World Health Organization

Emerging technologies and dual-use concerns: a horizon scan for global public health

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Preface

This publication presents the findings of an international horizon scan on dual-use research of concern (DURC) in the life sciences. Horizon scans have proved useful in identifying emerging opportunities and risks due to social and technological change. For this study, the scan was based on structured elicitation of information from experts convened by the Science Division of the World Health Organization (WHO). The final 15 priority issues were classified by the experts as to be expected in timelines from < 5 years to ≥ 10 years. The identified priorities range from governance to new and converging technologies. A clearer understanding of the areas in which life sciences research could be most seriously misused could strengthen governance and national, regional and international preparedness and response.

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Introduction

Advances in the life sciences and technology are making vital contributions to improving global health. New scientific insights that are subsequently translated into technology and refined, adapted and assimilated by innovative processes play a crucial role in advancing knowledge and addressing critical societal challenges. Yet, transformative developments in a wide range of fields can also pose risks to global health. It is therefore prudent to assess the potential adverse consequences of choosing particular technological pathways and potentially deleterious applications of technologies.

Dual-use research of concern (DURC) is defined as life science research that is intended for benefit but which might be misapplied to do harm *(1)*. Such research has increased substantially in the past two decades. It includes, for instance, synthesis of the poliovirus *(2)*, modification of the mousepox virus *(3)*, production of mammal-transmissible strains of H5N1 avian flu *(4, 5)* and, more recently, de-novo synthesis of the horsepox virus *(6)*. Dual-use issues can arise in a range of disciplines, beyond experiments for gain of function.

WHO both assesses and addresses concerns about dual use of scientific and technological developments by setting normative standards, issuing guidance and guidelines and facilitating discussions among stakeholders. In 2010, WHO issued guidance on responsible research *(7)*, and, more recently, the WHO's Thirteenth General Programme of Work (2019-2023) mandated that WHO should "be at the forefront of … new scientific fields and the challenges they pose" and should closely monitor and provide guidance on "developments at the frontier of new scientific disciplines" *(8)*. In 2020, WHO convened discussions with key stakeholder groups, including funding organizations, scientific journals and scientific academies and councils *(9)*, and issued guidance on biosafety and biosecurity in biomedical laboratories *(10)*. WHO is currently developing a new guidance framework on responsible use of life sciences.

We report here the results of an international horizon scanning exercise, organized by WHO to ensure foresight. The group of experts, from a range of disciplines, undertook a broad examination of scientific and technological developments that could give rise to concern over the next two decades and identified 15 priorities.

A horizon scan of dual-use research of concern

The WHO Science Division established a Global Health Foresight function to monitor developments and assist Member States in building "futures-thinking" and "horizon-scanning" into strategic health planning. The aim is help Member States better anticipate and prepare for a changing world, to accelerate and fully harness the gains from emerging technologies, while monitoring the risks and challenges that might arise from those technologies.

Horizon-scanning is a systematic process for identifying plausible threats and opportunities from future developments *(11, 12)*. It has been applied widely, including in related areas of biosecurity *(13)* and public health *(14)*. Previous scans have been effective in capturing impactful emerging issues *(15)*. Horizon scans are not designed to predict the future but rather to identify areas that deserve further attention and deliberation. It can provide useful information for policy and for risk mitigation.

For this horizon-scanning exercise, WHO used a structured elicitation process to identify issues that were considered plausibly to raise significant dual-use concerns and convened a multidisciplinary group of global experts to discuss them. The issues were anonymously scored and prioritized and, after discussion, reduced to a shortlist of 32 topics. The shortlist was debated before anonymous rescoring and refinement and reduced to the final list of priorities, presented below.

For the purposes of this exercise, we used the WHO definition of DURC as "life science research that is intended for benefit, but which might easily be misapplied to do harm" *(1)*. This deliberately broad definition casts a wide net to capture a wide range of issues. It emphasizes the ostensibly beneficial nature of research in the life sciences but also the risks of misuse. Such risks could have at least three sources: information generated by well-intended research; methods and technologies developed and used in such research; and the products of such research. Additional risks stem from accidents (biosafety) and possible malicious use (biosecurity). Addressing biosecurity risks can in some cases address biosafety risks and vice versa.

The issues presented consequently cover a range of areas, from governance to disease agents and new methods of delivery. We do not present a ranked list of the issues in order to avoid giving a misleading sense of precision and certainty and to avoid overemphasizing minor differences in scoring. Rather, we present the priorities according to their most likely timelines to realization, as identified by the expert group, with the exception of the identified priority governance issues, which are listed separately. The list should not be seen as one of disconnected, discrete technologies but as a system of interlinked trends. The list is also not an exhaustive list of DURC issues. The horizon scan provided a basis for further deliberation by policy-makers and researchers and for wider public engagement.

