Session II
Examination of Ethical Issues Associated with Gain-of-Function Studies and Discussion of Potential Decision Frameworks

Moderators:
Susan M. Wolf, J.D.
Francis L. Macrina, Ph.D.
Members, NSABB Working Group

Examination of Ethical Issues Associated with Gain-of-Function Studies

Purpose

The RBA provides information about risks and benefits associated with GOF studies but interpreting that information and making policy recommendations requires judgements and values

To aid the NSABB in its deliberations the USG commissioned an ethical analysis that:

- Reviews the ethical literature associated with GOF studies
- Discusses existing ethical and decision-making frameworks
- Proposes an ethical and decision-making framework for NSABB to consider when crafting its final recommendations

Examination of Ethical Issues – Values

NSABB WG has begun identifying values that should inform deliberations on GOF studies

- Substantive values that should be considered include:
  - Non-maleficence
  - Beneficence
  - Social justice
  - Respect for persons
  - Scientific freedom
  - Responsible stewardship
- Important procedural values in decision-making include:
  - Public participation and democratic deliberation
  - Accountability
  - Transparency

Decision-Making Strategies for Managing Risks

NSABB WG has considered a number of decision-making strategies, including the following. These, and others, are discussed in the WG's working paper and Professor Selgelid's paper.

- **Maximax –** choose the option with the best possible outcome
- **Expected Utility –** choose the option that maximizes expected utility, where expected utility for a possible outcome = probability x utility
- **Maximin –** choose the option with best outcome among the worst possible outcomes
- **Precaution –** take reasonable measures to prevent, minimize, or mitigate risks that are significant and plausible

Session II – Examination of Ethical Issues Associated with Gain-of-Function Studies and Discussion of Potential Decision Frameworks

Presenter:

Michael Selgelid, Ph.D.
Principal Author, commissioned Ethical Analysis of GOF Research

White Paper

Gain-of-Function Research: Ethical Analysis

Discussion Panelists:

- R. Alta Charo, J.D., University of Wisconsin Law School
- Jonathan Moreno, Ph.D., University of Pennsylvania
- David Fidler, J.D., M.Phil., Indiana University, Bloomington
- John Kadvany, Ph.D., Independent consultant on decision science

Submit questions: nsabb@od.nih.gov

Examination of Ethical Issues – Discussion

Questions for Discussion

- What ethical values should NSABB consider in moving beyond the risk and benefit assessments in order to formulate policy recommendations on GOF studies involving pathogens with pandemic potential?
- What ethical or other decision-making frameworks should be brought to bear when considering whether to fund and conduct certain GOF studies?
- How can ethical decisions be made in light of the inherent uncertainty associated with potential risks and benefits?
- Is there GOF research that should not be funded or conducted? If so, what are the features of such studies and what considerations should guide the identification of GOF studies that might meet such designation?

MONASH University
Centre for Human Bioethics

Gain of Function Research: Ethical Analysis

Professor Michael J. Selgelid
Director, Centre for Human Bioethics & WHO Collaborating Centre for Bioethics
Monash University
Melbourne, Australia
michael.selgelid@monash.edu

GOF Research Ethics White Paper

I. Review and summarize ethics literature on GOF research

II. Identify and analyze existing ethical- and decision-making frameworks relevant to (1) evaluation of risks and benefits of GOF research, (2) decision making about the conduct of GOF studies, and (3) the development of US policy regarding GOF research

III. Develop ethical and decision-making framework to be considered by NSABB when analyzing information provided by risk-benefit analysis, and when crafting its final recommendations

→ especially focused on policy issues regarding funding of GOF research.

→ Neutral/objective analysis explicitly requested.

Ethical/Decision Framework for GOFRC Funding

1. Research Imperative
2. Proportionality
3. Minimization of risks
4. Manageability of risks
5. Justice
6. Good Governance—Democracy
7. Evidence
8. International Outlook and Engagement

Preliminary Comments

- Should not expect formula/algorithm—judgments will inevitably need to be made.
- Suggested framework aims to highlight ethical desiderata rather than state necessary conditions.
- Emphasis on importance of democracy.

Preliminary Comments

- Judgment that a study should not be published entails judgment that it should not be funded (given HHS policy)—but need not entail judgment that the research in question should not occur.
- Decision not to fund in light of concerns about publication less weighty than decision to censor would be—because former does not involve (negative) liberty violation or interference with science.

1. Research Imperative

- Ethical acceptability of GOFR posing extraordinary risks partly depends on the importance of the research question it aims to address.
  - The more important the target research question, the more ethically acceptable a study posing a given magnitude of risk would be.
  - The riskier the research would be, the more important the research question would need to be in order for the research to be justifiable.

2. Proportionality

- The ethical acceptability of extraordinarily risky GOFR partly depends on the extent to which there is reasonable expectation that the research in question will (1) yield answers to the target public health question, and (2) ultimately result in benefits that outweigh risks involved.
  - The greater the confidence that (1) and (2) are satisfied, the greater the ethical acceptability of funding/conducting/publishing a study posing a given magnitude of risk, and vice-versa.
  - Other things being equal, the greater the expected benefits of any given case of GOFR posing a given magnitude of risk, the more ethically acceptable the study would be.

3. Minimization of Risks

- Other things being equal, the ethical acceptability of (a case of) GOFR is a function of the degree to which (1) there is confidence that no less risky forms of research would be equally beneficial and (2) reasonable steps have been made to minimize risks of the GOFR in question.

- Standard idea in human research ethics, much appealed to in GOF debate.
- Parallel to “least restrictive alternative” principle in public health ethics.
- This principle does not (necessarily) imply that a less risky study should be preferred to a more risky study if the former would be less beneficial.

4. Manageability of Risk

- Other things being equal, the more manageable the risks of GOFR study, the more ethically acceptable the study would be. Conversely, the more important/beneficial (a case of) GOFR is expected to be, the more we should be willing to accept potentially unmanageable risks.
  - Some unmanageable risks may be less severe than others.
  - GOFR might itself aim to address (other/severe) unmanageable risks.

