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Special Feature

Global Catastrophic Biological Risks: Toward a Working Definition

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The Johns Hopkins Center for Health Security is working to analyze and deepen scientific dialogue regarding potential global catastrophic biological risks (GCBRs), in a continuation of its mission to reduce the consequences of epidemics and disasters. Because GCBRs constitute an emerging policy concern and area of practice, we have developed a framework to guide our work. We invited experts from a variety of disciplines to engage with our underlying concepts and assumptions to refine collective thinking on GCBRs and thus advance protections against them.

GCBRs are a subset of global catastrophic risks (GCRs). GCRs have been previously defined as events that have the potential to produce tens to hundreds of millions of fatalities, alter the long-term trajectory of humanity, or cause the extinction of humanity as a whole.[1-3] While presumed to be of low probability, the consequences would be profound. Interest in understanding and countering GCRs has increased in recent years, because they are perceived as being poorly addressed by national governments or international organizations.[2,4] GCRs could emanate from the natural world but are more commonly thought of as a man-made consequence of powerful technologies. Frequently cited examples of GCRs include nuclear war, climate change, and pandemics of naturally occurring or deliberately engineered pathogens.[4,5]

We see GCBRs as a special category of biological threats that deserve careful study and action to counter them, because of the extraordinary consequences they would have for humanity and because they are potentially tractable. A broadly shared definition and understanding of these risks could help focus collective efforts, direct resources where needed, and communicate more clearly about what these challenges are and how to prevent and respond to them.

The Johns Hopkins Center for Health Security's working definition of *global catastrophic biological risks* (GCBRs): those events in which biological agents—whether naturally emerging or reemerging, deliberately created and released, or laboratory engineered and escaped—could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international governments and the private sector to control. If unchecked, GCBRs would lead to great suffering, loss of life, and sustained damage to national governments, international relationships, economies, societal stability, or global security.

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To describe GCBRs as a special category of risks is not to divert attention from the larger world of biological events that do not meet these criteria. Biological threats not in this category are far more common, and many have major, widespread, and complex impacts. Such biological threats are highly deserving of scientific, public health, and societal attention, and they have been and will continue to be the focus of much of our work at the Center. However, we hope that describing GCBRs as a special form of biological risk will help place new focus on extraordinary risks that have received too little study and action given their potential for harm to humanity.

We are inclined to include in the definition of GCBRs biological events with world-reaching impacts on humanity, marked by profound and lasting social, economic, and political consequences, even if those events don't necessarily carry the potential to cause millions of fatalities. This would be a distinction from prior definitions of GCRs that do have absolute fatality numbers as part of the criteria.

Goals of GCBR Study and Action

The goals of GCBR-related work should be to (1) prevent GCBRs, and, if prevention fails, (2) to make a nascent GCBR controllable before it is beyond containment, and, finally, (3) to prevent highly counterproductive responses that could turn a potentially manageable biological event into a widespread economic, civil, or security catastrophe.

Identifying pathogens most likely to fulfill GCBR criteria is of high importance, but GCBRs may emerge that are not on any planning horizon. Information needed to assess whether a large, sudden, and novel biological event has the potential to develop into a GCBR may not be available for some time after an event has begun. So, it is of high value to understand what drivers and conditions could initiate biological events with the potential to become GCBRs.

Defining Characteristics and Elements of GCBRs

- A defining characteristic of GCBRs is sustained catastrophic damage to national governments, international relationships, economies, societal stability, or global security that results from a major biological event.
- Some working definitions of GCBRs have used absolute numbers of dead or the percentage of populations killed as defining criteria; however, catastrophic societal damage may be possible by biological events that do not cause mass casualties or that cannot be quantified. For instance, a GCBR could involve widespread negative effects on human fertility or present a terrible future consequence to humanity, up to and including large reduction in the future human population or the extinction of whole peoples and the cultural diversity they represent.
- GCBRs are most likely to be sudden developments, novel, and unresponsive to available medical countermeasures (MCMs).
- Not all GCBRs are pandemics, and not all pandemics are GCBRs (see examples below).

Past Epidemics and Future Scenarios

Why Some Meet the Definition, But Many Don't

It is valuable to examine cases of actual past and hypothetical future biological events to consider to what extent they would meet the above criteria for a GCBR. The point of examining these cases is to provoke thinking about GCBR events and the prevention and containment challenges they represent and how to respond. In some cases, small changes or conditions might have transformed certain of these events into GCBRs.