Methods

We used the Investigate, Discuss, Estimate, Aggregate (IDEA) protocol of the Delphi opinion elicitation method to survey a panel of experts. The IDEA protocol is a structured process in which a group of subject-area experts propose issues, anonymously score them and then discuss and rescore them in a final step. This approach has outperformed both the traditional Delphi method as well as prediction markets in forecasting tournaments *(16)*. The approach has been used in various areas, including bioengineering and natural resource management *(17)*.

Phase I. Contributor and issue recruitment

For recruitment, we followed both the practical guide for using the IDEA protocol *(18)* and its previous successful applications. Our aim was to identify a diverse group of experts balanced by gender, geographical distribution and discipline. We explicitly set these criteria and ensured that the participants met them, as discipline, age, cultural background and gender are effective proxies for diversity in perspectives, which ensures broad issues and improves the quality of deliberation *(19)*.

We began by drawing on relevant individuals known to the organizers and then used a "snowballing" technique, whereby these well-networked, diverse individuals were asked to recommend other relevant experts. Further candidates were identified in a brief literature review. The combination of sampling from the literature, snowballing and screening according to explicit criteria helped to ensure that the group was diverse. Each individual submitted a declaration of interests as a condition for participation. The selection exercise yielded a pool of participants with a gender balance of 49% women to 51% men, half of the participants with a natural science background and the other half with a social science background, and 40% affiliated with countries other than those that are members of the Organization for Economic Co-operation and Development.

We identified and contacted 45 participants, of whom 34 confirmed their participation and identified and scored the initial list of issues for consideration. Of the 34, 20 participated until the end of the exercise, the other 14 having time constraints, other commitments or declared interests. The participants were asked to identify plausible, high-impact, (preferably) novel issues "that will shape the future of dual-use research of concern". Participants were provided with resources and directions for drawing on scientific literature review platforms such as Meta and the WHO's Global Observatory on Health Research and Development, a short primer on mitigating biases and practising good judgement, some background reading *(20-22)* and a template for noting issues. The contributors, with input from a larger pool of colleagues,[1] proposed 78 issues. The organizers curated these into a list of 73 issues, including five created by merging overlapping proposals.

Phase II. Scoring and refining

Contributors were given a scoresheet corresponding to the long list and asked to allocate each issue a score from 1 to 100 reflecting its impact and plausibility. The voting sheet provided space for contributors to comment on the issues, and they were also asked to indicate whether they had heard of an issue, with a simple yes/no response. We calculated the z-scores for each participant's scores, which are created by subtracting the mean and dividing by the standard deviation for each issue against the participant's set. Thus, the

[1] We estimate that the participants consulted about 455 colleagues. Contributors reported only the number of people they consulted for each issue they submitted, and there may be some overlap among contributor networks.

scores account for variation in a participant's scoring. We then ranked the average z-scores across the issues and shortened the list by approximately half. This led to the creation of a shortlist of 32 issues, which included the merging of four issues into two according to participant comments. The shortlist gave the rank, novelty score and comments for each issue. This list was then sent back to participants with a second, updated scoresheet.

