International Best Practices regarding Biosafety and Biosecurity

A Report for TRUST working towards Equitable North South Research Partnerships

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Executive Summary

Working with infectious agents and toxins is frequently regulated by law at the national level. Safety and security considerations play key roles in driving such national regulatory activities. Substantial divergence exists at the national level when it comes to biosafety but even more so in biosecurity, despite the issuance of harmonising guidance documents issued by international stakeholders. While in the safety area common risk management concepts have emerged, national differences often arise due to lack of adequate implementation in some countries. On the other hand, international standardization in security risk management, even on a conceptual level, is still missing.

Biosafety and Biosecurity

Biosafety denotes protecting humans, animals, plants and the environment from unintentional harm, whereas biosecurity refers to intentional harm (e.g. in a military context).

This report presents and assesses the risk management elements common to widely available and used guidance documents. It concludes that the high costs of engineering controls and personal protective equipment in high risk biosafety environments precludes low-income countries from implementing such controls. Alternatives which rely on external collaborations or develop low cost alternatives exist, but also pose challenges to sustainability and capacity building of human resources. Regarding biosecurity an international risk management framework with generally agreed risk management principles is still missing. Nevertheless, international guidelines (e.g. ISO, WHO, Clean Water Act, CWA) addressing specific work environments are available or under development. In addition, the role and effect of export control legislation is briefly assessed.

This report also concludes that substantial efforts are needed to develop uniform standards in biosafety and biosecurity globally. The heterogeneous situation today poses risks to global research, where the lack of safety risk management measures increase the risk of accidental releases of infectious agents. Patchy and national security centred biosecurity risk management frameworks pose serious risks to the exchange of materials, technologies and information in international research activities. Therefore, development and implementation of accepted international frameworks in biosafety and biosecurity are urgently needed to create the necessary trust among stakeholders and limit negative impacts on global research.

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Introduction

Biosafety and biosecurity are related values, both protecting individuals and societies from harm arising from biological agents. Together they have been framed under the umbrella concept of biorisk.[2] Risks arising from biological agents are not evenly distributed among countries, and diseases that affect certain countries might not be as significant to others. For example, a unique palm tree disease relevant only to countries with palm oil production capacities challenged the international legal framework in bioweapons non-proliferation in the late 1990s.[3]

In addition, unlike biosafety assessments which include objective risk elements such as virulence, transmissibility, and pathogenicity, biosecurity risks also consider subjective elements like perceptions which vary tremendously between countries and have resulted in substantially different approaches to how countries address biosecurity. For example, the effect that the Amerithrax cases[4] had on US biosecurity policy was tremendous.[5] In such a complex environment which is defined by varying vulnerabilities and differences in national risk perceptions, developing international best practices for biosafety, and especially biosecurity becomes challenging, and consequently levels of and ways to ensure safety and security vary considerably between countries.

Biosafety also has different facets, ranging from laboratory-based framings focusing on human infectious diseases[6] to environmental-related framings focusing on the introduction of genetically modified organisms (GMOs) into the environment.[7] Biosafety-relevant risk management approaches are currently addressed in legal instruments like international treaties[8] and national laws as well as in legally non-binding international[9] and national guidelines,[10,11] as well as in best practice guidance documents covering both safety and security within the framework of biorisk management.[12,13]

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[2] WHO Laboratory Biorisk Management: Strategic Framework for Action 2012–2016. http://www.who.int/ihr/publications/strategic_framework/en/

[3] Raymond A. Zilinskas (1999) Cuban Allegations of Biological Warfare by the United States: Assessing the Evidence, Critical Reviews in Microbiology 25:3

[4] Federal Bureau of Investigation: Amerithrax or Anthrax Investigation. https://www.fbi.gov/history/famous-cases/amerithrax-or-anthrax-investigation

[5] Matt Davenport. (2016) After Amerithrax: Biodefense in a post-9/11 America. Chemical and Engineering News. 94 (38): 36-40

[6] WHO Laboratory biosafety manual: Third edition (2004) http://www.who.int/ihr/publications/WHO_CDS_CSR_LYO_2004_11/en/

[7] Convention on Biological Diversity: Cartagena Protocol, https://bch.cbd.int/protocol/background/

[8] The Cartagena Protocol on Biosafety. https://bch.cbd.int/protocol/

[9] World Health Organisation: Laboratory Biosafety Manual - Third Edition. http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/