2009 H1N1

At the start of this influenza pandemic, there was concern that the virus, which infected between 20% and 30% of the population, would have a high case fatality rate. Based on early indications from cases in Mexico, health authorities worried that this pandemic could lead to catastrophic loss of life (perhaps 100 million deaths or more). Moreover, experts projected that if countries started to take increasingly drastic actions to protect themselves, then national governments, international relationships, social order, and economies would sustain severe damage. However, most countries did not take such measures. Within 6 months, it became clear that the case fatality rate for 2009 H1N1 was no higher than for seasonal influenza, and concerns abated.[6] This pandemic resulted in an estimated 284,000 deaths worldwide and, because of the age distribution of the deaths it caused,[7] also led to millions of life years lost. Nonetheless, it did not have the sustained negative consequences or impact on society that would be consistent with the above working definition of a GCBR.

H5N1

In 2005-2007 there was great alarm over the pandemic potential of the H5N1 influenza virus fueled by a fast-spreading epizootic among birds throughout Asia, Europe, and Africa. Associated with this outbreak in birds were hundreds of related human cases with an alarmingly high case fatality rate. Today, H5N1 poultry outbreaks remain largely controlled, and the virus rarely infects humans. However, when human infection does occur, its case fatality rate is on the order of 50%. If this virus were to evolve—either through natural evolution or through laboratory

manipulation—to be readily transmissible between humans while maintaining its high human case fatality rate, it could be a GCBR. A virus with the capacity to spread around the world that kills 50% of those infected would lead to great suffering and loss of life, but also to sustained damage to national governments, international relationships, economies, societal stability, and global security. It is possible that extraordinary actions by governments and industry to develop vaccine and therapies could diminish some portion of the consequences. But in the current context, that process would take time, and extraordinary sustained damage to humanity would occur in the meantime.[8]

HIV/AIDS

Since the pandemic's start, more than 70 million people have been infected with the HIV virus and approximately 35 million people have died of HIV.[9] The HIV/AIDS pandemic is instructive in the potential containment of a GCBR: its possibility but also its difficulty and unevenness. Entering its fourth decade, HIV infection has evolved from a universally fatal condition to—through advances in treatment and prevention—what some consider a chronic disease, though such benefits are not uniformly distributed within and between countries.[10,11] How HIV/AIDS meets the definition of a GCBR depends upon one's perspective across time and geography. The impact on society, economies, and governments has been profound in many parts of the world.[12] In the more developed parts, effective prophylactics and treatment and a strong health infrastructure have led to substantial containment of the HIV epidemic.[13] By contrast, sub-Saharan Africa accounts for nearly 70% of the people living with HIV worldwide.[9] There, due to the high burden of disease, life expectancy has been reduced by several decades, gross domestic product has been significantly curtailed, and high rates of orphanhood and disrupted family structures have reshaped society.[12,14] To improve the global response to HIV/AIDS, strategic targeting of prevention and treatment are necessary, along with a creative mix of biomedical, behavioral, and structural interventions.[10]

The Black Death

Major demographic, social, economic, and religious transformations in the wake of the Black Death illustrate the power of GCBRs to influence the trajectory of civilization. Introduced from the Asiatic steppes, where the disease had long been endemic, bubonic plague erupted in an epidemic that spread across Europe, the Eastern Mediterranean, and North Africa from 1347 to 1352 and that came later to be called the Black Death. Overall mortality estimates for affected areas are difficult to obtain because of inadequate records but currently range from 45% to 60%.[15] Immediate local effects of the epidemic in Europe varied and included communities with a resilient social fabric as well as settlements engaged in panicked flight, searches for scapegoats, and revolt against authority.[15] The rapid depopulation and agonized efforts to explain what was seen as a divine scourge had broad, lasting, and complex effects in Europe: laborers, now in scarce supply, wielded more power in relation to the landed class and had more access to richer soils;[15,16] the persecution of Jews intensified, including mob violence, expulsion, and confinement to ghettos;[16,17] the church's institutional authority weakened, and an anti-clerical movement burgeoned;[18,19] and the resulting intellectual upheaval and discontinuity may have prompted conditions in which an age of technological innovation and the Renaissance could flourish.[15,16]

