House Foreign Affairs Committee
Subcommittee on Asia, the Pacific, Central Asia, and Nonproliferation

Pandemic virus prediction and the proliferation of accessible weapons of mass destruction

Congressional Testimony of Professor Kevin M. Esvelt, Massachusetts Institute of Technology

Introduction

Chairman Bera, Ranking Member Chabot, and members of the subcommittee, thank you for inviting me to testify today on the subject of pandemic weapons of mass destruction.

More U.S. citizens have lost their lives to COVID-19 than have perished in combat in all of our nation's wars. While pandemic prevention is commonly viewed to be a problem of public health, recent technological advances have made pandemics a still greater, largely unappreciated challenge for national security and nonproliferation.

Bluntly, any virus capable of causing another pandemic is a weapon of mass destruction (WMD).

If successful, efforts to identify particular viruses that could cause pandemics, whatever their motive, would deliver blueprints for how to make biological WMDs. At that point, anyone who could obtain samples of the virus would have their hands on an arsenal.

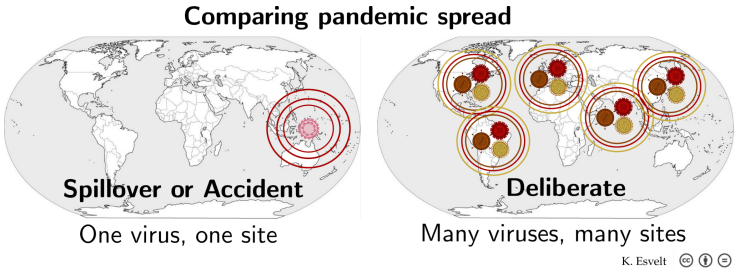
Thanks to advances in virology and biotechnology, many actors are capable of producing most viruses by following detailed step-by-step protocols – hundreds of times more actors than there are nuclear-armed states. Worse, a subset of our well-meaning efforts to prevent or mitigate natural pandemics explicitly seek to identify particular viruses that could cause them, inadvertently threatening our security without accelerating vaccine development.

As a practicing biotechnologist who specializes in controlling evolution, using viruses as engineering tools, and inventing ways to edit organisms in the lab that will controllably spread to affect wild species,[1] I am reasonably confident that pandemic virus prediction poses a greater immediate and potentially catastrophic national security risk than anything else in the life sciences.

To help understand the framework for this conclusion, my assessment considers questions of threat magnitude, proliferation, credibility, utility, and potential defenses. Fortunately, there is much we can do to delay the identification of pandemic-class weapons for long enough to build sufficient defenses.

Pandemic weapons can inflict harm greater than nuclear weapons or equivalent natural pandemics

SARS-CoV-2 has demonstrated that a single pandemic virus spreading from a single point of origin can cause more deaths than any nuclear weapon, inflicting trillions in economic damages and disrupting lives worldwide. This can occur regardless of whether the origin is a natural spillover or a lab accident, which are known to occur at high rates no matter what did or did not occur in Wuhan in 2019.[2]



[1] Esvelt, Carlson, and Liu, "A System for the Continuous Directed Evolution of Biomolecules"; Esvelt et al., "Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations"; Noble et al., "Daisy-Chain Gene Drives for the Alteration of Local Populations."

[2] Sewell, "Laboratory-Associated Infections and Biosafety"; Merler et al., "Containing the Accidental Laboratory Escape of Potential Pandemic Influenza Viruses"; Klotz and Sylvester, "The Consequences of a Lab Escape of a Potential Pandemic Pathogen"; Lipsitch and Inglesby, "Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens"; Gryphon Scientific, "Risk and Benefit Analysis of Gain of Function Research"; Manheim and Lewis, "High-Risk Human-Caused Pathogen Exposure Events from 1975-2016"; Bloom et al., "Investigate the Origins of COVID-19."