5. Justice

- Justice: fair sharing of burdens and benefits (of research).
- Ethical acceptability of GOFR depends on the degree to which (1) risks fall on some people more than others, (2) risks fall on those who are unlikely to benefit, and/or (3) any resulting harms are uncompensated.
  - Inter alia, this principle entails that countries conducting/funding GOFR should aim to mitigate risks for those who are especially vulnerable, ensure wide availability of GOFR research benefits, and compensate those who suffer harm.

6. Good Governance--Democracy

- Hard questions about GOFR turn on important questions—about ultimate values, value weightings, and risk-taking strategies—regarding which there is reasonable disagreement.
- In a democracy, decision- and policy-making regarding GOFR should reflect the values and risk-taking strategies, etc. of the people.
- Thus need systematic ongoing engagement with key stakeholders and community at large—e.g. via processes of deliberative democracy.
- Need for transparency.
- Important r/e value of public/confidence trust.

7. Evidence

- Need for evidence based policy making r/e: risks, benefits, risk-minimization, who is likely to benefit or be harmed, values and risk-taking strategies of the people.
  - Ongoing RBA, etc.
  - Social research (r/e values and risk-taking strategies of people)
  - Monitoring of GOFR

8. International Outlook and Engagement

- Because risks and benefits of GOFR (can) affect the global community at large, the ethical acceptability of GOFR partly depends on the extent to which it is accepted abroad. Decision- and policy-making regarding GOFR should (insofar as possible) involve consultation, negotiation, coordination, and related forms of active engagement with other countries.

Notes on Framework

- Ethically relevant dimensions/desiderata (and epistemic state r/e them) are matters of degree (rather than either-or).
- Ethical acceptability of any give study will come in degrees: a spectrum of cases.

Acknowledgment:

Thank you to Dr. Nicholas G. Evans (University of Pennsylvania, Department of Medical Ethics and Health Policy) for research assistance with literature review.

NSABB Ethics Panel

Jonathan D. Moreno

January 7, 2016

How do biosecurity considerations introduce additional dimensions to the RBA and ethics analyses and what are they?

Risks

White Paper
Gain-of-Function Research: Ethical Analysis
(Draft 7 Dec 2015)

- Biosafety—i.e. dangers associated with laboratory accidents;
- ***Biosecurity***—i.e., dangers associated with crime and ***terrorism*** if pathogens are not physically secure and/or if ***malevolent actors*** gain access to them;
- Proliferation—i.e., dangers that might grow proportionally with an increased rate of GOFR, potentially in different settings with varying biosafety standards;
- Information risk—i.e., if published studies facilitate ***malevolent action*** (e.g., by ***terrorists***) or, possibly, breach of intellectual property;
- Agricultural—i.e., risks to agriculturally-relevant animals if enhanced pathogens arising from GOFR are accidentally or ***intentionally released*** into animal populations, and possible implications for human health;
- Economic risks—i.e., ***financial implications*** of (accidental or intentional) pathogen release or, possibly, opportunity costs; and
- Loss of ***public confidence***—i.e., compromise of trust (in the scientific enterprise) that could result from (accidental or ***intentional***) pathogen release.

Gryphon Report

- “Given the frequency with which these events [laboratory attacks] have happened, this analysis suggests that biosecurity be given as much consideration as biosafety.”

- As Tom Inglesby noted, even these significant incidents only tell us about known events at relatively well-managed labs.

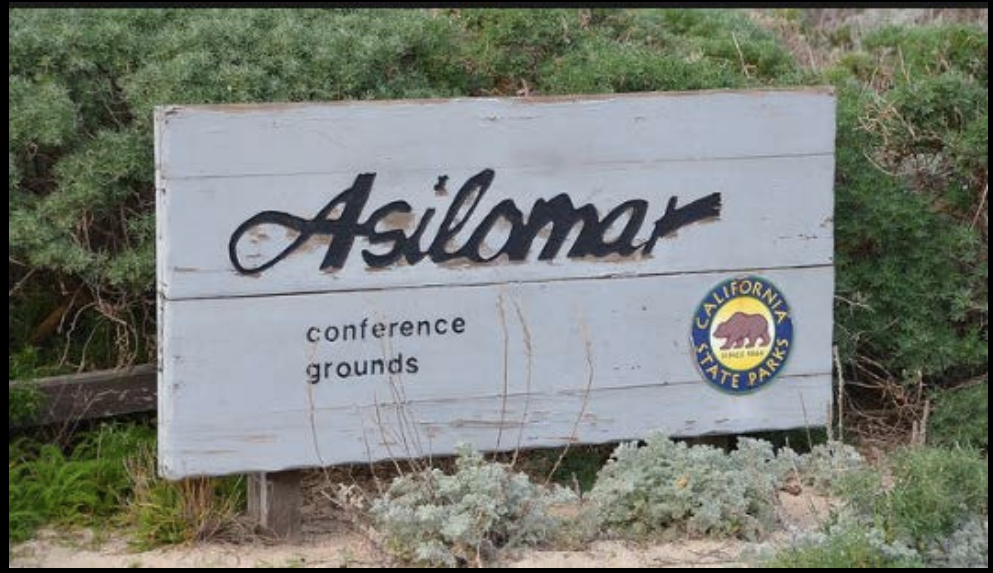
Criteria for GOF Studies of Concern

1. Highly transmissible
2. Highly virulent
3. Likely resistant

This sets a high bar for additional review. Isn't virulence enough to justify additional review?

Confidence levels for each criterion may be different if seen through a biosecurity lens, even if a long way from a "doomsday" scenario.