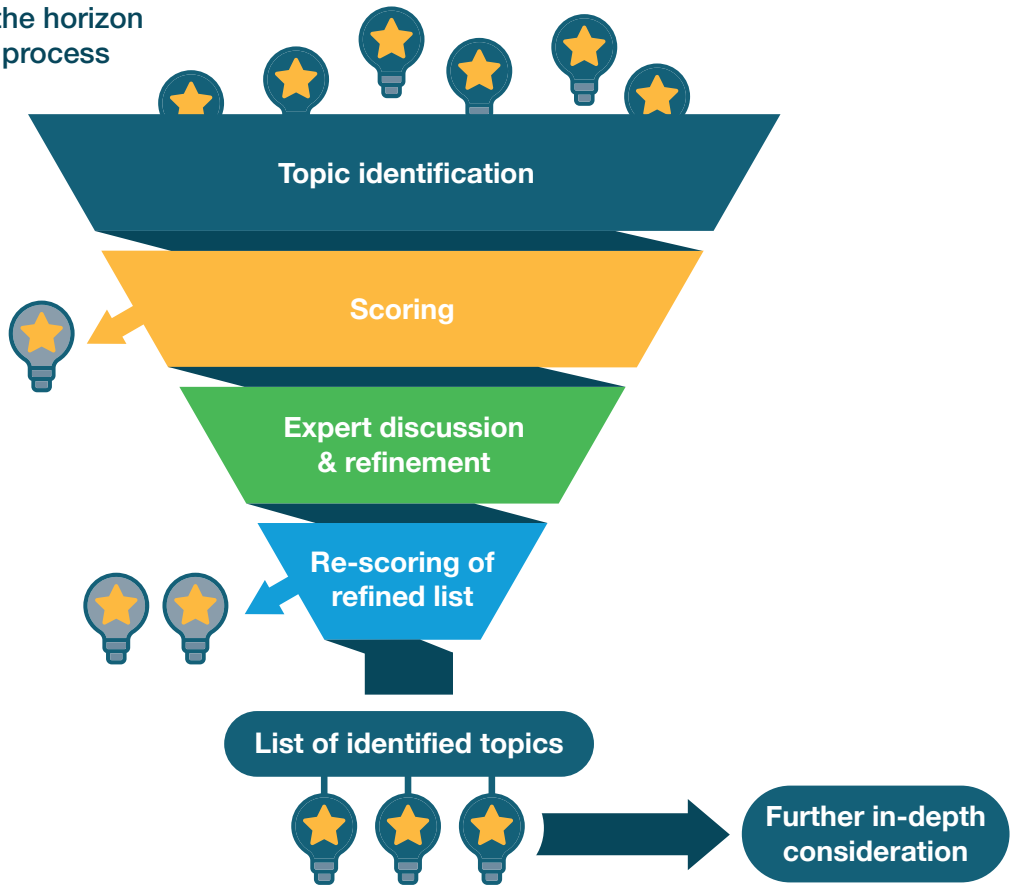
Phase III. Deliberation and aggregation

The third phase included additional research into the issues on the shortlist, online discussions and a final round of scoring. We used an online discussion forum on Microsoft Teams to allow discussion among participants. Face-to-face meetings have benefits, including making it easier for facilitators to ensure the involvement of all participants and to steer discussions; however, they allow individual non-verbal cues and charisma to bias conversations. We decided on a discussion forum both to eliminate this potential bias and because of the difficulty of convening participants during the COVID-19 pandemic.

Before the discussion forum, we allocated each researcher at least two issues, neither of which was one that they had proposed. Thus, every issue was discussed by at least three informed participants: the proposer and two researchers.

Participants were given two and a half weeks (22 October-13 November 2020) to discuss the issues critically on the online forums. These included two "summits", in which participants were asked to deliberate over 2 h. Participants were requested to contribute to at least half the issues in the forum and to attend at least one summit. After closure of the online discussion, participants scored the issues according to the same process as in phase II. Z-scores were recalculated on the basis of the new scoresheets, and the issues were re-ranked. We again shortened the list by approximately half, resulting in the final list of priorities. The organizers decided by consensus to restrict the list to 15 topics both because of the larger difference in z-scores beyond issue 15 and in order to limit the issues to a manageable number that could be discussed in sufficient detail.

Fig. 1 **Steps of the horizon scanning process**



Results

Below we summarize the 15 issues identified (Table 1). The issues are ordered by time to realization (< 5 years, 5-10 years, ≥ 10 years). These timeframes are estimates arrived at by consensus among the participants; thus, they are value judgements, not concrete, calculated timelines. Three issues were identified in this exercise that are related more closely to governance and socio-economic factors rather than technical issues. These are: the infodemic, lack of a global DURC framework and safety by design in dual-use research projects. We discuss these three issues separately below, as they do not fit the probable timelines.

Table 1 **Priority DURC issues ordered by probable timeframes**

Timeframe	Issue	Governance issues
< 5 years	Bioregulators Cloud Laboratories De Novo Synthesis of Variola Virus Research on SARS-CoV-2 Synthetic Genomics Platforms for Virus Reconstruction	The Infodemic, Misinformation, Disinformation and DURC The Lack of a Global DURC Framework Implementing Safety by Design in Dual-Use Research Projects
5–10 years	Identification of Novel Biological Constructs with Deep Learning Extreme High Throughput Discovery Systems Gain of Function Experiments in Vectors Stabilised Biological Particles for Compound Delivery Targeted Gene Drive Applications	
≥ 10 years	Hostile Exploitation of Neurobiology Nanotechnology and Nanoparticle Toxicity	

Issues identified as likely to occur within 5 years

Bioregulators

Bioregulators are biochemical compounds, such as peptides, that affect cellular processes. Research has identified a number of bioregulators and synthetic analogues that can modify life processes, including cognition, reproduction and development. Bioregulators can be used therapeutically and for diagnostic purposes. They can also be misused, and such compounds can have profound effects within minutes of exposure *(23)*. While the potential misuses of bioregulators have been known for decades, discoveries in neuroscience and neurochemistry mean that bioregulators could be used for more targeted, hostile purposes, including damage to the central nervous system, soldier enhancement, crowd suppression and behaviour manipulation *(24)*. Misuse of bioregulators, whether naturally occurring or synthetic, could include their dispersal or manipulation of functions in a target.

