to BTWC key provisions have been made throughout. This working paper takes a One Health approach to S&T review and thus presents developments covering human, animal and plant health and discusses emerging benefits and potential risks of misapplication or misuse relevant to the Convention.

III. Infectious Diseases & Drug Resistance

4. The BTWC sets the global norms against biological weapons and the deliberate misuse of biological sciences. Given the properties of biological agents, however, the response and underpinning technological capabilities to respond to a deliberate biological event would look very similar to a response to a natural infectious disease outbreak. As such, strengthening national capacities to deal with the challenge of managing prevention, protection from and response to infectious diseases and high consequence pathogens is integrally linked to BTWC provisions, in particular Articles IV, VII, and X.

5. One such enduring challenge that BTWC States Parties face on a large scale is Antimicrobial Resistance (AMR). AMR refers to the emergence of bacteria, viruses, fungi, and parasites that do not respond to antimicrobials and continue to spread infection. AMR is the collective result of global under regulated prescription and use of antibiotics, lack of

access to quality and affordable medicines, and lack of clean water, sanitation, hygiene and infection prevention and control procedures across medicinal and agricultural sectors[1].

A. Human and Animal Health

6. The World Health Organisation (WHO) have previously described how the threat of AMR is so significant that it threatens to send modern medicine back to the pre-antibiotic era where what is now considered as routine surgeries would become extremely dangerous[2]. This enormous challenge also extends to animal health. In 2017, animals represented 73 % of all global antimicrobial use[3]. The World Animal Health Organisation (WOAH) also recognise the threat of AMR to animal health. In 2022, WOAH launched ANIMUSE, which is a digital platform to gather data on antimicrobial use in animals in an effort to better coordinate efforts to counter AMR. International Organisations are recognising the necessity of collaborative work to overcome the threat posed by AMR from a One Health perspective and as such, The Food and Agriculture Organization of the United Nations (FAO), the UN Environment Programme (UNEP), the WHO and WOAH, known as the Quadripartite are joining forces on this initiative to underscore the threat AMR presents to humans, animals, plants, ecosystems and livelihoods[4].

7. The rate of emerging AMR pathogens is also drastically outpacing new antimicrobial discovery. Over the last few decades, only a select few antimicrobials have been identified and successfully developed including Xerava[5], Nuzyra[6], and Lefamulin[7]. A compounding challenge of particular relevance to the BTWC is the concept of deliberately engineering drug resistance in pathogens using biotechnology techniques such as gene editing.

8. The scientific research community has recognised that efforts to address AMR now need to go beyond traditional methods for drug discovery. Below are illustrative examples of how bioscience advancements in combination with other scientific disciplines such as AI, are being harnessed to counter the threat of AMR.

9. Traditional screening for novel antimicrobials utilises High Throughput Screening, which is time consuming, resource intensive, and reliant on access to existing data alone. However, AI is proving to be a promising new screening tool through the application of deep-learning (DL) algorithms. In 2020, Halicin became the first AI discovered antimicrobial[8]. Researchers screened approximately 2300 compounds, assessing the ability of all compounds to inhibit the growth of *E.coli*. The results were then used to train a deep neural network (DNN) for predicting antimicrobial activity from chemical structures of compounds. Halicin was identified as a general kinase inhibitor and a potent inhibitor of ESKAPE (**E**nterococcus faecium, **S**taphylococcus aureus, **K**lebsiella pneumoniae, **A**cinetobacter baumannii, **P**seudomonas aeruginosa, and **E**nterobacter spp), and other Multi Drug Resistant (MDR)

[1] https://www.who.int/health-topics/antimicrobial-resistance

[2] https://www.who.int/news-room/photo-story/photo-story-detail/urgent-health-challenges-for-the-next-decade

[3] Mulchandani R, Wang Y, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in food-producing animals: 2020 to 2030. PLOS Glob Public Health. 2023 Feb 1;3(2):e0001305. doi: 10.1371/journal.pgph.0001305. PMID: 36963007; PMCID: PMC10021213.