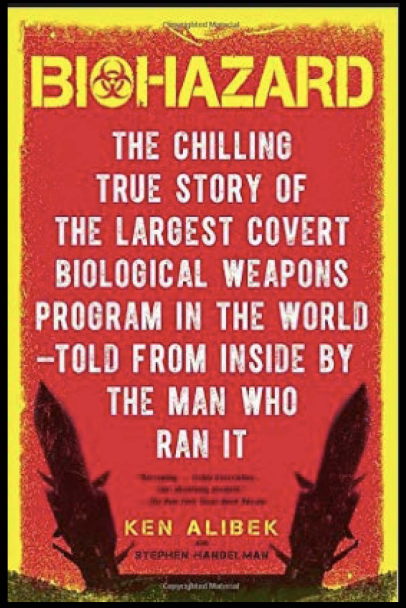
An ethnographic note on biosafety v. biosecurity in the recent history of science



Plasmid Working Group

"We believe that perhaps the greatest potential for biohazards involving alteration of microorganisms relates to possible military applications. We believe strongly that construction of genetically altered microorganisms for any military purpose should be expressly prohibited by international treaty, and we urge that such prohibition be agreed upon as expeditiously as possible."

(quoted in Krimsky 1982, Genetic Alchemy, p. 130)


BIOHAZARD
THE CHILLING TRUE STORY OF THE LARGEST COVERT BIOLOGICAL WEAPONS PROGRAM IN THE WORLD –TOLD FROM INSIDE BY THE MAN WHO RAN IT
KEN ALIBEK

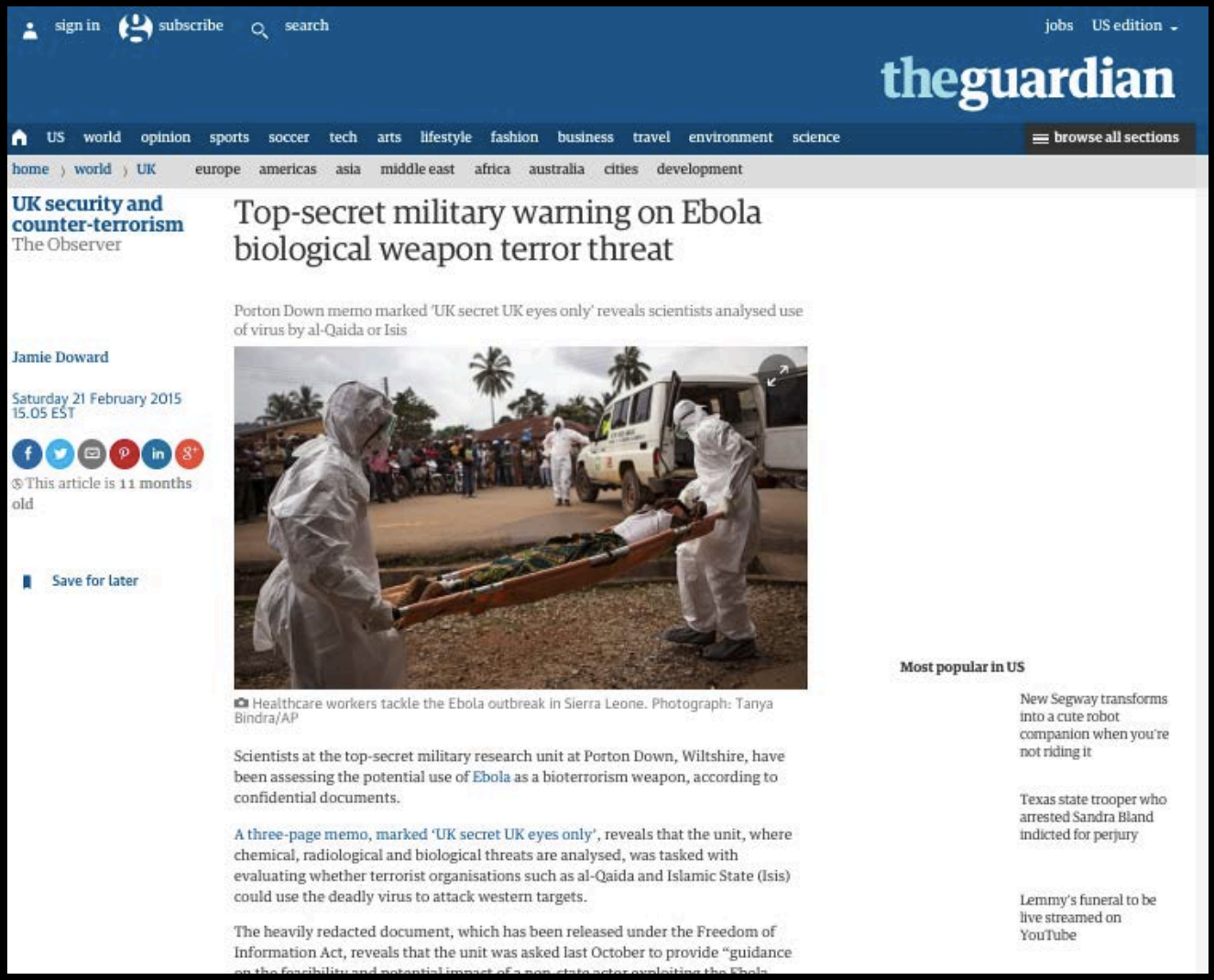

SOVIET BIOLOGICAL WARFARE INSTALLATIONS
reserve mobilization facility
biological weapon research
storage
biological weapon production facility
testing grounds
other
SWEDEN
NORWAY
FINLAND
POLAND
Baltic Sea
Vilnius
Minsk
Kirishi
Leningrad
Moscow
Zagorsk
Kuibyshev
Penza
Sverdlovsk
Volgograd
Saratov
Kurgan
Stepnogorsk
Novosibirsk
Aralsk
Aral Sea
Caspian Sea
Black Sea
TURKEY
IRAQ
IRAN
Persian Gulf
Tashkent
Almaty
AFGHANISTAN
CHINA
URAL MOUNTAINS
Barents Sea
Kara Sea
Laptev Sea
East Siberian Sea
Bering Sea
Kamchatka
Sea of Okhotsk
Lake Baikal
Irkutsk
Vladivostok
JAPAN
Sea of Japan
MONGOLIA
CHINA


DANGER ОПАСНО
BIOSAFETY LEVEL
4
УРОВЕНЬ БИОБЕЗОПАСНОСТИ

Globalsecurity.org

“Reports suggested that the Ebola virus was researched and weaponized by the former Soviet Union's biological weapons program Biopreparat. Dr. Ken Alibek, former the First Deputy Director of Biopreparat, speculated that the Russians had aerosolized the Ebola virus for dissemination as a biological weapon. The Japanese terrorist group Aum Shinrikyo reportedly sent members to Zaire during an outbreak to harvest the virus.”