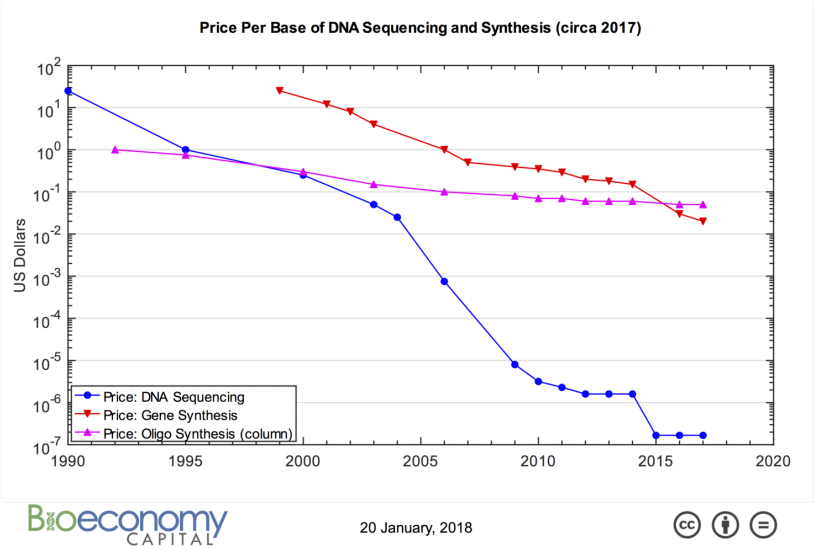
Engineered viruses could be much worse than any natural pandemic, at least for a time. However, enhancement requires a full-scale and uncertain research project. A malevolent actor could much more easily cause severe damage by releasing many natural pandemic viruses – perhaps more than would normally spill over from animals in a century – across several travel hubs. This possibility suggests we should not only strive to reduce the number of individuals capable of acquiring pandemic weapons of mass destruction, but also to minimize the number of known pandemic viruses.

Successful pandemic virus prediction will increase WMD proliferation at least a hundred-fold

How many actors currently have access to credible pandemic-class weapons? As far as we know, zero.
How many are likely to acquire them in the near future? Thousands.
Can such proliferation be delayed or prevented? Yes.

This is why pandemic nonproliferation appears to be a national security issue of the utmost importance.

Acquiring a pandemic-class weapon requires 1) knowing of a virus that would cause a new pandemic, and 2) obtaining an infectious sample. Twenty years ago, the only way to obtain physical virus samples was from clinical specimens or laboratory stocks. Today, most viruses can be assembled using synthetic DNA and a virus assembly protocol.



Synthetic DNA

In 2002, poliovirus was successfully assembled from chemically synthesized DNA.[3] Since then, the cost of synthetic genes has fallen by a factor of a thousand. The members of the International Gene Synthesis Consortium, an industry group, have taken the lead in voluntarily screening customer orders for dangerous agents at their own expense, going well beyond the weak regulatory requirements imposed by the Department of Health and Human Services.[4] However, members comprise only an estimated 80% of the market and the membership list is publicly available[5], making it straightforward to obtain DNA that is not screened.

Virus assembly protocols and skilled individuals

Meanwhile, virus assembly instructions have been developed for nearly all families of viruses to aid research on treatments. For well-studied viral subfamilies, these step-by-step protocols are so detailed that they are readily accessible to non-specialists. A recently published step-by-step protocol to engineer

[3] Cello, Paul, and Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template."
[4] Diggans and Leproust, "Next Steps for Access to Safe, Secure DNA Synthesis."
[5] International Gene Synthesis Consortium, "Harmonized Screening Protocol V2."

SARS-CoV-2 explicitly stated that it aimed to "enable researchers from different research backgrounds to master the use of the reverse genetic system" and was made freely and indefinitely available.[6]

As a result, many scientists, engineers, and lab technicians have the skills required to obtain infectious viruses from publicly available genome sequences. In the U.S. alone, twenty-five new individuals receive their doctorate in the life sciences or bioengineering each day.[7] Over the last 30 years, over two million people have received an equivalent degree per OECD records.[8] Even assuming that only one in twenty received any training in mammalian cell culture – which is especially common among biomedical researchers – and that just one in twenty of the remainder are skilled and well-practiced enough to successfully follow a virus assembly protocol, over 5,000 doctorates worldwide can generate most known viruses for which a relevant assembly protocol is available. The number of research technicians and students may be comparable. Many presumably already have access to relevant laboratory facilities, which can in any case be obtained with an upper-middle-class salary in most developed nations.

The skills of these individuals are vital to developing the bioeconomy, which will be essential to human health, industrial production, environmental protection, and the continued development of a flourishing and sustainable society. Therefore, it is safe to assume that the number of individuals capable of single-handedly assembling viruses from synthetic DNA will continue to grow.

With publicly accessible viral assembly protocols, many individuals with the skill and facilities to use them, and a lack of comprehensive DNA synthesis screening for illicit activity, it's safe to assume that thousands of individuals could assemble an infectious pandemic-capable virus once we identify one.

Credibility is required before a pandemic virus can be used as a weapon

Malevolent actors won't bother trying to assemble a virus as a weapon unless they're at least marginally confident that it would cause a pandemic. There are millions of viruses in nature and probably only a few hundred could cause pandemics, so the odds are poor. Even if a foreign weapons program were to identify or create one, they can't use it to threaten or coerce the United States or the international community without evidence: we don't believe nations are nuclear powers until they've conducted a nuclear test. The global scientific community, arguably the arbiter, will only believe a virus is pandemic-capable if the right experiments are performed, ideally by multiple independent laboratories. If governments block the key experiments required to raise the scientific credibility that a given virus could cause a pandemic, it won't be assembled, used to threaten others, or released as a weapon.