[4] https://www.who.int/news/item/18-11-2022-quadripartite-launches-a-new-platform-to-tackle-antimicrobial-resistance-threat-to-human-and-animal-health-and-ecosystems#:~:text=The%20Food%20and%20Agriculture%20Organization,AMR%20presents%20to%20humans%2C%20animals%2C

[5] Mui, E. (2019). Eravacycline (Xerava). Infectious Disease Alert, 38(6).

[6] Proteus, M. (2019). Omadacycline (Nuzyra)—A New Tetracycline Antibiotic.

[7] Veve, M. P., & Wagner, J. L. (2018). Lefamulin: review of a promising novel pleuromutilin antibiotic. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 38(9), 935-946.

[8] Stokes, J. M., Yang, K., Swanson, K., Jin, W., Cubillos-Ruiz, A., Donghia, N. M., ... & Collins, J. J. (2020). A deep learning approach to antibiotic discovery. Cell, 180(4), 688-702.

pathogens[9]. It is now hopeful that the ability of AI to identify novel antimicrobials can be applied to diseases that have serious AMR complications.

B. Plant Health and the Environment

10. Antibiotics have also been used to treat plant disease. For example, *Erwinia amylovora* is the causative agent of fire blight disease in several plants in the Rosaceae family including apple, pear and quince. So far, Streptomycin has used to treat fire blight bacteria. Oxytetracyline is another common plant disease antibiotic demonstrating effectiveness at treating *Pseudomonas* spp., *Xanthomonas* spp. and phytoplasmas (intracellular parasites in phloem tissue). However, similarly to medical and veterinary sciences, there are concerns the agricultural sector is simultaneously becoming vulnerable to AMR itself whilst also elevating AMR risk more broadly.

11. Plants are also at risk from drug resistance in the form of pesticides; compounds that are chemically synthesised to mitigate plant disease. Pesticide resistance is also a global health concern, with scientific researchers warning of pesticide-resistant bacteria becoming widespread throughout agricultural products. Pesticide resistance, similarly to antibiotic resistance, is caused by persistent and widespread use, where bacteria can utilise adaptation techniques including biofilm formations, mutations, increased expression of enzymes, and horizontal and vertical gene transfer. Cross-resistance is also an increasing problem in plant health security and refers to resistance to a particular pesticide that results in resistance to other pesticides through a common mechanism. This is usually found among pesticides with a similar binding target site or detoxifying pathways. The prevalence of pesticide resistance along with cross-resistance is likely to increase with continued widespread use of pesticides.

12. Given the emergence of plant resistance to traditional pesticides and chemical based pest management options, researchers are now focused on developing novel treatments through biological pesticides, often termed ‘bio pesticides’. Comparative to traditional, broad-spectrum chemical pesticides, bio pesticides are compounds that manage agricultural pests through specific biological effects. These bio pesticides utilise allelochemicals, toxic secondary metabolites produced by plants, microalgae, bacteria and fungi that affect the development of other organisms[10].

IV. Novel therapeutics

13. The world has experienced just how vulnerable we all are to a novel viral pathogen with pandemic potential. A key aspect of the response to the COVID-19 pandemic and previous large-scale outbreaks such as the Ebola Virus outbreak of 2014-2016, was the scientific community’s work to develop novel therapies in a short space of time. National and global capabilities to respond to infectious disease outbreaks such as these is of clear relevance to BTWC provisions including national implementation under Article IV, assistance, preparedness and response under Article VII and international cooperation and assistance under Article X. An example of a UK national capability that was stood up in response to the COVID-19 pandemic was the Department of Health and Social Care (DHSC) COVID-19 Antivirals and Therapeutics Taskforce, which co-ordinated the end-to-end provision of treatments for coronavirus in the UK so that patients were able to access safe and effective treatments as soon as possible[11]. One such therapy option that has continued to

[9] Talat, Absar, and Asad U. Khan. "Artificial intelligence as a smart approach to develop antimicrobial drug molecules: a paradigm to combat drug-resistant infections." Drug Discovery Today (2023): 103491.