1918 Influenza

The influenza pandemic of 1918-19 killed an estimated 20 to 50 million people.[20] It has been cited as the most devastating epidemic in recorded world history, killing more people in a single year than died in 4 years of the bubonic plague. The impact of the novel flu virus that caused the 1918 pandemic was likely exacerbated by the congregation and movement of troops involved in WWI. Extraordinarily high death rates among young adults were experienced. By several measures, the 1918 flu pandemic has the characteristics of a GCBR. In addition to causing large numbers of deaths, the pandemic also caused extreme economic and social disruption in cities that struggled to care for the large number of sick and dead caused by the virus.[21] However, the impact on governments, society, and economies was not sustained over the long run. Compared to other more lethal biological threats, the 1918 flu pandemic's 1% to 2% mortality rate was lower. But today a high level of global travel could spread a flu pandemic further and faster than occurred in 1918. In addition, a high degree of workplace absenteeism from illness, fear, or government policy could cause significant interruptions to modern society, which is increasingly interconnected and dependent on just-in-time inventories. For instance, provision of drinking water relies on a functioning electric grid and cybersecurity that is personnel dependent. If a virus with similar characteristics were to emerge in today's world, it could become a GCBR, depending on the speed and character of global reaction. Certainly, if viruses emerged with similar capacity to spread but higher case fatality rates, it would be even more likely to present the broad and severe systemic challenges of a GCBR.

Wide-Area Anthrax Attack on a Major City

While anthrax is not contagious and would not spread like a virus, a large-scale anthrax attack on a major city does have the potential for major consequences. It has the

potential to cause great loss of life, especially if large amounts of anthrax bacteria were used, overwhelming the immune response of victims.[22] While medical countermeasures are available, including antibiotics, surviving inhalational anthrax depends greatly on timing of countermeasure administration and on the provision of intensive care.[23,24] Many people could die before an attack is recognized and countermeasures can be deployed, and hospitals could be overwhelmed with critically ill patients in need of respiratory assistance.[23] In the 2001 anthrax attacks in the United States, the case fatality rate for inhalation anthrax infection was 45%, even with treatment and supportive care, and there were only 11 inhalation cases.[23]

In addition to illness and loss of life, an anthrax attack on a major city would be highly disruptive to that city and would in turn likely affect national and global economies. Experts estimate that a wide-area attack would render a city uninhabitable for a prolonged period of time and cost extraordinary amounts to remediate.[25] This kind of prolonged disruption could alter a regional or a national economy over the longer term and could have much wider-ranging impacts on national and international political stability as reactions to such an event changed security and trade broadly.[25] An anthrax attack could have additional features that would make its consequences even more globally significant: resistance to medical countermeasures and repeat attacks. If multiple anthrax attacks were to occur in cities around the world, or the bacteria were resistant to drugs and vaccines, loss of life would be greatly increased, and the economic, social, and political implications would be very serious.[26]

For all those reasons, strategic efforts should be made to prevent such an event and to prepare for one should it happen. However, for the purposes of this analysis, it is not clear that even a major wide-area anthrax attack, or simultaneous such attacks on multiple cities, would have long-term GCBR impact in the way that other biological events could. There is no doubt that a country would be profoundly changed by such an attack and that other countries would take major action to prevent and respond to future anthrax events, but it is not clear that it would have lasting impact on humanity. It warrants further examination.

Smallpox

Prior to its eradication in 1977, smallpox was endemic in much of the world. It primarily affected children and had a case fatality rate of about 30%. Survivors had lifelong immunity.[27] Throughout human history, smallpox was one of many life-threatening childhood infectious diseases around the world. It was most feared and most devastating to society when it was introduced into an immunologically naïve population. When smallpox, measles, and other contagious infectious diseases were introduced into the Western hemisphere in 1492, there was an explosive epidemic that reduced the human population by an estimated 90% over a century. Native societies were decimated, and social order and economies collapsed.[28] Now, a generation after smallpox eradication and the end of routine smallpox vaccination in 1972, we have a naïve population once again—but this time it is the entire world rather than just one hemisphere. If smallpox were reintroduced, it could spread quickly and widely in a highly susceptible population.[29] Public health measures such as isolation, quarantine, and infection control practices could significantly slow the spread, and ring vaccination strategies could contain the spread eventually.[26] The societal impact of the reintroduction of smallpox would likely be a function of the efficacy of the response: how quickly exposed populations get vaccinated and how efficiently other public health interventions are implemented. Depending on the global response, the availability of vaccine, and the success or failure of government policies, a reintroduction of smallpox today would have the potential to become a GCBR.