[10] Center for Disease Control: Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition. https://www.cdc.gov/biosafety/publications/bmbl5/

[11] Canadian Biosafety Standard (CBS) Second Edition https://www.canada.ca/en/public-health/services/canadian-biosafety-standards-guidelines/second-edition.html

[12] CWA 15793 Laboratory biorisk management. http://www.uab.cat/doc/CWA15793_2011

[13] CWA 16393 Laboratory biorisk management - Guidelines for the implementation of CWA 15793:2008. file:///C:/Users/JRath/Downloads/Cen-Laboratorybiorisk management-GuidelinesfortheimplementationofCWA157932008%20(1).pdf

Practical challenges to biosafety risk management today are often not about defining principal standards, but about resource deficiencies and their impact on implementing adequate engineering controls, acquiring relevant individual protective equipment (IPE) and establishing training resources.[14]

Biosecurity on the other hand is addressed at the international level through United Nations Security Resolutions[15] and national implementation efforts related to an international treaty, the Biological and Toxin Weapons Convention.[16] Non-binding international guidelines[17] and CWA standards[18] have been developed. The development of an ISO Biorisk management standard is currently underway.[19] An additional practical challenge to the ones already faced in a biosafety context is that threat perceptions are country-based, and often national security interests consider other countries as threats. Biosecurity risks posed by other countries are usually addressed through restricting access to knowledge, information, materials, and technologies. Restricting such assets has potential negative implications on public health and biosafety of the country affected by such access restrictions.[20,21]

Export controls are one way to limit access to resources. Export licences are built on trust. The development of an international biosecurity framework should be a confidence building measure that also supports the exchange of dual use goods. Where trust does not exist, valuable collaborations to resolve global public health problems may be at risk. The recent controversy regarding the publication of public health information addressing the transmissibility of H5N1 influenza viruses stands as an example of the practical reality of such concerns.[22]

Where trust does not exist, valuable collaborations to resolve global public health problems may be at risk.

[14] Yeh KB, Adams M, Stamper PD, Dasgupta D, Hewson R, Buck CD, Richards AL, Hay J. (2016) National Laboratory Planning: Developing Sustainable Biocontainment Laboratories in Limited Resource Areas. Health Secur. 14(5):323-30.
[15] United Nations Security Council Resolution 1540, http://www.un.org/en/sc/1540/
[16] The Biological Weapons Convention. https://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument
[17] World Health Organisation: Biorisk management Laboratory biosecurity guidance (2006) http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf
[18] Laboratory biorisk management (2011) http://www.uab.cat/doc/CWA15793_2011
[19] http://www.internationalbiosafety.org/index.php/news-events/news-menu/news-items/571-iso-35001-biorisk-management-for-laboratories-and-other-related-organizations
[20] Atlas RM, Dando M. (2006) The dual-use dilemma for the life sciences: perspectives, conundrums, and global solutions. Biosecur Bioterror.;4(3):276-86.
[21] *Global Policy* Forum *Iraq Sanctions: Humanitarian Implications and Options for the Future*. https://www.globalpolicy.org/component/content/article/170/41947.html
[22] Ruth R. Faden, Ruth A. Karron The Obligation to Prevent the Next Dual-Use Controversy Science. 2012 Feb 17;335(6070):802-4. doi: 10.1126/science.1219668.

Common Risk Management Standards in Biosafety

As identified above, several international and national actors have issued guidance documents regarding biosafety risk management (Table 1). All of those addressing infectious diseases in humans build on a congruent framework starting with a standardized risk assessment stage followed by a risk mitigation stage.

Table 1: Examples of Internationally used Risk Management Guidance Documents in Biosafety

Area	Title	Issuer
Laboratory Biosafety	Laboratory Biosafety Manual - Third Edition	WHO
	Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition	Center for Disease Control
	Canadian Biosafety Standard, Second Edition	Canadian Government
Environmental Biosafety	Cartagena Protocol, Annex III	Convention on Biological Diversity
Food Safety	Principles for the risk analysis of foods derived from modern biotechnology	Codex Alimentarius
	Guideline for the conduct of food safety assessment of foods produced using recombinant – DNA micro-organsims	Codex Alimentarius
	Guideline for the conduct of food safety assessment of food derived from recombinant - DNA plants	Codex Alimentarius