Public confidence: Biosecurity focuses the public mind



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UK security and counter-terrorism
The Observer

Top-secret military warning on Ebola biological weapon terror threat

Porton Down memo marked 'UK secret UK eyes only' reveals scientists analysed use of virus by al-Qaida or Isis

Jamie Doward

Saturday 21 February 2015 15.05 EST

This article is 11 months old

Save for later

Healthcare workers tackle the Ebola outbreak in Sierra Leone. Photograph: Tanya Bindra/AP

Scientists at the top-secret military research unit at Porton Down, Wiltshire, have been assessing the potential use of Ebola as a bioterrorism weapon, according to confidential documents.

A three-page memo, marked 'UK secret UK eyes only', reveals that the unit, where chemical, radiological and biological threats are analysed, was tasked with evaluating whether terrorist organisations such as al-Qaida and Islamic State (Isis) could use the deadly virus to attack western targets.

The heavily redacted document, which has been released under the Freedom of Information Act, reveals that the unit was asked last October to provide "guidance

Most popular in US

New Segway transforms into a cute robot companion when you're not riding it

Texas state trooper who arrested Sandra Bland indicted for perjury

Lemmy's funeral to be live streamed on YouTube

Public confidence: Biosecurity focuses the public mind

SCIENCE | THE STATE OF THE UNIVERSE. | OCT. 10 2014 11:39 AM

Slate

Ebola Is Not a Weapon

Conspiracy theories are highly contagious. Here's why they're wrong.

211

By Nicholas G. Evans

Don't let this stock image of a mad scientist gaslight you. Ebola is not a bioweapon and never will be.

Photo by science photo/Shutterstock

Stop it. Just stop it. Ebola isn't a potential weapon for terrorists.

It isn't, as reported by *Forbes* and the *Daily Mail*, a **low-tech weapon of bioterror for ISIS.** It isn't the final refuge of a **lone wolf on a suicide mission,** in the words of Fox News. It isn't a U.S.-built race-targeting bioweapon, as **the leader of the Nation of Islam declared.**