Cloud laboratories

Cloud laboratories are emblematic of a host of advanced service providers that are reducing the costs of and barriers to access to biotechnology through automation, robotics and the Internet. In 2017, a review of 1628 scientific papers found that 86-89% reported one or more methods that could be conducted in a cloud laboratory *(25)*. The potential impact of broader access to biotechnology services is far-reaching. Cloud laboratories offer important benefits, including reproducibility in synthetic biology *(26)* and extending access to advanced biotechnology to low- and middle-income countries.

Improved access also brings issues of biosecurity. Cloud laboratories "de-skill" research by reducing some of the knowledge requirements for conducting sophisticated research protocols. Regulations lag in this area, although voluntary measures, such as in so-called "genome foundries", have been adopted, although not universally.

De-novo synthesis of variola virus

Many viral agents have been successfully synthesized, including poliovirus, influenza virus and horsepox virus, an orthopoxvirus *(6)*. Reconstruction of orthopoxviruses has raised concern about the possibility of reconstructing the variola virus (the causative agent of smallpox), which could pose a significant public health risk. The genomic sequence of the variola virus is available, and there are few technical barriers to its re-creation *(27)*. Furthermore, other technologies are being developed that will facilitate even more rapid virus reconstruction.

WHO spearheaded the eradication of smallpox in the 1970s and continues to play a prominent role in overseeing the remaining stocks of the virus. WHO convenes an annual meeting of the Advisory Committee on Variola Virus Research to discuss research that requires use of live virus, which is held in two WHO repositories for the purpose of research into medical countermeasures. WHO also conducts biennial biosafety and biosecurity inspections of the two designated repositories. There is continuing debate about destruction of variola virus stocks *(28)*. De-novo synthesis of variola virus is prohibited by WHO recommendations *(29)*, which are currently under review in order to address the issue of research involving variola virus DNA that may be present in human remains or museum specimens. De-novo synthesis would undermine protection of the sources of the virus.

Research on SARS-CoV-2: Pathogenesis, host range and cell tropism

Research on novel infectious pathogens such as SARS-CoV-2 requires careful attention to biosafety and biosecurity. The expert group expected that there will be significant research into the determinants of the infectivity, severity and host specificity of SARS-CoV-2 within the next 5 years, as well as of its immune evasion strategies. An influx of funding for research on gain-of-function to elucidate such mechanisms may facilitate the development of better countermeasures to the virus but also the discovery of more virulent strains. The availability of such strains risks both accidental release and hostile use. The tremendous health, social and economic disruptions occasioned by COVID-19 have already led to calls to rethink gain-of-function research *(30)*.

Other emerging technologies, discussed in the next section, further heighten the risks associated with potential modification of this and other viruses.

Synthetic genomics platforms for virus and bacteria reconstruction, evolution and engineering

Recent yeast-based synthetic genomics platforms are facilitating rapid reconstruction of both large viruses and bacteria from genomic fragments found in isolation or produced elsewhere. In 2020, SARS-CoV-2 was reconstructed by this technique within 1 week *(31)*. In earlier studies with a similar approach, transformation-associated recombination, an infectious clone of herpes simplex virus type 1 was reassembled by in-vivo recombination of DNA fragments in yeast *(32)*. One significant advantage of the methods is that larger DNA and RNA segments can be used than was previously possible.

These new platforms could accelerate the development of therapeutics and vaccines and also rapidly increase understanding of genomic function. They might also allow recombination and selection of traits and wider access to potent pathogens. With rapid reconstruction of SARS-Cov-2 as proof of concept, researchers have highlighted the biosecurity implications of this technology *(33)*.

Issues identified as likely to occur within 5–10 years

Identification of novel biological constructs by deep learning

Deep-learning algorithms have a range of applications in biology and medicine, from genomic mining to identification of new treatments and pharmaceuticals *(34)*. When such deep-learning applications are extended to complex biological molecules, they are expected to increase the identification and development of new biologically active constructs with novel functions. There are many ways in which deep learning could help in finding and creating novel compounds, from library and dataset mining (for example, from genetic libraries) to predicting gene functions *(35)* and molecular functions (including for antibiotics) *(36)*.

These techniques could also be used to produce novel biologicals with properties that are not found in nature, to create toxins unrelated to any known types or to create pathogens with unique pathological properties. Conversely, these techniques could support forensic investigations of biological events *(37)*. In early studies, neural nets were used to identify the laboratory of origin of engineered DNA. Although their accuracy was initially low *(38)*, it has since improved markedly *(39)*.