Risk assessment in working with infectious diseases

A critical element in the risk assessment is the nature of the infectious disease rather than the nature of the infectious agent. Therefore, it is not of critical importance whether the agent belongs to the group of bacteria, viruses, protozoa or prions. What is important is the capacity of any of these agents to cause a severe disease, the ease of spreading the disease and the existence of effective countermeasures. The output of the risk assessment step is the assignment of the agents to risk classes, ranging from 1 to 4.[23] For animal and plant pathogens different frameworks for risk classification exist.[24]

[23] DIRECTIVE 2000/54/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work. http://www.biosafety.be/PDF/2000_54.pdf

[24] http://www.biosafety.be/RA/Class/ClassBEL.html

Complications of a standardized risk assessment exist in various contexts. First, the existence of effective countermeasures (e.g. vaccination of the population) may vary from country to country and result in country-specific risk classification of identical agents. Second, genetic modifications may change the risks, and the introduction of genetic elements warrants an additional risk assessment step.[25] Third, for the use and release of genetically modified organisms in the environment and/or the use of gene drives in disease eradication more complex risk assessments are needed.[26,27] Fourth, risk analysis of GMOs in a nutritional context follows established standards with different foci than classical infectious disease-related biosafety assessments.[28, 29, 30] Finally, in the context of uncertainty regarding the existence of risks, different principles like the precautionary principle come into play.[31] The application of a precautionary approach in the context of uncertainty regarding clinical specimens Biosafety Level 2 should be followed by default.[32]

Risk Treatment

Treatment of biosafety risks builds on the outcome of the risk assessment. In the context of infectious diseases, risk assessments result in assigning the agents to one of four risk categories. Corresponding to the four risk categories are four Biosafety Levels (see Table 3). Like many other risk treatment strategies in safety they build on elimination and substitution,[33] engineering controls,[34]

[25] Hong B, Du Y, Mukerji P, Roper JM, Appenzeller LM. (2017) Safety Assessment of Food and Feed from GM Crops in Europe: Evaluating EFSA's Alternative Framework for the Rat 90-day Feeding Study. J Agric Food Chem. 12;65(27):5545-5560.

[26] Haslberger AG (2006) Need for an "integrated safety assessment" of GMOs, linking food safety and environmental considerations. J Agric Food Chem. 54(9):3173-80.

[27] Akbari OS, Bellen HJ, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P, Edwards OR, Esvelt KM1, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA, O'Connor-Giles KM, Parks AL7, Perrimon N, Port F, Russell S, Ueda R, Wildonger J. (2015) BIOSAFETY. Safeguarding gene drive experiments in the laboratory. Science 349 (6251):927-9.

[28] Codex Alimentarius: PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY CAC/GL 44-2003, http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B44-2003%252FCXG_044e.pdf

[29] Codex Alimentarius: GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODSDERIVED FROM RECOMBINANT-DNA PLANTS. http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B45-2003%252FCXG_045e.pdf

[30] Codex Alimentarius: GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS PRODUCED USING RECOMBINANT-DNA MICROORGANISMS. http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B46-2003%252FCXG_046e.pdf

[31] Jank B, Rath J. (2000) The precautionary principle. Nat Biotechnol. 18(7):697.

[32] World Health Organisation: Laboratory Biosafety Manual - Third Edition. http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/

[33] Torres L, Krüger A, Csibra E, Gianni E, Pinheiro VB, (2016) Synthetic biology approaches to biological containment: pre-emptively tackling potential risks. Essays Biochem. 60(4):393-410.

[34] Bohannon JK, Janosko K, Holbrook MR, Barr J, Pusl D, Bollinger L, Coe L, Hensley LE, Jahrling PB, Wada J, Kuhn JH, Lackemeyer MG. (2016) Safety Precautions and Operating Procedures in an (A)BSL-4 Laboratory: 3. Aerobiology. J Vis Exp. (116).

administrative controls[35] (including training,[36] work practice[37]) as well as personal protective equipment.[38] Deviations from strict compliance to guidance standards occur in practical settings especially when resources (e.g. expensive engineering controls) are missing and need to be compensated by alternatives.[39]

Biosafety-related risk treatment in environmental settings follows less standardized frameworks[40] and is often further complicated by political interests[41] while at same time unfolding within a considerable amount of risk uncertainty. Biosafety in the context of genetically modified food and feed carries similar challenges.[42]