[10] Casanova LM, Macrae A, de Souza JE, Neves Junior A, Vermelho AB. The Potential of Allelochemicals from Microalgae for Biopesticides. Plants. 2023; 12(9):1896. https://doi.org/10.3390/plants12091896

[11] https://www.gov.uk/government/groups/the-covid-19-therapeutics-taskforce

see increasing attention is antibody therapy, which is especially important when considering treatment options for viral infections.

Human and Animal Health

14. Antibodies can be used as a type of low toxicity, targeted drug therapy for many autoimmune, viral and cancer diseases. With widespread and previously proved effectiveness, there is ever increasing demand for improved and novel antibodies, however, traditional screening methods are time consuming and labour intensive. AI now presents the opportunity to overcome these challenges, with researchers already demonstrating the beneficial applications of AI in drug discovery. For instance, researchers are focused on utilising AI to suggest protein sequences capable of boosting the potency of antibodies against viruses such as SARS-CoV-2 and Ebolavirus[12]. Here, AI tools would be trained to recognise and process millions of protein sequences in a similar way that ChatGPT has been fed text, and reach information that is not obvious to even antibody engineering experts. Long-term, researchers are also hopeful that AI could be utilised to design and develop entirely new antibodies, as opposed to improving existing ones, and incorporate these into new drugs that bind to specific target sites. In nature, somatic hyper mutation refers to the evolution of antibody lineages to have higher affinity for an antigen following repeated mutations rounds. This is a process that scientists are keen to replicate in the laboratory because generating antibodies with higher affinity presents the opportunity to develop better therapeutics for disease targets. In one recent study, researchers utilised AI as a method to investigate guided affinity evolution using seven antibodies, screening 20 or fewer variants of each across two rounds of laboratory evolution. As a result, the binding affinity of four clinically important antibodies were improved sevenfold, with data also demonstrating favourable thermostability and viral neutralization activity against Ebola and SARS-CoV-2 [13].

V. Vaccine Development

A. Human and Animal Health

15. At the core of strategies for the prevention and/or treatment of infectious diseases are vaccines. Efficient vaccine development and distribution is a public health issue on a global scale. The UK, among other BTWC States Parties have identified many lessons from the global response to the COVID-19 pandemic for future development and distribution of vaccines to treat novel viral pathogens with pandemic potential. Since the COVID-19 pandemic, research has been done to integrate AI into vaccine development to optimise mRNA gene sequences. Specifically, this involves prolonging the presence of mRNA, which can lead to improved vaccine potency and stability due to a higher production of antibodies. The research community is also hopeful that AI can be deployed to optimise vaccine administration within precision medicine. For instance, LinearDesign is an AI tool for optimisation models. In previous validation tests, it has yielded vaccines, that when evaluated in mice, triggered an antibody response up 128 times greater than those following conventional, codon-optimised vaccines. LinearDesign has already been used to optimise SW-BIC-213, the COVID-19 vaccine from StemiRNA[14].

16. An emerging area of research is that of mucosal vaccines including plant-based edible vaccines. Edible vaccines offer the opportunity to activate both mucosal and systemic immune responses, whilst reducing the burden of storage conditions and administration by

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[12] https://www.nature.com/articles/d41586-023-01516-w

[13] Hie, B.L., Shanker, V.R., Xu, D. et al. Efficient evolution of human antibodies from general protein language models. Nat Biotechnol (2023). https://doi.org/10.1038/s41587-023-01763-2

[14] Zhang, H., Zhang, L., Lin, A. et al. Algorithm for Optimized mRNA Design Improves Stability and Immunogenicity. Nature (2023). https://doi.org/10.1038/s41586-023-06127-z

qualified health care professionals. So far research has focused on the potential of a tomato based edible vaccine (TOMAVAC) against COVID-19[15], the production of hepatitis B in potato[16], and the conversion of several common crops into vaccine antigens including banana, rice and tobacco[17]. The major advantage of edible vaccines to treat diseases such as malaria, measles, hepatitis, cholera and norovirus is the reduction in the logistical burden and required cold chain associated with current vaccines, which could prove especially helpful in Low and Middle Income Countries.