Extreme high-throughput discovery systems

Extreme high-throughput screening systems allow screening of large sets of chemical, genetic or pharmacological compounds. These systems are not new, but they are becoming more modularized and accessible. In the near future, high-throughput screening could improve drug screening and the development of biological agents with greater stability, resistance to environmental stress and host range. Computational approaches have been combined with high-throughput systems and used for repurposing drugs for novel therapy *(40)*.

Pathogenicity and transmissibility remain too complex to be identified with these systems in the foreseeable future. Structures that could potentially be misused cannot be listed a priori, indicating a potential challenge for implementation and enforcement of control regimes.

Gain-of-function experiments in vectors

Vector-borne diseases impose a substantial burden on a large portion of the world's population *(41)*. Research into vectors, especially arthropods, could help to control these diseases. Aspects that are under-studied include their life cycle, trans-ovarial (intergenerational) transmission and viral replication. Manipulation of vectors might reduce risks from vector-borne diseases. Already, gene drives have been used to control vector populations, and other population-level alterations are conceivable *(42, 43)*.

Knowledge on vector modification could also be misused. Insect vectors have been used in the past to deliberately spread disease, generally crudely and inefficiently. However, research on vector physiology, including the immunological *(44)* and autophagic responses to infection, could potentially be misused to make vector-borne diseases more dangerous. This area has received scant attention in DURC policy discussions, although it is covered by regulatory frameworks *(45)*.

Compound delivery on stabilized biological and toxin particles

Novel, sophisticated ways are emerging for reliably stabilizing proteins and other biological particles. Research indicates, for instance, that tetanus antigens encapsulated in silica retain their immunogenicity *(46)*. Proteinaceous compounds have been thermo-stabilized by cyclizing *(47)* and are already being used for scaffolding biopharmaceuticals *(48)*. Encapsulation of mRNA in lipid nanoparticles has allowed stable, targeted delivery of small molecules, including, most recently, in COVID-19 vaccines *(49)*, and can be done on an industrial scale. Encapsulation and stabilizing techniques also aid in the delivery of pharmaceuticals, including vaccines, by lessening or eliminating cold-chain requirements, which would be particularly beneficial for low- and middle-income countries.

Unfortunately, stabilization technologies and techniques could also be applied to biological weapons. Environmental effects and the stability of agents have been limiting factors in many biological weapons programmes *(50)*. New approaches to stabilizing agents could make them more resistant to environmental degradation and therefore more resilient and useful for hostile deployment.

Targeted gene drive applications

Research and application of gene drives are still significantly uncertain in terms of "off-target" and "knock-on" ecological effects. Apart from its inadvertent effects, this technology could be used for various hostile purposes, from agricultural sabotage and entomological warfare to ecocide. For instance, use of gene drives in agriculture could allow widespread manipulation of crop pests *(51)*. Such research could be misappropriated to deliver hostile biological agents to agricultural systems *(52)* or have implications for vector-borne diseases, as discussed above.

Issues identified as likely to occur within ≥ 10 years

Hostile exploitation of neurobiology

Research in neurochemistry, neurobiology and neuroscience is vital to finding treatments for various neurological, neurodegenerative and mental and psychiatric disorders. This area has attracted considerable funding, particularly during the past decade *(53)*. Large research frameworks such as the European Union-funded Human Brain Project and the US National Institutes of Health Brain Initiative are examples. New insights into human neurology could, however, also be the basis for problematic applications *(54)*.

Of particular concern is neuroscientific research into assessing or modifying human thought, emotions and actions and means to affect the nervous system and alter cognitive states, behaviour and functions for performance enhancement and degradation *(55)*. This broad topic overlaps substantially with other issues raised in this horizon scan. For instance, nano-technological delivery could erode one of the main barriers to the use of agents that act on the central nervous system *(56)*. Similarly, understanding of the neurological function of bioregulators could provide another means of exploiting neurological advances for hostile purposes.

Development of chemicals that act on the central nervous system has also raised concern, as evidenced by the fact that aerosolized chemical agents that attack the central nervous system are not permitted for law enforcement purposes under the Chemical Weapons Convention *(57)*.

Nanotechnology and nanoparticle toxicity

Nanotechnology covers a wide range of technologies with an equally wide range of applications in many industries. Dual-use concern includes their application in drug conjugation and encapsulation, as well as direct targeting and specific drug release. These advances have clear health benefits, as they improve the delivery and targeting of drugs *(58)*. Several applications that benefit from nanoscale properties are already in use, such as targeted delivery of pharmacologically active compounds *(56)* and intranasal delivery of biologicals that act on the central nervous system *(59)*.

There are, however, risks of both accidental and deliberate harm. Evidence suggests that nanoparticles can have neurotoxic effects *(60)* and that nanomaterials can bio-accumulate and pose risks as environmental pollutants. In addition, nanotechnology has direct application in both defensive and offensive military technology *(56)*.