Malevolence and Intent

Jihadi v. non-Jihadi killings in U.S. since 9/11

New America Foundation, December 2015

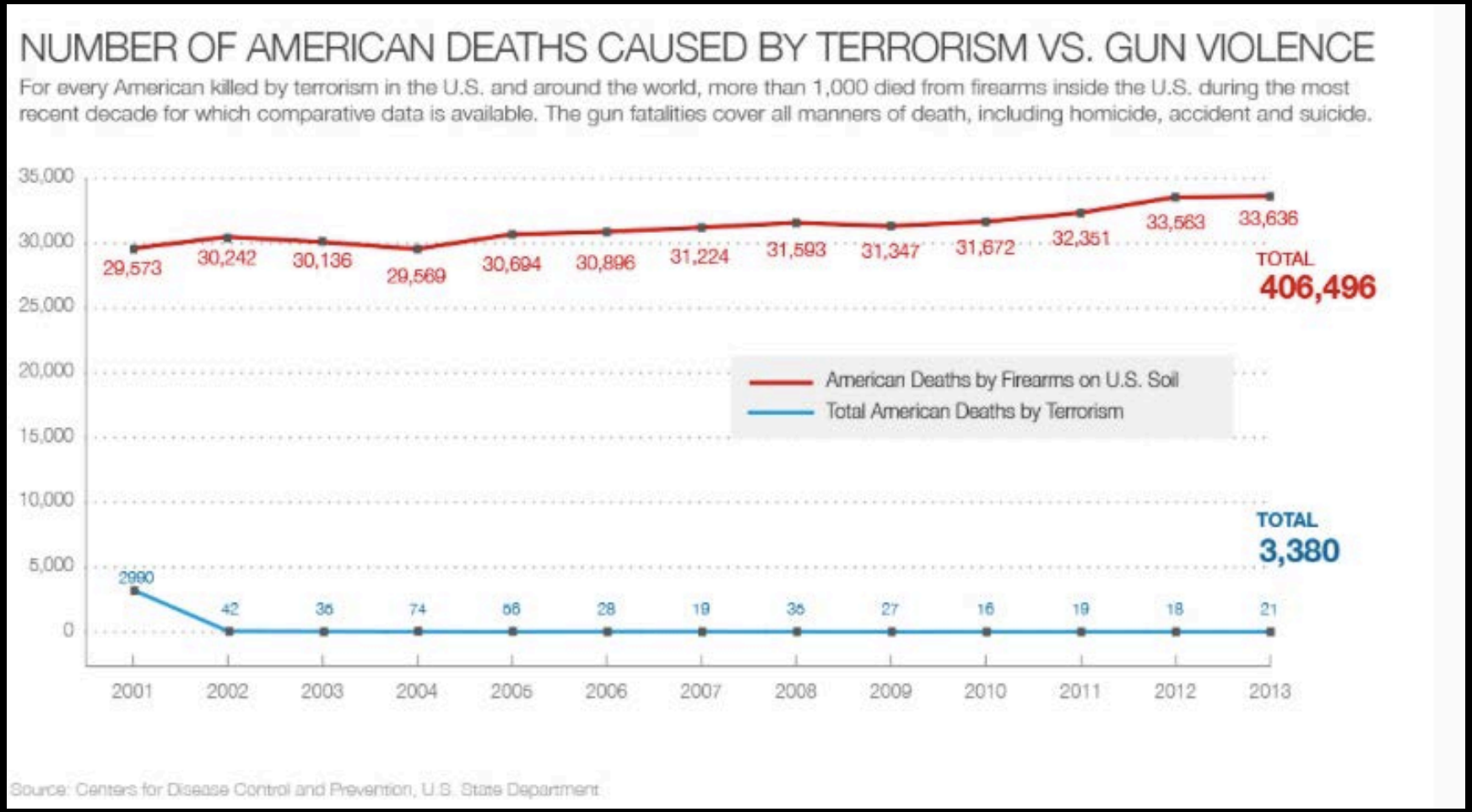
Total number of people killed: 45

Plot name	Persons killed
2015 San Bernardino Shooting	14
2015 Chattanooga, TN Military Shooting	5
2014 Washington and New Jersey Killing Spree	4
2014 Oklahoma Beheading	1
2013 Boston Marathon Bombing	4
2009 Little Rock Shooting	1
2009 Fort Hood Shooting	13
2006 Seattle Jewish Federation Shooting	1
2002 Los Angeles Airport Shooting	2

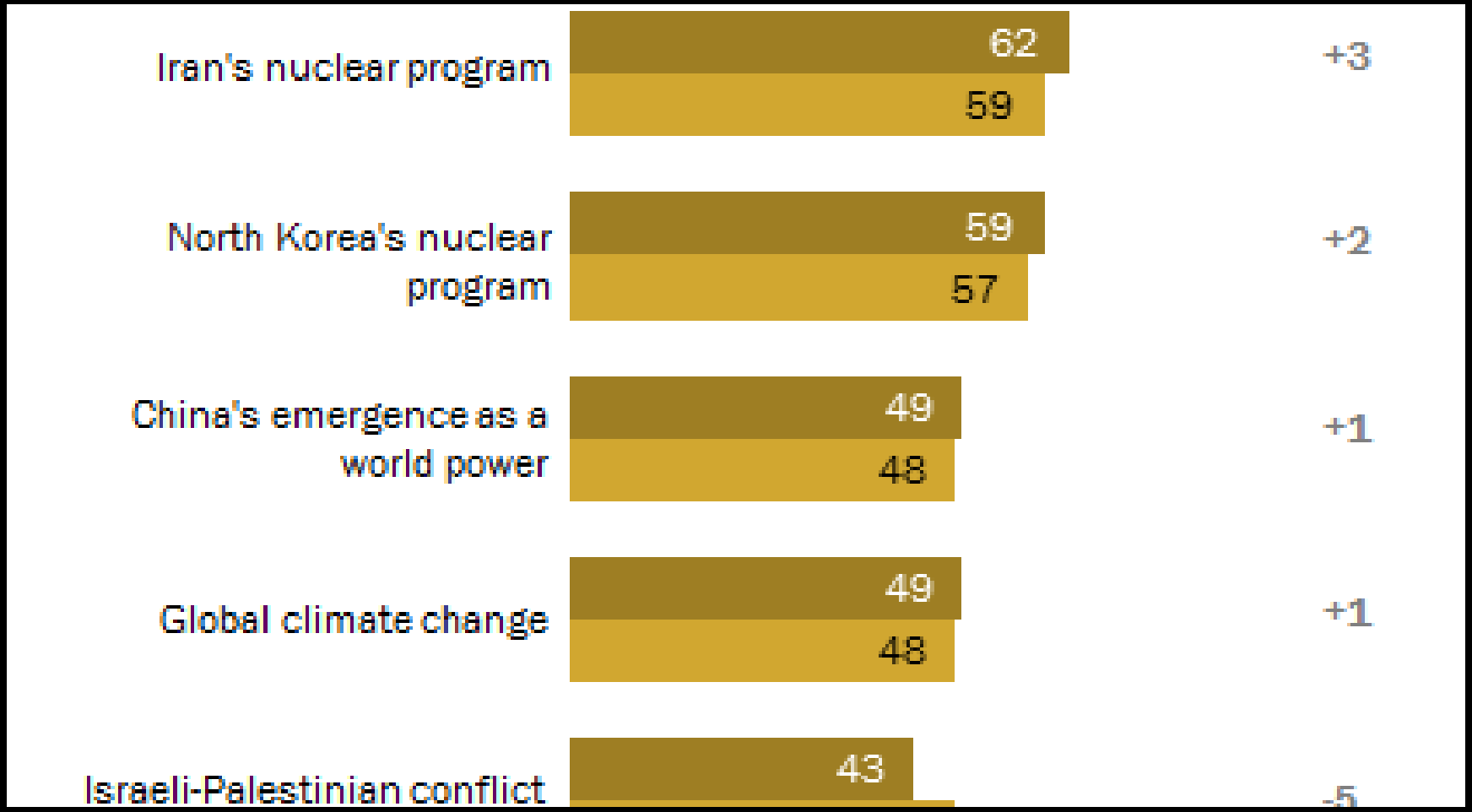
Total number of people killed: 48

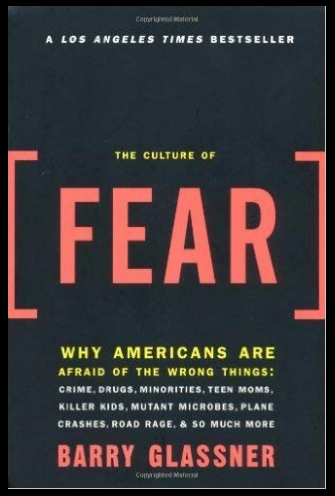
Plot name	Persons killed
2015 Colorado Planned Parenthood Shooting	3
2015 Charleston Church Shooting	9
2014 Las Vegas Police Ambush	3
2014 Kansas Jewish Center Shooting	3
2014 Blooming Grove Police Shooting	1
2012 Tri-State Killing Spree	4
2012 St. John's Parish Police Ambush	2
2012 Sikh Temple Shooting	6
2011 FEAR Militia	3
2010 Carlisle, PA Murder	1
2010 Austin, TX Plane Attack	1
2009 Pittsburgh Police Shootings	3
2009 Holocaust Museum Shooting	1
2009 George Tiller Assassination	1