Risk Monitoring and Risk Communication

Effective biosafety relies on risk monitoring and risk communication; both require access to adequate and up-to-date information and detection technologies. Accessibility to relevant information as well as technologies however can be limited (e.g. high costs, information and technology access restrictions[43]), or in the event of certain gene editing technologies be undetectable.[44]

To conclude on biosafety in international research, globally standardized and accepted risk management frameworks for biosafety have been developed (see Table 1). However, many of these frameworks have not been updated for several years to adequately account for the emergence of new risk environments like genome editing[45] or environmental release of GMOs[46] and therefore are often limited in scope. Furthermore, these guidelines build on operational standards established for high containment labs in high income countries and assume access to such resources, whether they

[35] Munson E, Bowles EJ, Dern R, Beck E, Podzorski RP, Bateman AC, Block TK, Kropp JL, Radke T, Siebers K, Simmons B, Smith MA, Spray-Larson F, Warshauer DM. (2017) Laboratory Focus on Improving the Culture of Biosafety: Statewide Risk Assessment of Clinical Laboratories That Process Specimens for Microbiologic Analysis.J Clin Microbiol. 56(1).
[36] Yeskey K, Hughes J, Galluzzo B, Jaitly N, Remington J, Weinstock D, Lee Pearson J, Rosen JD. (2017) Ebola Virus Training: A Needs Assessment and Gap Analysis. Health Secur. 15(3):225-229.
[37] Barkham TM. (2004) Laboratory safety aspects of SARS at Biosafety Level 2. Ann Acad Med Singapore 33(2):252-6.
[38] Nikiforuk AM, Cutts TA, Theriault SS, Cook BWM (2017) Challenge of Liquid Stressed Protective Materials and Environmental Persistence of Ebola Virus. Sci Rep. Jun 29;7(1):4388.
[39] Gilbert GL. (2015) Laboratory testing in management of patients with suspected Ebolavirus disease: infection control and safety. Pathology. Aug;47(5):400-2.
[40]Convention on Biological Diversity, Cartagena Protocol. GUIDANCE ON RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS AND MONITORING IN THE CONTEXT OF RISK ASSESSMENT https://www.cbd.int/doc/meetings/bs/mop-08/official/bs-mop-08-08-add1-en.pdf
[41] Ishii T, Araki M (2017) A future scenario of the global regulatory landscape regarding genome-edited crops.GM Crops Food. Jan 2;8(1):44-56.
[42] Jank B, Rath J. (2014) Codex guideline and Food and Agriculture Organization database on low-level presence of genetically modified plants. Trends Biotechnol. 32(4):168-9.
[43] Kaiser D, Moreno J. Dual-use research: Self-censorship is not enough. Nature. 2012 Dec 20;492(7429):345-7.
[44] Krishan K, Kanchan T, Singh B. Human Genome Editing and Ethical Considerations. (2016) Sci Eng Ethics. (2):597-9.
[45] Shinwari ZK, Tanveer F, Khalil AT. (2017) Curr Issues Ethical Issues Regarding CRISPR Mediated Genome Editing. Mol Biol. 26:103-110.
[46] Pirondini A, Marmiroli N.Riv Biol. (2010) Environmental risk assessment in GMO analysis. 103(2-3):371-402.

relate to technologies, or simply knowledge and information. Low- and middle income countries, which ironically are often the most vulnerable when it comes to biosafety risks, usually have limited financial means to implement adequate engineering controls,[47] train and educate their work force and establish robust oversight structures.[48] Nonetheless, successful examples have been reported[49] and approaches to providing adequate protection despite resource limitations have been discussed[50, 51, 52, 53] and implemented.[54] Relying on external support in establishing and maintaining high containment laboratories can be a solution,[55] however, questions have been raised about the sustainability of such an approach.[56] No structured guidance is provided on how limitations in one area (e.g. engineering controls) could be substituted by increased safeguards in other areas (e.g. administrative controls) while still reaching the relevant safety level. Recent failures in effectively containing disease outbreaks in Africa,[57] and severe safety incidents in labs at highly developed research sites highlight the need for rethinking current biosafety procedures.[58] Biosafety Culture[59,60]