Governance

Governance issues have been separated from more technical issues in this review. They were identified, scored and discussed at the same time as the other issues, but they are listed separately as they do not conform to the timelines and also to improve the overall flow and consistency of the discussion.

The infodemic, misinformation, disinformation and DURC

Disinformation and misinformation continue to undermine global public health initiatives. Disinformation (deliberate sharing of false information to cause harm) and misinformation (sharing of false information with no harm intended) *(61)* can distort discussions, misdirect regulation and undermine social cohesion and trust. The effect of misinformation and disinformation on public health has been magnified by greater reliance on social media and the Internet as sources of news, fragmentation of the information landscape and coordinated, targeted use of disinformation at unprecedented speed and scale *(62, 63)*.

Disinformation can also be used to exploit and amplify the negative social and economic effects of public health events. It presents a powerful, low-cost way to de-legitimize scientific bodies, divert attention and resources and impede public health responses. We have included this emerging phenomenon as a priority because it directly affects the public and policy discourse, including on DURC.

WHO is working to build resilience to misinformation and disinformation. For example, in 2020, it organized three global conferences on countermeasures to infodemics, including the first "infodemiology conference", on evidence-based interventions for managing an overabundance of both accurate and inaccurate information during a health emergency *(64)*.

Safety by design in dual-use research projects

The aim of the safety-by-design approach is to consider risks and implications at the outset of a research project and making these considerations an integral part of the study design rather than an addition. A comprehensive approach to identifying the potential benefits and risks of research may improve the design and flag potential pitfalls early in the research. Safety-by-design protocols have been used widely, including in contexts relevant to DURC, in nanomedicine *(65)* and in projects in the International Genetically Engineered Machine competition. In some cases, it is a requirement for funding approval. A certain degree of flexibility will probably be required, including oversight for safety and allowing projects to change their direction and approach in light of security concerns without compromising funding.

Continued lack of a global framework for DURC

The governance of dual-use research is intrinsically international. The number of scientific collaborations is increasing, and new findings and developments diffuse quickly among countries. Previous WHO consultations have highlighted the lack of a global framework as a critical gap *(67)*, and regulations, norms and laws to address DURC remain fragmented among stakeholders and countries. This environment complicates an effective approach to addressing the risks of misuse.

DURC governance poses unique problems because of its complexity, breadth and scope. It covers a wide range of stakeholders, from individuals, community laboratories, academic institutions, funders and publishers, to industry, governments and international organizations. Governance is interconnected and multi-layered, covering policies, regulations, norms, legislation, codes and law enforcement at both national and international levels *(67)*.