17. In 2020, DeepMind revealed how AlphaFold, a machine learning based model, was able to successfully predict protein structures previously only characterised by using of x-ray crystallography and cryoelectron microscopy (cryo-EM), with a high degree of accuracy compared to traditional techniques[18]. Prediction of protein structures through AI is accelerating new discoveries and advancements at incredible pace. For example, in the discovery of novel drugs to treat Leishmaniasis, a disease caused by the *Leishmania* parasite, which is spread through sand fly bites across Asia, Africa, the Americas, and the Mediterranean. Currently, there is no fully effective treatment option for Leishmaniasis. Researchers at the Drugs for Neglected Diseases initiative (DNDi) used an AI-based approach to characterise a novel molecule and how it interacted with a target enzyme. The researchers discovered that the enzyme interaction led to interference with the *Leishmania* metabolism, ultimately killing the parasite. AlphaFold was used to confirm the target enzymes structure, allowing researchers to understand better how the drug-enzyme binding happens[19].

18. AlphaFold was also recently utilised in combination with existing experimental work to identify the structure of Pfs48/45, an essential protein for development of the parasite that causes malaria, enabling researchers to start deciding which proteins would be most suitable to be incorporated into a vaccine. Human clinical trials of this protein in relation to a vaccine are due to commence in early 2023[20].

B. Plant Health

19. A novel area of scientific research is that of vaccinating plants to protect them against crop diseases. Similar to the mammalian immune system functionality, when a virus infects a plant cell, the plant produces defensive proteins that recognise the viral RNAs and breaks them down into pieces called small interfering RNAs (siRNAs). However, only a few of these siRNAs have the suitable chemical composition and thus properties to be completely defensive against the viral RNA. As such, researchers are investigating the use of siRNAs to generate plant vaccines whereby plant growth and yield can be increased. In a previous study, researchers demonstrated that selective siRNA sprayed onto tobacco plant leaves produced defensive capability against tomato bushy stunt virus[21]. Similarly, the PHC279 peptide has been identified as a potential defensive protein that could be incorporated into a universal plant vaccine[22].

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15 Abdurakhmonov, I., et al,. (2023). The edible tomato COVID-19 vaccine, TOMAVAC, induces neutralising IgGs.

16 Richter, Liz J., et al. "Production of hepatitis B surface antigen in transgenic plants for oral immunization." Nature biotechnology 18.11 (2000): 1167-1171.

17 Kurup VM, Thomas J. Edible Vaccines: Promises and Challenges. Mol Biotechnol. 2020 Feb;62(2):79-90. doi: 10.1007/s12033-019-00222-1. PMID: 31758488; PMCID: PMC7090473.

18 Jumper, J., Evans, R., Pritzel, A. et al. Highly accurate protein structure prediction with AlphaFold. Nature 596, 583–589 (2021). https://doi.org/10.1038/s41586-021-03819-2

19 https://unfolded.deepmind.com/stories/accelerating-the-search-for-life-saving-treatments-for-leishmaniasis

20 Ko, KT., Lennartz, F., Mekhaiel, D. et al. Structure of the malaria vaccine candidate Pfs48/45 and its recognition by transmission blocking antibodies. Nat Commun 13, 5603 (2022).

21 Selma Gago-Zachert et al. Highly efficacious antiviral protection of plants by small interfering RNAs identified in vitro, Nucleic Acids Research, Volume 47, Issue 17, 26 September 2019, Pages 9343–9357, https://doi.org/10.1093/nar/gkz678

22 https://ir.design-portfolio.co.uk/viewer/57/56135

VI. Disease Surveillance, Diagnostics and Monitoring

20. Infectious disease and biological agent surveillance, monitoring and diagnosis are cross cutting themes of relevance to many aspects of the implementation and operation of the BTWC. Key themes identified for further discussion by States Parties at the Ninth Review Conference that rely on such capabilities include: national implementation under Article IV, assistance, preparedness and response under Article VII, international cooperation and assistance under Article X, confidence building and transparency, and compliance and verification.