[47] Yeh KB, Adams M, Stamper PD, Dasgupta D, Hewson R, Buck CD, Richards AL, Hay J. (2016) National Laboratory Planning: Developing Sustainable Biocontainment Laboratories in Limited Resource Areas. Health Secur. 14(5):323-30.
[48] Sinebo W, Maredia K. (2016) Innovative farmers and regulatory gatekeepers: Genetically modified crops regulation and adoption in developing countries GM Crops Food. 7(1):1-11.
[49] Ssengooba W, Gelderbloem SJ, Mboowa G, Wajja A, Namaganda C, Musoke P, Mayanja-Kizza H, Joloba ML. (2015) Feasibility of establishing a biosafety level 3 tuberculosis culture laboratory of acceptable quality standards in a resource-limited setting: an experience from Uganda. Health Res Policy Syst. 13:4.
[50] Yeh KB, Adams M, Stamper PD, Dasgupta D, Hewson R, Buck CD, Richards AL, Hay J. (2016) National Laboratory Planning: Developing Sustainable Biocontainment Laboratories in Limited Resource Areas. Health Secur. 14(5):323-30.
[51] Mourya DT1, Yadav PD, Majumdar TD, Chauhan DS, Katoch VM. (2014) Establishment of Biosafety Level-3 (BSL-3) laboratory: important criteria to consider while designing, constructing, commissioning & operating the facility in Indian setting. Indian J Med Res. 140(2):171-83.
[52] Cui Y, Zhao J, Bei Z, Zhang K, Tong Y, Sun Y, Fang T. (2015) The application and Expectation of mobile BSL-3 laboratory during outbreak of Ebola virus disease in Serra Leone. Zhonghua Liu Xing Bing Xue Za Zhi. (9):1038-9.
[53] Diers J, Kouriba B, Ladan Fofana L, Fleischmann E, Starke M, Diallo S, Babin FX, von Bonin J, Wölfel R. (2015) Mobile laboratories for rapid deployment and their contribution to the containment of emerging diseases in Sub-Saharan Africa, illustrated by the example of Ebola virus disease. Med Sante Trop. 25(3):229-33.
[54] Salu OB, James AB, Oke BO, Orenolu MR2, Anyanwu RA, Abdullah MA, Happi C, Idris J, Abdus-Salam IA, Nasidi AS, Ogunsola FT, Tomori O, Omilabu SA. (2016) Biosafety level-2 laboratory diagnosis of Zaire Ebola virus disease imported from Liberia to Nigeria. Afr J Lab Med. 5(1):468.
[55] Wang Q, Zhou WM, Zhang Y, Wang HY, Du HJ, Nie K, Song JD, Xiao K, Lei WW, Guo JQ, Wei H, Cai K, Wang YH, Wu J, Kamara G, Kamara I, Wei Q, Liang MF, Wu GZ, Dong X. Good laboratory practices guarantee biosafety in the Sierra Leone-China friendship biosafety laboratory. Infect Dis Poverty. 2016 Jun 23;5(1):62.
[56] Bridges DJ, Colborn J, Chan AS, Winters AM, Dengala D, Fornadel CM, Kosloff B. (2014) Modular laboratories--cost-effective and sustainable infrastructure for resource-limited settings. Am J Trop Med Hyg. (6):1074-8.
[57] Kelland K (2015) Global health experts accuse WHO of 'egregious failure' on Ebola https://www.reuters.com/article/us-health-ebola-response/global-health-experts-accuse-who-of-egregious-failure-on-ebola-idUSKBN0TB10K20151122
[58] Jocelyn Kaiser (2014) Lab incidents lead to safety crackdown at CDC. http://www.sciencemag.org/news/2014/07/lab-incidents-lead-safety-crackdown-cdc
[59] Munson E, Bowles EJ, Dern R, Beck E, Podzorski RP, Bateman AC, Block TK, Kropp JL, Radke T, Siebers K, Simmons B, Smith MA, Spray-Larson F, Warshauer DM (2017) Laboratory Focus on Improving the Culture of Biosafety: Statewide Risk Assessment of Clinical Laboratories That Process Specimens for Microbiologic Analysis. J Clin Microbiol. in press
[60] Trevan T. (2015) Biological research: Rethink biosafety. Nature. Nov 12;527(7577): 155-8

has been proposed as way forward, however, it would require substantial investment in training, individual skills development and overall awareness raised.