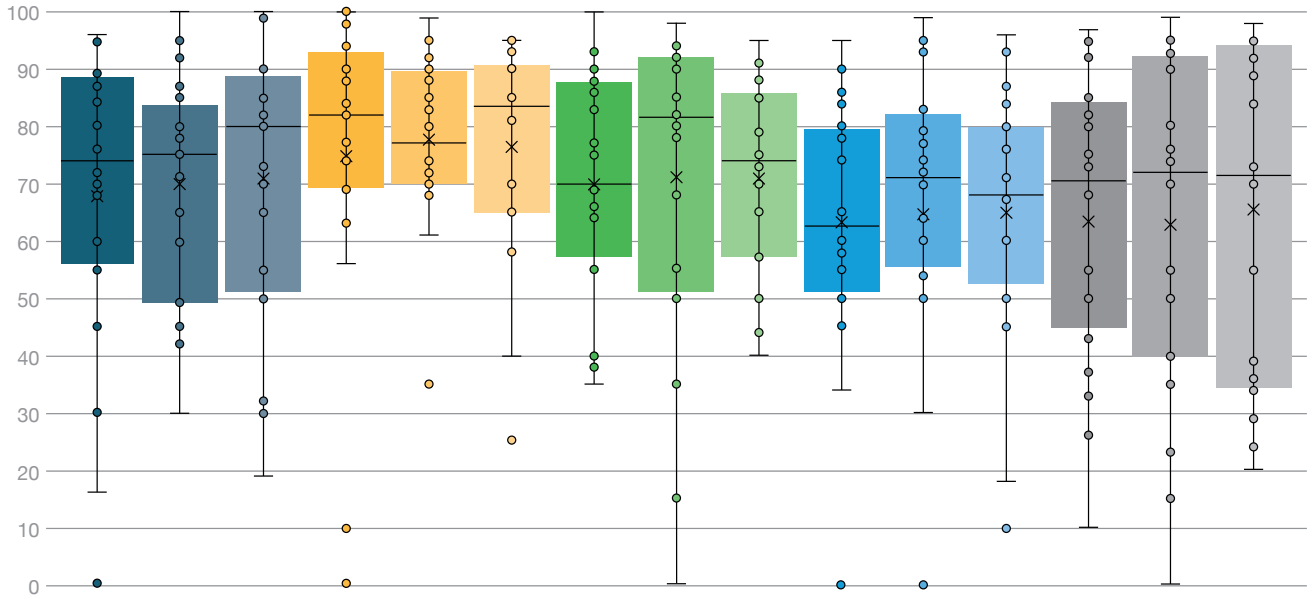
Discussion

Emerging themes

Our priority issues fall largely into three overlapping areas: new technologies, issues associated with the convergence of technical areas and governance of the life sciences. In addition to the discussion of particular issues, the definition of DURC and governance issues received sustained attention in this exercise. Fig. 2 provides an overview of variations in the scoring of the final list of priorities. Notably, the issues for which the scores varied most are those related to governance, which probably reflects differences among participants in interpretation and opinion about the significance, costs and benefits, appropriateness, sufficiency and relevance of these issues.

Fig. 2 **Variation in second-round scores for each of the final priority issues**

The 'box' represents the interquartile range, and the extending lines show the minimum and maximum scores. Thus, the issues with the smallest boxes and shortest lines were associated with the greatest convergence of opinion (with score as a proxy) and vice versa.



- Bioregulators
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- Stabilised Biological Particles for Compound Delivery
- Targeted Gene Drive Applications
- Hostile Exploitation of Neurobiology
- Nanotechnology and Nanoparticle Toxicity
- The Infodemic
- The Lack of a Global DURC Framework
- Implementing Safety by Design in Dual-Use Research Projects

Definition of DURC

While we used a broad definition for the purposes of this exercise, the contributors agreed that there are various conceptions of DURC, and different issues found in the scan were framed in different ways. The issues discussed vary widely and are multidisciplinary; their assessment is contingent on individual understanding of the area and the specific framing of the problem, whether scientific, social, economic, ethical, legal, political or related to security. They way in which these considerations are weighted against each other will result in different interpretations, even of agreed texts.

We were unable to reach consensus on a specific definition or its application. This has two important implications, one for the results of this project and one for future work on DURC. In terms of this project, different definitions of DURC may have influenced the scoring by participants and contributors. In future work, it will be difficult to agree on and apply a universally shared definition of DURC.

While a universal definition of DURC will continue to be elusive, our discussions underlined the importance of having a definition that can be applied by all countries and organizations. Issues that arise as the definition is used in specific scientific areas and in different domains of misuse should be explicitly recognized and discussed.

Governance

The governance of DURC was the second issue of significant debate in the expert group. Two issues on the priority list are specific to governance – the continued lack of a global DURC framework and safety-by-design in dual-use projects. Many more were on the initial long list, including issues such as export controls, codes of conduct, awareness-raising and capacity-building.

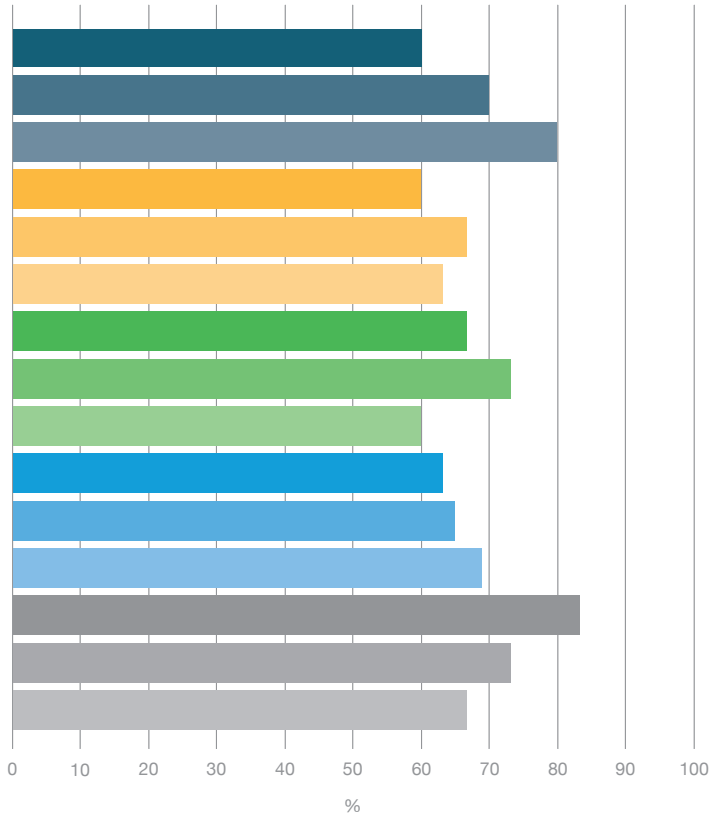
DURC governance has been widely discussed, including in multilateral and national bodies. Many proposals have been made, from codes of conduct, awareness-raising and moratoria to risk assessment and management strategies, including application of the precautionary principle *(68)*. The question is how to balance the promotion of legitimate scientific inquiry while supressing less desirable developments without excessive regulation *(69)*.