21. A key aspect of the response to the COVID-19 pandemic was the ability to carry out disease surveillance and monitoring on a global scale, underpinned by effective diagnostic approaches such as real time PCR and enabling technologies such as whole Genome Sequencing (WGS). Surveillance is also of great importance to the agricultural sector including tracking of expanding niches of plant pathogens as a result of climate change, for example. Examples below, particularly in relation to plant health and the environment, focus on harnessing benefits from AI approaches for plant health related surveillance and monitoring.

A. Human and Animal Health

22. Avian Influenza has been a significant health security concern of recent years. Since December 2021, 10 human cases of avian influenza H5N1 have been reported globally and between 1 October 2022 and 31 May 2023, influenza H5N1 has been confirmed in birds at 185 premises in the UK. During the same period, H5N1 has also been detected in 1,024 wild birds across the UK. The UK Health Security Agency's (UKHSA) surveillance and diagnostic expertise coupled with genomic sequencing capabilities are crucial to the early detection, assessment and response to emerging health and biosecurity threats such as avian influenza. This national capability aims to identify human cases early (possible animal to human infections to help learn about transmission), assess the overall risk to human health and allow the scale up of the public health response at pace[23]. This work also contributes to initiatives such as the WHO Global Influenza Surveillance and Response System.

23. UKHSA has also demonstrated the ability to scale pathogen genomics and enable world-leading insights and analysis through well-established programmes for tuberculosis, gastrointestinal infections and COVID-19. UKHSA has built partnerships with academia and industry that could develop a future pan-pathogen genomics programme. Currently, routine whole-genome sequencing (WGS) is capable for pathogens covering some 50, 000 genomes[24].

B. Plant Health

24. AI is being used in combination with sensor data and drones, to process real time images and video analytic data for plant abiotic and biotic stress surveillance. Specifically, Machine Learning (ML) algorithms are incorporated for yield and disease surveillance and to aid prediction, with the aim of maximising crop productivity. ML is being used to predict yield pressure points, as well as pest infestations before they occur, which in turn informs overall disease severity and disease progression[25].

25. AI is also being applied in the characterisation of plant phenotypes. Image based plant phenotyping to evaluate morphological features is common practice in current plant sciences. However, practical application of this data has often been restricted by the extensive datasets

[23] https://ukhsa.blog.gov.uk/2023/06/06/ukhsas-asymptomatic-avian-influenza-surveillance-programme/

[24] https://www.gov.uk/government/publications/ukhsa-board-meeting-papers-january-2023/ukhsa-advisory-board-preparedness-for-infectious-disease-threats

[25] Singh, A.; Ganapathysubramanian, B.; Singh, A.K.; Sarkar, S. Machine learning for high-throughput stress phenotyping in plants. Trends Plant Sci. 2016, 21, 110–124.

that are difficult to process and analyse. AI now offers opportunities to overcome this burden. For instance, taking lab based and unmanned aerial vehicle (UAV) field based imaging, AI has been able to successfully detect different disease development stages of powdery mildew in squash, which will be key to the long-term management of this plant pathogen[26].

VII. Recommendations

26. The UK encourages BTWC States Parties to take into consideration S&T advancements that have dual use potential. Emphasis should be around harnessing benefit across One Health and strengthening operation and implementation of the Convention. For example, harnessing AI applications for enhanced national capacities for disease surveillance and monitoring of plant health. BTWC States Parties should also be cognisant of the ever-increasing risks posed by AMR. The UK encourages States Parties to work collaboratively with each other and with International Organisations or other relevant entities to combat the threat posed by AMR. The UK encourages States Parties to identify further examples of how S&T advancements can be collated and reported to BTWC States Parties, as part of a structured S&T review process.

[26] Abdulridha, Jaafar, et al. "Detecting powdery mildew disease in squash at different stages using UAV-based hyperspectral imaging and artificial intelligence." Biosystems engineering 197 (2020): 135-148.