Common Risk Management Standards in Biosecurity

The term biosecurity has multiple meanings according to different disciplines.[61] Originally, biosecurity was used to describe a set of preventive measures designed to limit the risk of transmission of infectious diseases in crops and livestock, quarantined pests, invasive alien species, and living modified organisms. For the purpose of this report biosecurity describes measures which prevent dangerous biological materials from falling into the hands of malevolent parties and follows the definition developed by the US National Academy of Sciences, which defines biosecurity as "security against the inadvertent, inappropriate, or intentional malicious or malevolent use of potentially dangerous biological agents or biotechnology, including the development, production, stockpiling, or use of biological weapons as well as outbreaks of newly emergent and epidemic disease".[62]

In contrast to globally agreed standards in biosafety, biosecurity suffers from a lack of harmonization.[63] Although international codes, guidelines and best practice models have been developed over the last 20 years (see Table 2) they either fall short in providing clear and detailed guidance on practical risk management[64] and/or are accepted only within a limited number of countries or institutions.[65] This lack of agreed standards is a problem and undermines trust between countries. Meetings of the States Parties to the Biological Weapons Convention[66] as well implementation efforts related to UNSCR 1540[67] have repeatedly focussed on promoting national implementation measures related to biosecurity. A substantial challenge in harmonizing risk management in biosecurity relates to the diversity of biosecurity concerns (e.g. national biological weapons programs, terrorist or criminal misuse) which require specific and different risk assessment and risk treatment approaches. Current guidance documents often do not distinguish between these differing risks and are therefore not practical.[68]

Lack of agreed global standards on biosecurity is a problem and undermines trust between countries

[61] https://en.wikipedia.org/wiki/Biosecurity

[62] http://nas-sites.org/biosecurity/biosecurity-101/commonly-used-terms/

[63] Sundqvist B, Bengtsson UA, Wisselink HJ, Peeters BP, van Rotterdam B, Kampert E, Bereczky S, Johan Olsson NG, Szekely Björndal A, Zini S, Allix S, Knutsson R (2013) Harmonization of European laboratory response networks by implementing CWA 15793: use of a gap analysis and an "insider" exercise as tools. Biosecur Bioterror. Sep;11 Suppl 1: S36-44.

[64] http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf

[65] http://www.uab.cat/doc/CWA15793_2011

[66] https://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument

[67] http://www.un.org/en/sc/1540/

[68] Rath J , Ischi M, Perkins D. (2014) Evolution of different dual-use concepts in international and national law and its implications on research ethics and governance. Sci Eng Ethics.20(3):769-90.

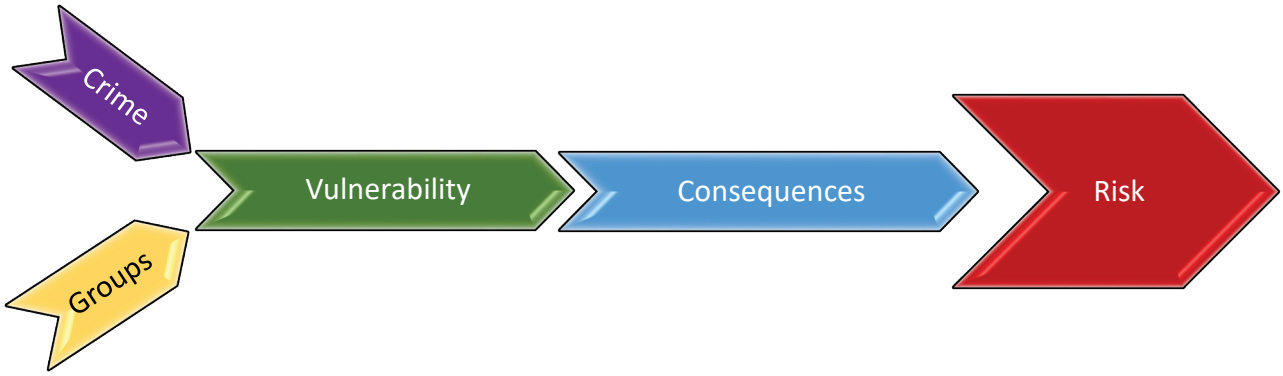
Table 2: Examples of internationally used Risk Management Guidance Documents in Biosecurity

Area	Title	Issuer
Laboratory Biosecurity	WHO, Biorisk Management: Laboratory Biosecurity Guidance	WHO
Resource Centers	OECD Best Practice Guidelines on Biosecurity in Biological Resource Centers	OECD

Risk assessment in biosecurity

Risk assessment in security is more complex than in safety and often follows a so-called threat-vulnerability-consequence (TVC) risk assessment (see Figure 1).