While some action has been taken at the national level *(70)*, and a number of scientific journals have instituted review processes for articles on DURC, there are still large gaps in oversight mechanisms for the funding and publication of dual-use experiments. Our study suggests that a global framework is necessary to harmonize work on the governance of DURC and for use of a safety-by-design protocol. This conclusion nevertheless raised much discussion.

Limitations and ways forward

While our exercise proved fruitful, it has several limitations. Two are inherent to Delphi-style expert elicitation, while the others apply to this particular exercise. First, any Delphi-style expert elicitation ultimately represents the subjective judgement of its participants. Ours is no exception, although a diverse group of experts participated. Secondly, the Delphi technique and its variations are not well suited for identifying high-impact, low-probability events *(71)*. We tried to address this shortcoming partly by encouraging contributors to propose "high-impact" issues according to their plausibility. Moreover, the average novelty score of priority issues was 68% (with a median of 67%), six issues having a score ≤ 65% (see Fig. 3 for an overview). These scores indicate the percentages of participants who had prior knowledge of an issue. As the group was interdisciplinary, such slight majorities in novelty scores suggest that these issues are likely to be new to many non-experts, including policy-makers. Although the participants were relatively equal with regard to gender and discipline, some areas were less well represented, and there were no participants from South or Central America.

Fig. 3 **Spread of scores for novelty**



The figure presents a graphical summary of the novelty scores for each issue, as the percentage of participants who were aware of it. It is therefore a proxy for how well known an issue was to an expert audience. The median novelty score was 67%, and the average was 68%.

- Bioregulators
- Cloud Laboratories (Outsourcing Biotechnology)
- De Novo Synthesis of Variola Virus
- Research on SARS-CoV-2: Pathogenesis, Host Range, and Cell Tropism
- Synthetic Genomics Platforms for Virus Reconstruction
- Identification of Novel Biological Constructs with Deep Learning
- Extreme High Throughput Discovery Systems for Life Sysyems
- Gain of Function Experiments in Vectors
- Stabilised Biological Particles for Compound Delivery
- Targeted Gene Drive Applications
- Hostile Exploitation of Neurobiology
- Nanotechnology and Nanoparticle Toxicity
- Infodemic, Misinformation, Disinformation and DURC
- The Lack of a Global DURC Framework
- Implementing Safety by Design in Dual-Use Research Projects

The participants were experts with a particular interest in DURC. Therefore, with the framing of the exercise, the potential risks of technologies are emphasized in both the summaries and scoring.

COVID-19 significantly affected the study, imposing virtual engagement rather than in-person deliberation. This shift removed some of the barriers to participation, as it was easier to involve experts around the world, and contributions to discussions could be made asynchronously. In-person meetings nevertheless have a dynamic that is difficult to re-create in a virtual environment. Delays at all stages and restrictions on how much time individuals could commit to the exercise were unavoidable, given that the participants and contributors were in disciplines and professions in high demand during the pandemic. We hope that the latter two limitations will be overcome in future horizon scanning exercises in this area.

Conclusions

This horizon scan identified a range of technical areas in the life sciences and related fields and gaps in governance that give rise to concern. Governance of responsible use of the life sciences and suppression of misuse concern a wide variety of stakeholders, from individuals to international organizations. They also involve multiple sectors, including health, research, environment, defence, customs, border controls and agriculture.

WHO plays a pivotal role in the complex area of governance. It addresses a number of such issues and is active, for example by convening expert groups, issuing guidelines and guidance and setting norms and standards on a wide range of topics.

Lack of a comprehensive DURC governance framework is the overarching issue and, in some sense, the most salient and germane. WHO is preparing a new guidance framework on responsible use of the life sciences, building on its guidance for "Responsible life sciences research for global health security" in 2010 *(7)* and on previous work and initiatives on research on dual use and responsible life sciences research. The new framework will also consider developments in governance, security, science and technology.

A number of areas identified in this horizon scan deserve attention, and WHO could play a critical role. For example, gain-of-function in disease vectors has considerable potential for misapplication, as described above. Monitoring and control of vector-borne diseases is a key priority for WHO, and research into the vectors of vector-borne diseases is critical to reduce the disease burden in large parts of the world. Currently, potential misuse appears to be largely overlooked in policy discourse on dual use. WHO engagement is, however, subject to resource availability and funding constraints.

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