Software tools can help predict whether a given virus might infect humans using its sequenced genome, and knowing that a virus is present in many different species is a useful indicator, but infection alone doesn't make a pandemic. Anyone who wants to learn whether a given virus could cause another human pandemic must perform laboratory experiments: the virological equivalent of nuclear testing.

Here's the general logic: viruses currently circulating among humans are very good at infecting us and making our bodies churn out more viruses. But because most of us have already been infected and acquired some immunity, they mostly spread to kids who haven't previously been exposed or people

[6] Xie et al., "Engineering SARS-CoV-2 Using a Reverse Genetic System."
[7] National Center for Science and Engineering Statistics, "Doctorate Recipients from U.S. Universities, 2019."
[8] OECD, "OECD: Graduates by Field."

with weaker immune systems. Pandemics happen when a new virus jumps from animals to people, and is able to spread well between people: no one has much immunity, so it spreads like wildfire. Once most people have encountered the new virus and developed resistance, it becomes much like its relatives.

That means any virus that can infect human cells, replicate in human cells, and/or be transmitted between animals chosen for their similarity to humans nearly as well as a human-infecting virus from the same family is much more likely to cause a pandemic in humans. Even if it's subpar at one or two of these, it just needs to be good enough for a variant to arise with a mutation that makes it better, just as the original SARS-CoV-2 has been outcompeted by the more infectious variants.

This explains why scientists attempting pandemic virus prediction perform experiments measuring infection and replication in human cells and transmission in model animals such as engineered mice, ferrets, or primates. Virus hunters perform them on newly collected agents, such as the bat coronaviruses gathered by the Wuhan Institute of Virology, to learn whether they might cause new pandemics.[9] Scientists working to enhance the transmissibility of especially lethal animal viruses, like the bird flu strains engineered to be transmitted more efficiently between ferrets, also run these experiments to see whether mutated versions of these viruses have acquired the ability to cause a pandemic.[10]

The utility of pandemic virus prediction: who can do it and who would benefit

Pandemics killed over a million people in 1889-90, 1918-19, 1957-58, 1968-69, and 2019-20. Would pandemic virus prediction actually prevent or mitigate future pandemics? If governments limit virus prediction research over proliferation, would bad actors conduct it, and would that increase risks?

Whether prediction would enable prevention is hotly disputed; it wouldn't plausibly accelerate vaccines; and other actors appear to lack the capability or the strategic interest to pursue prediction if we don't.

Groups promoting prediction research – like EcoHealth Alliance and the Global Virome Project – appear to believe that identifying a pandemic virus before the first cases appear will both catalyze vaccine development and help prevent spillover by limiting human-animal contact and blocking transmission. But other researchers have argued that pandemic virus prediction will not actually help with either.

Vaccine acceleration seems highly unlikely now that we have mRNA vaccines. As Moderna's SARS-CoV-2 vaccine was designed in less than two days, if they're possible at all, they can be done quickly. Knowing the identity of the virus in advance can't possibly save any development time during any severe pandemic in which we sensibly combine Phase I and II trials unless we're willing to run Phase II challenge trials (i.e., deliberately infect people) with a large number of viruses that have never infected a human and may never do so. Moreover, there are so many viruses that we're unlikely to identify the next one to actually cause a pandemic, and pandemic virus prediction siphons resources away from early warning efforts often funded by the same program.[11]

[9] Hu et al., "Discovery of a Rich Gene Pool of Bat SARS-Related Coronaviruses Provides New Insights into the Origin of SARS Coronavirus."
[10] Herfst et al., "Airborne Transmission of Influenza A/H5N1 Virus between Ferrets"; Imai et al., "Experimental Adaptation of an Influenza H5 HA Confers Respiratory Droplet Transmission to a Reassortant H5 HA/H1N1 Virus in Ferrets."
[11] Holmes, Rambaut, and Andersen, "Pandemics: Spend on Surveillance, Not Prediction"; Wille, Geoghegan, and Holmes, "How Accurately Can We Assess Zoonotic Risk?"

Judging by the history of nuclear weapons, many will argue that malevolent actors will eventually perform the research anyway, so it's better for the good guys to find all the dangerous advances first. This may have been true of the atom bomb, but the strategic calculus is different for pandemic weapons.