Figure 1: Threat Vulnerability Consequence



In such TVC assessments vulnerabilities can be expressed in objective terms (e.g. virulence and pathogenicity of agents, vaccination status of individuals, access abilities, risks of information leakage). Uncertainty levels on the extent of consequences are usually high. For example, due to the non-linearity of disease development and uncertainties over attack scenarios and exposure routes, wide varieties of scenarios with a broad range of potential outcomes are frequently discussed.[69] An even more challenging task is to define the nature (motivation) and likelihood of a threat (attack) in biosecurity. For example, the question of whether bioterrorism by certain groups is possible or likely or certain, and whether such groups would be willing to cause mass causalities makes a big difference in risk assessment. Information on such issues, if available at all, is often speculative, politically

[69] Risk and Benefit Analysis of Gain of Function Research, Gryphon Scientific (2016) http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf

motivated and/or classified. Threat assessments in biosecurity are highly challenging, making international harmonization and standardization very difficult.[70,71]

Risk Treatment

Biosecurity risk treatment usually focusses on the vulnerability element rather than the threat element. Current guidance documents outline risk treatment measures that can usually be broken down into five different categories (see Table 3).

Table 3: Biosecurity Risk Treatment Options

Type Security	Description
Physical Security	Access restrictions for external intruders to hazardous materials (e.g. stocks of pathogenic organisms)
Personnel Security	Individual reliability checks of employees with access to hazardous materials to reduce the insider-threat
Information Security	Access restrictions on security sensitive information (e.g. DNA sequence data of pathogens)
Transfer Security	Special security provisions during transfer of materials on road, plane or ship often integrated in transport safety protocols
Material controls	Keeping inventories and applying export controls allow the detection diversion of biosecurity sensitive materials

Out of the five risk treatment measures information security has been perceived as especially problematic within the research environment, for three main reasons. First, no established confidentiality procedures are established outside the area of security research. Second, classification contravenes the principles of openness and peer review which are critical to ensuring high quality research. Third, classification can have negative implications on public health because relevant information for disease surveillance, diagnostics and therapeutics development is not shared. Therefore, the use of information security measures to manage biosecurity risks needs to be carefully assessed on a case by case basis.

[70] http://www.independent.co.uk/news/world/americas/us-politics/north-korea-biological-weapons-us-revenge-trump-kim-jong-un-pyongyang-a8120376.html
[71] http://www.mirror.co.uk/news/uk-news/isis-trying-buy-chemical-biological-6886940

Although these risk treatment approaches have been clearly identified in relevant guidance documents[72,73] their practical implementation has proven to be challenging. Stringent physical security measurements (e.g. access controls) are expensive and often unaffordable in low-income settings. Personnel security measures rely on the reliability and availability of background information on individuals and quickly risk becoming discriminatory due to the application of general exclusion criteria (e.g. citizenship of a certain country). Classification and information security frameworks are not established within the international research area, and if available at all, only at the national level (e.g. national security classification, export control limitations). Although transfer security of biological materials has been addressed by relevant international institutions[74] (e.g. ADR, IATA, ICAO) it is still very limited in scope.

Risk treatment approaches in biosecurity at an international level are at best patchy and offer limited protection against state-sponsored or terrorism-related bioweapons proliferation.

The non-existence of accepted international standards and governance in this area has potential negative implications on international research collaborations. Developing and establishing such standards which are globally accepted would increase trust between stakeholders and promote more effective collaborations in infectious disease research with immediate impacts on public health.

The initiative to develop a Biorisk ISO standard therefore deserves attention.[75]

A different strategy to reduce biosecurity vulnerabilities rests on a strengthened public health system which would make societies more resilient to future bioweapons attacks. One of the reasons for the differences in national biosecurity vulnerabilities relates to national differences in public health standards, which often makes those countries with high threat levels (e.g. countries in conflict/war) also the most vulnerable to bioweapons attacks resulting in potentially catastrophic consequences. Therefore, strengthening international cooperation in infectious disease research and public health also has an immediate impact on reducing biosecurity risks.