Future Hypothetical Scenarios

We have outlined several areas that are potential sources of technological risk that could create GCBRs:

Targeted Population Threats

GCBRs may not affect all humans uniformly; biotechnological tools, if used maliciously, would allow the targeting of specific populations with pathogens. In recent years, there has been concern about the potential to create a weapon that targets an individual or a group of people with a shared genetic history. The 2012 *Atlantic* article "Hacking the President's DNA" exemplified this concern.[30] The future described in the *Atlantic* article was thought to be possible in the near term by several elite scientists—even before the development of CRISPR techniques, which will make gene editing significantly easier.[31] The ability to develop a biological weapon that preferentially targets specific populations or specific genetic characteristics could be exploited to result in a GCBR.[32,33]

Novel Strains of Known Contagious Pathogens

Established scientific techniques allow the creation of novel strains of known viruses, particularly influenza, which have never been detected in nature, and to which no population has prior immunity. These novel strains could be deliberately engineered with the goal of maintaining high virulence (such as that of H5N1) or adding respiratory transmissibility, but such refinement may not be necessary; the ability to create multiple strains through the shortening of the design-build-test cycle makes the experimental

creation of multiple strains of viruses more possible. If such a highly virulent and highly transmissible strain of influenza is released, the resulting epidemic could be a GCBR. It is also possible that such an event could result from a laboratory accident.

Widespread Eradication of Food Sources

The ability to manipulate and design pathogens is not limited to those that affect humans; with the growing understanding of the genomes of plants and animals, it will be possible to target their vulnerabilities with greater precision. If plant or animal pathogens were engineered to spread widely in the world in crops or herds, respectively, the result could be widespread and lasting food shortages.[34] This instance could lead to famines and lasting negative consequences to humanity and could be classified as a GCBR.

Novel or Artificial Organisms Harmful to Existing Life

Designing entirely novel organisms that have the broad capacity for harm is not now considered within the reach of current biotechnologies, even by accident. Over time, however, it is possible that will change. But given the uncertainties, this is a scientific area that needs to be studied and very carefully understood as it evolves, with close attention to biosafety.

Conclusion

There are natural, deliberate, and accidentally derived biological threats that could theoretically pose GCBRs. The consequences of such events could be sudden widespread disaster beyond the collective capability of national and international governments and the private sector to control, and such events could lead to great suffering and loss of life. The sustained damage to national governments, international relationships, economies, societal stability, or global security could further exacerbate the deadly effect. While GCBRs represent a small portion of biological threats in the world and should not distract us from the work to prevent and respond to other vital disease priorities, GCBRs pose such extraordinary potential consequence for humanity that they deserve their own high-level attention, risk assessment, resources, and strategic planning.