Malevolence and Intent



Malevolence, terrorism and public confidence

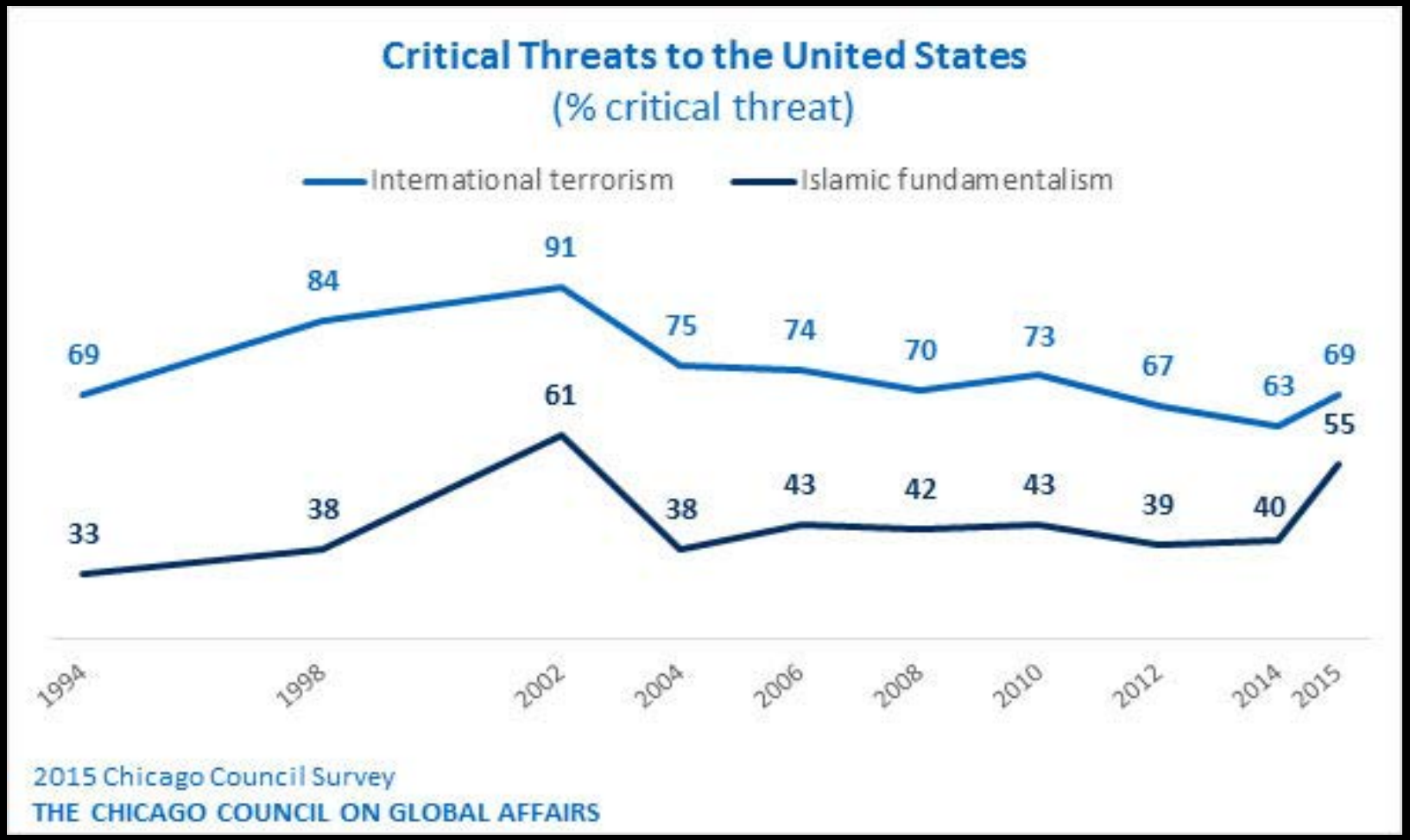




Rationality plays a very modest role in everyday risk assessment.
(see, e.g., B. Glassner, *The Culture of Fear*, 1999)

Terrorism fears are easily stimulated and provoke a loss of public confidence.

Malevolence, terrorism and public confidence



ISIS executes Head of Physics Department for refusing to develop bioweapons in Mosul

November 14, 2015 - 5:10 PM

Source : **IraqiNews** News Code : **719877**

A local source in Nineveh province said that ISIS has executed the head of the Department of Physics at the University of Mosul because of his refusal to develop biological weapons.

A local source in Nineveh province said that ISIS has executed the head of the Department of Physics at the University of Mosul because of his refusal to develop biological weapons.

The source said: "militants belonging to ISIS executed the president of the Department of Physics at the Faculty of Science in the University of Mosul," adding that, "the execution came on the back of his rejection to cooperate with the organization in the development of biological weapons, which ISIS is seeking to possess and use in the fighting against government forces."

The source, who requested to remain anonymous, noted: "The execution took place in a public square in the center of Nineveh," pointing out that, "the organization has handed over the body to the forensic medicine department."