[72] World Health Organisation. Biorisk management Laboratory biosecurity guidance (2006) WHO/CDS/EPR/2006.6, http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf
[73] CWA 15793 Laboratory biorisk management, http://www.uab.cat/doc/CWA15793_2011
[74] https://www.bureaubiosecurity.nl/en/transport_security
[75] http://www.internationalbiosafety.org/index.php/news-events/news-menu/news-items/571-iso-35001-biorisk-management-for-laboratories-and-other-related-organizations

Risk Monitoring and Risk Communication

Monitoring levels in biosecurity preparedness is hardly addressed in national and international guidance documents. The reasons for this are multi-fold, ranging from non-existent competent authorities, to the uncertain nature of risks and/or missing metrics in assessing effective security measures.

With regards to monitoring, information on how biosecurity risk communication should be done is not addressed in relevant guidance documents. Communicating risks responsibly in order to avoid unnecessary hypes and fears becomes challenging when any information on the existence of threats, attack scenarios and potential consequences is highly speculative and often politically motivated. Therefore guidance in how to do this responsibly is urgently needed.

Biorisk Management

Recent international initiatives have put integrated risk management approaches which combine safety and security under one risk management framework called biorisk management (see Table 3). The advantage of such a comprehensive approach is that overlapping risk assessment (e.g. pathogen characteristics) and risk treatment elements (e.g. inventory keeping, containment/physical security) are addressed within one framework, avoiding duplication and ensuring a more effective use of resources. Furthermore, potential conflicts between safety and security (e.g. in the context of risk communication) can be resolved within one assessment framework.

Table 4: Examples of internationally used Risk Management Guidance Documents in Biorisk Management

Area	Title	Issuer
Laboratory Biorisk Management	CWA 15793 Laboratory biorisk management	CWA
	Laboratory biorisk management - Guidelines for the implementation of CWA 15793:2008	CWA
Health Research	Responsible life sciences research for global health security	WHO

Biosafety and Biosecurity Culture

Initiatives to move beyond simple legal compliance systems have emerged in both biosafety and biosecurity.[76] These frameworks usually build on organisational culture models and focus on awareness, knowledge and responsibility at the individual and institutional level.[77] Building on a culture approach recognises that most of the incidents in safety are related to human errors. Governance models that build on culture are usually comprehensive but also introduce flexibility relative to strict compliance-based governance models in achieving desired safety and security levels. Such flexibility may allow for compensation of limitations in one area; for example the lack of engineering controls can be compensated through additional administrative controls. In a security context, the integration of security concerns into the organisational culture of an institution becomes a critical issue as awareness and vigilance are important elements in improving security. Specific frameworks for biosecurity culture have recently been developed.[78,79]

Conclusion

Several guidance documents issued by a number of national and international stakeholders dealing with biosafety and biosecurity are available. In recent years, there has been a move for the integration of biosafety and biosecurity into a comprehensive biorisk management framework. While biosafety risk management is well standardized internationally, there is still substantial divergence between countries when it comes to biosecurity. New developments like the integration of biosafety and biosecurity into one risk management framework as well as the adoption of new governance concepts building on organisational culture might provide suitable ways forward in developing a consistent global approach that is flexible enough to account for country-specific circumstances. The establishment of globally accepted frameworks, however, will be important to create trust among stakeholders and ensure that international collaborations can move ahead and are not restricted by biosafety and biosecurity concerns.

[76] Perkins D, Danskin K, Rowe AE Fostering an International Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences (2017) www.sciencediplomacy.org/article/2017/biosafety

[77] Khripunov I. Biorisk Management Culture https://www.researchgate.net/profile/Igor_Khripunov/publication/301688862_Bio_Risk_Management_Culture/links/5722347708ae262228a5ce8f/Bio-Risk-Management-Culture.pdf

[78] Rath J. Effective Implementation of UNSCR 1540 in Research and Academia: the Role of CBRN Security Culture (2014) 1540 Compass http://pakistanhouse.net/wp-content/uploads/2016/11/CBRN-2-1.pdf

[79] Khripunov I, Smidovich N, Williams DM (2017) Bio-risk Management Culture: Concept, Model, Assessment. Cyber and Chemical,Biological,Radiological,Nuclear,ExplosiveChallengesThreats and Counter Efforts ISBN 978-3-319-62107-4