References

1. Bostrom N, Ćirković M. Introduction. In: Bostrom N, Ćirković M, eds. *Global Catastrophic Risks.* 1st ed. New York: Oxford University Press; 2008.
2. Bostrom N. Existential risk prevention as global priority. *Global Policy* 2013;4(1):15-31.
3. Beckstead N. The long-term significance of reducing global catastrophic risks. The GiveWell blog. August 13, 2015; updated September 16, 2015. http://blog.givewell.org/2015/08/13/the-long-term-significance-of-reducing-global-catastrophic-risks/. Accessed May 10, 2017.
4. Cotton-Barratt O, Farquhar S, Halstead J, et al. Global catastrophic risks 2016. Global Priorities Project website. April 2016. http://globalprioritiesproject.org/2016/04/global-catastrophic-risks-2016/. Accessed March 24, 2017.
5. Casadevall A. The future of biological warfare. *Microb Biotechnol* 2012;5(5):584-587.
6. Fineberg HV. Pandemic preparedness and response—lessons from the H1N1 influenza of 2009. *N Engl J Med* 2014;370(14):1335-1342.
7. Viboud C, Miller M, Olson D, Osterholm M, Simonsen L. Preliminary estimates of mortality and years of life lost associated with the 2009 A/H1N1 pandemic in the US and comparison with past influenza seasons. *PLoS Curr* 2010;2:RRN1153.
8. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus; Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, et al. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008;358(3):261-273.
9. World Health Organization. Global Health Observatory (GHO) data: HIV/AIDS. http://www.who.int/gho/hiv/en/. Accessed March 29, 2017.
10. Piot P, Quinn TC. Response to the AIDS pandemic – a global health model. *N Engl J Med* June 6, 2013;368(23):2210-2218.
11. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* November 2, 2013;382:1525-1533.
12. Piot P, Bartos M, Ghys PD, Walker N, Schwartländer B. The global impact of HIV/AIDS. *Nature* 2001;410(6831):968-973.
13. Joint United Nations Programme on HIV/AIDS, and World Health Organization. *AIDS Epidemic Update: 2016*. http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf. Accessed March 29, 2017.
14. Vitoria M, Granich R, Gilks CF, et al. The global fight against HIV/AIDS, tuberculosis, and malaria: current status and future perspectives. *Am J Clin Pathol* 2009;131:844-848.
15. Bowers KW. Black death (1347-1352). In: Byrne JP, ed. *Encyclopedia of Pestilence, Pandemics, and Plagues, Volume 1, A-M.* Westport, CT: Greenwood Press; 2008:56-63.
16. Hays JN. *The Burdens of Disease: Epidemics and Human Response in Western History.* New Brunswick, NJ: Rutgers University Press; 1998.
17. Caramenico DG. Black death, flagellants, and Jews. In: Byrne JP, ed. *Encyclopedia of Pestilence, Pandemics, and Plagues, Volume 1, A-M.* Westport, CT: Greenwood Press; 2008:67-69.
18. Totaro R. Black death and late medieval Christianity. In: Byrne JP, ed. *Encyclopedia of Pestilence, Pandemics, and Plagues, Volume 1, A-M.* Westport, CT: Greenwood Press; 2008:63-65.
19. Gottfried RS. *The Black Death: Natural and Human Disaster in Medieval Europe.* New York: Free Press; 1983.

20. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. *Bull Hist Med* 2002;76(1):105-115.
21. Schoch-Spana M. "Hospital's full-up": the 1918 influenza pandemic. *Public Health Rep* 2001;116(Suppl 2):32-33.
22. Gerstein DM. Countering bioterror [commentary]. RAND Corporation. January 18, 2016. http://www.rand.org/blog/2016/01/countering-bioterror.html. Accessed April 3, 2017.
23. Bartlett JG, Inglesby TV, Borio L. Management of anthrax. *Clin Infect Dis* 2002;35(1):851-858.
24. Adalja AS, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. *N Engl J Med* 2015;372:954-962.
25. Regional Recovery Framework for a Biological Attack in the Seattle Urban Area. September 2010. Prepared for the Interagency Biological Restoration Demonstration Program. http://nwrtc.pnnl.gov/PDFs/RegionalRecoveryBioAttack201009.pdf. Accessed April 3, 2017.
26. Jump Start: Accelerating Government Response to a National Biological Crisis. UPMC Center for Health Security. July 2015. http://www.centerforhealthsecurity.org/our-work/2015%20Jump%20Start/Jump%20Start. Accessed April 3, 2017.
27. Fenner F, Henderson DA, Arita I, et al. *Smallpox and Its Eradication*. Geneva: World Health Organization; 1988:1460.
28. Mann CC. *1491: New Revelations of the Americas Before Columbus*. New York: Knopf; 2005.
29. Henderson DA, Inglesby TV, Bartlett J, et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 1999;281(22):2127-2137.
30. Hessel A, Goodman M, Kotler S. Hacking the president's DNA. *Atlantic* November 2012. https://www.theatlantic.com/magazine/archive/2012/11/hacking-the-presidents-dna/309147/. Accessed April 7, 2017.
31. Church G, Casci J, Brin D, Maria CS. Sci-fi political thriller, or fact? In: Soboroff J, ed. *HuffPost Live* 2012. http://live.huffingtonpost.com/r/segment/sci-fi-political/50a06c402b8c2a65eb00070e. Accessed May 10, 2017.
32. Bowen CD, Renner DW, Shreve JT, et al. Viral forensic genomics reveals the relatedness of classic herpes simplex virus strains KOS, KOS63, and KOS79. *Virology* 2016;492:179-186.
33. Gronvall GK. Mitigating the risks of synthetic biology. Council on Foreign Relations website. February 2015. http://www.cfr.org/health/mitigating-risks-synthetic-biology/p36097. Accessed May 10, 2017.
34. Esvelt KM, Smidler AL, Catteruccia F, Church GM. Concerning RNA-guided gene drives for the alteration of wild populations. *Elife* Jul 17, 2014;3.