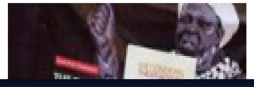
PICTORIAL

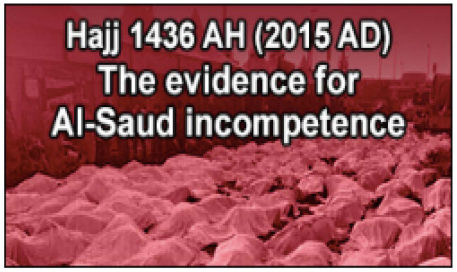
Photos: Imam Khamenei receives participants of Intl. Islamic Unity Confab

December 29, 2015 - 4:22 PM

Photos: ISIS executes Iraqi youth in Mosul

December 29, 2015 - 3:54 PM





LAST NEWS MOST NEWS CULTURAL

Grand Ayatollah Makarem Sent an Open Letter to Sheikh of al-Azhar Warning of Anti-Shia Activities

December 29, 2015 - 10:35 PM

Belgium police arrests two suspects over 'New Year plot

December 29, 2015 - 5:55 PM

Sheikh Zakzaky in good health condition: Nigerian cleric

Considering the importance of scientific freedom and the benefits of discovery for human well-being, concerns in the scientific community about alarmism with regard to what are often imponderable risks are reasonable.

Nonetheless, paraphrasing David Hume, the future only *tends* to resemble the past.

Compared to physicists and engineers, biologists are far less accustomed to scrutiny for low probability/high magnitude risks that may eventuate from their work.

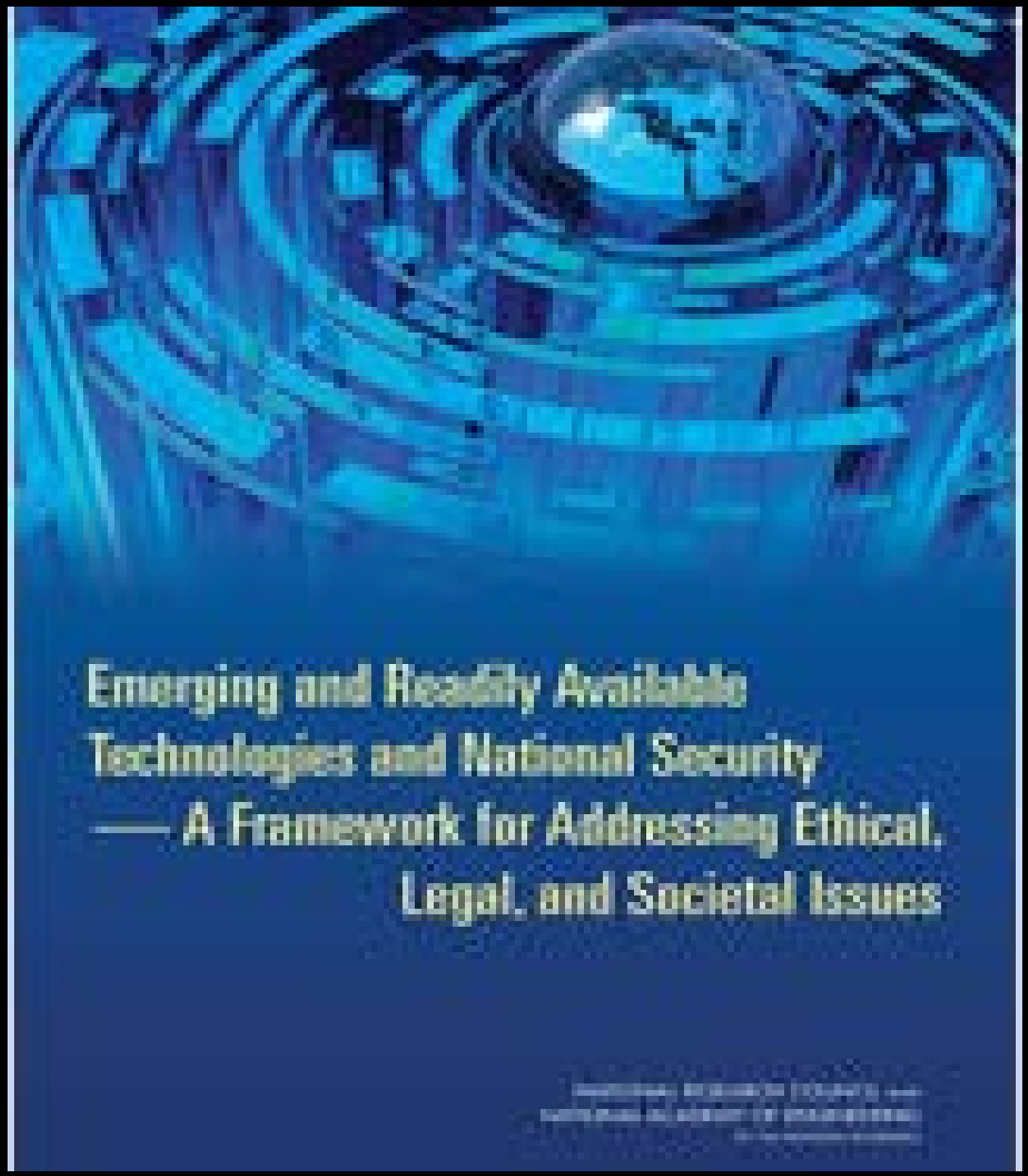
The Collingridge Dilemma

A methodological quandary in which efforts to influence or control the further development of technology face a double-bind problem:

- An information problem: impacts cannot be easily predicted until the technology is extensively developed and widely used.
- A power problem: control or change is difficult when the technology has become entrenched.

Report (2014) considered three “foundational technologies”: information technology, ***synthetic biology***, and neuroscience

“ERA technologies by their nature are associated with a very high degree of uncertainty about their future developmental paths, and thus a correspondingly broad range in the ethical, legal, and societal issues that are likely to emerge. Such breadth means that the ELSI concerns that may be associated with a given technology development are very hard to anticipate accurately at the start of that development.”



Biologic and Toxin Weapons Convention

Article I

Each State Party to this Convention undertakes never in any circumstances to **develop**, produce, stockpile or otherwise acquire or retain:

(1) Microbial or other biological agents, or toxins **whatever their origin or method of production**, of **types and in quantities** that have **no justification for prophylactic, protective or other peaceful purposes**;

Article III

Each State Party to this Convention undertakes **not to transfer to any recipient whatsoever**, directly or indirectly, and not in any way to assist, encourage, or induce any State, group of States or international organizations to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery specified in article I of this Convention.

Article IV

Each State Party to this Convention shall, in accordance with its constitutional processes, take any necessary measures to **prohibit and prevent** the **development,** production, stockpiling, acquisition, or retention of the agents, toxins, weapons, equipment and means of delivery specified in article I of the Convention, within the territory of such State, under its jurisdiction or under its control anywhere.

Article V

The States Parties to this Convention undertake to **consult one another and to cooperate** in solving any problems which may arise in relation to the objective of, or in the application of the provisions of, the Convention. Consultation and Cooperation pursuant to this article may also be undertaken through appropriate international procedures within the framework of the United Nations and in accordance with its Charter.

“Experiments of Concern”

NAS, “Biotechnology Research in an Age of Terrorism”, 2004

- demonstrating how to render a vaccine ineffective
- conferring resistance to therapeutically useful antibiotics
- ***enhancing the virulence of a pathogen or rendering a non-pathogen virulent***
- ***increasing the transmissibility of a pathogen***
- ***altering the host range of a pathogen***
- enabling the evasion of diagnosis and/or detection by established methods
- synthesizing the genome of a pathogen

- GOF appears to fall under the heading of several of these “experiments of concern”
- BTWC requires strong justification for pathogen development using any means
- As a prima facie matter, intent of the NAS and of the BTWC states parties appears to include GOF

Gain of Function Research simplified decision model

valued outcomes

(pandemic) morbidity, mortality

economic losses

new virology / public health science, tools

political outcomes

research sustainability

by demographics, regions

knowledge base

biosafety models, data

biosecurity models, data

GOFR designs, alternatives expertise

comparative history

influenza, CoV baselines 1918-now

viral spread models

policy / research options

virus type(s)	GOF / alt design	BSL design	total num labs	outbreak readiness	international coordination	editorial filters	. . .

existing practices, guidelines, pause

GOFR as public health ‘means’ and science ‘end’

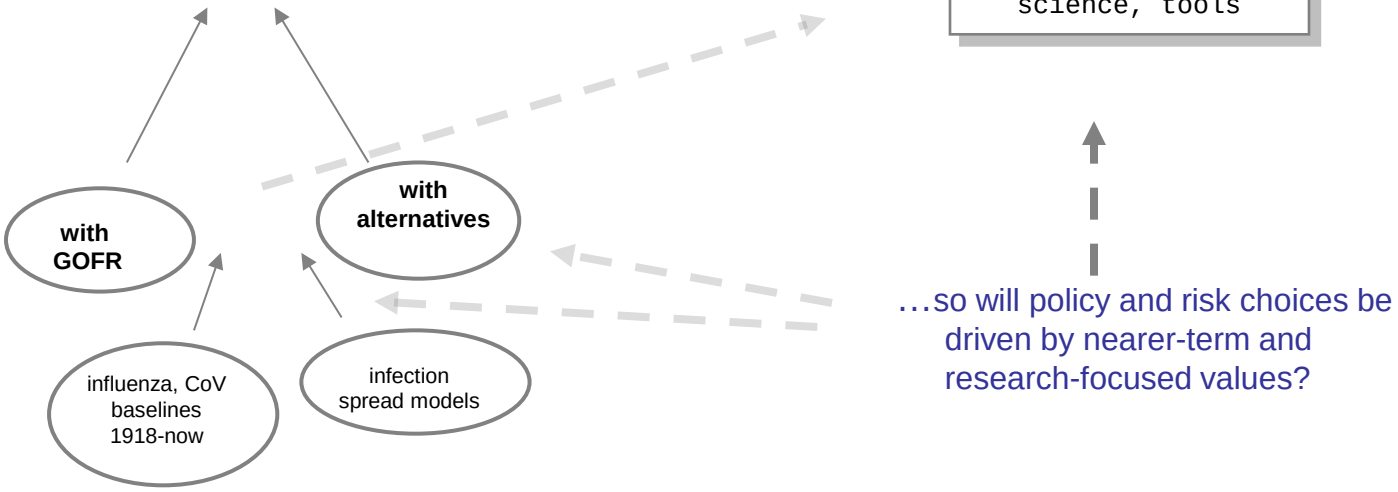
a ‘risk-risk’ tradeoff. . .

(pandemic) morbidity, mortality

… with potential risk reduction

… but often longer-term and combined with much else

new virology / public health science, tools



…so will policy and risk choices be driven by nearer-term and research-focused values?

Various risk / measurement criteria address these interactions

E.g.

- GOFR ‘of concern’
- ‘uniquely capable’ research

… a study that could generate a pathogen <u>with all of the following attributes</u>…

. . . highly transmissible in a relevant mammalian model

. . . highly virulent in a relevant mammalian model

. . . likely resistant to control measures or more capable of being spread.

(+ detail…. *NSABB draft* p.39)

GOFR risk management: complementary approaches

… a study that could generate a pathogen <u>with all of the following attributes</u>…

GOFR of concern
- … highly transmissible in a relevant mammalian model
- … highly virulent in a relevant mammalian model
- … likely resistant to control measures or more capable of being spread.

(+ detail…. *NSABB draft* p.39)

virology research risk model: virus source + event(s) → transmission / pathways → exposure / spread population outcomes

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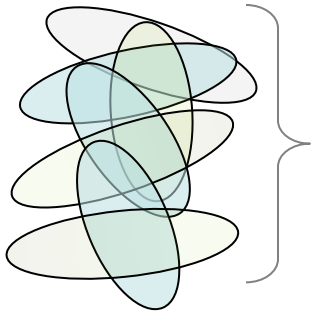
safety culture of research practice

- BSL standards, oversight, training, communication norms, management style, Select Agent Program, DURC criteria, HHS/NIH vetting, publication, etc.…



‘safety’ supported by redundancy and many mutually reinforcing risk reduction practices

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‘adaptive’ risk management process:

GOFR criteria → GOFR research decisions → research outcomes, changed epi / virus context, stakeholder views…