First, rogue nations and extremist groups would gain tremendous coercive power by gaining access to acknowledged weapons of mass destruction, which could serve as "dead-hand" switches for rogue regimes or as convenient ways to inflict mass death for extremists, mentally disturbed individuals, or terrorists such as the apocalyptic cult Aum Shinrikyo, the scientifically-inclined Aurora shooter James Holmes, or Ted Kaczynski.[12] But these actors generally lack the technical capability to perform basic science research, especially at the scale needed to find the pandemic needle in the animal virus haystack. Although recent technological advancements have made this process much more efficient, leading scientists have already spent well over $100m searching for pandemic viruses without finding any truly credible threats. Therefore, while rogue states or bioterrorists could assemble any pandemic-capable viruses that major nations helpfully identify for them, smaller malevolent actors probably can't find suitable viruses on their own even if they decide to try.

Second, even if some rogue actor defies the odds and eventually comes up with data pointing towards a pandemic weapon, and professional scientists are reckless enough to make it credible by confirming the results, "eventually" will give us time to develop defenses. As COVID-19 showed, we need it.

Third, larger nations can be persuaded that pandemic virus prediction is not in their strategic interest. Pandemic-class weapons are not useful to existing powers because they kill indiscriminately and cannot currently be engineered to spare one's own population. Large nations that attempt to vaccinate their own populations in advance would likely be discovered by foreign intelligence agencies, and even were population-specific targeting possible, its use by a nation-state would be so obvious as to invite mass retaliation. Therefore, pandemic-class weapons appear to offer little if any strategic utility to powerful nation-states. Indeed, to prevent rogue states, bioterrorists, or mentally disturbed individuals from acquiring the ability to blackmail the global community and cause large-scale harm, it is in the interest of global security to join forces on preventing the identification of credible pandemic capable viruses.

As the largest spender on pandemic virus prediction, if we and our allies don't identify believable pandemic WMDs, others probably won't either, at least for some years.

That means we just need to determine whether we ourselves believe the potential benefits of performing the small subset of virology experiments relevant to pandemic virus prediction are worth the cost, or not. With rare and little-publicized exceptions,[13] security concerns over pandemic weapons of mass destruction have seldom been raised at all.

One possible way to decide is to assume everything will work as perfectly as possible for pandemic virus prediction – there will be zero accidents and prediction will let us completely prevent every natural pandemic – then ask if that ideal outcome is worth proliferation:

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[12] Levy and Smithson, "Ataxia: The Chemical and Biological Terrorism Threat and the US Response"; Wikipedia contributors, "James Holmes (mass Murderer)"; Kaczynski, "The Unabomber Manifesto: Industrial Society and Its Future."

[13] Inglesby and Relman, "How Likely Is It That Biological Agents Will Be Used Deliberately to Cause Widespread Harm? Policymakers and Scientists Need to Take Seriously the Possibility That Potential Pandemic Pathogens Will Be Misused"; Katz et al., "Mapping Stakeholders and Policies in Response to Deliberate Biological Events"; "A Spreading Plague: Lessons and Recommendations for Responding to a Deliberate Biological Event"; Sandberg and Nelson, "Who Should We Fear More: Biohackers, Disgruntled Postdocs, or Bad Governments? A Simple Risk Chain Model of Biorisk."

Should we give thousands of actors the power to release dozens of million-plus-death pandemic viruses at multiple travel hubs throughout the world in exchange for preventing the natural pandemics that spread from a single animal once every 20 years or so?

If the answer is clearly yes, pandemic virus prediction might still be a very bad idea because real-world accident risks are far from zero and preventing every natural pandemic seems implausible. But if the answer is even equivocal, then the decision has been made without needing to argue over potential benefits vs accident risks.

Key defenses against pandemics

COVID-19 demonstrated that we remain profoundly vulnerable to pandemic viruses spreading outwards from a single point of introduction. There is no question that we would fail miserably if faced with multiple pandemic agents simultaneously released in travel hubs, let alone anything designed to inflict harm. But we need not remain helpless.

Recommendation I – aid nonproliferation by announcing findings, redirecting funds, and fixing oversight

Our best defense against pandemic weapons of mass destruction is to keep them from being developed in the first place. This may not last forever, but at worst it can buy us time to build other defenses.

- First, nonproliferation efforts would be easier if Congress made a clear finding about the threat. Specifically, Congress could release findings that research designed to make it more certain that a particular virus can cause a pandemic threatens the security of the United States.

- Second, the federal government should stop funding pandemic virus prediction efforts. Existing programs focused on naturally collected viruses or those generated by gain-of-function research are primarily funded by governments, especially ours. I deeply respect the researchers who run these programs, who have dedicated their lives to preventing natural pandemics. Most scientists seldom if ever are encouraged to consider the possibility of misuse,[14] and those who do are unlikely to be sufficiently aware of critical tech-specific national security considerations for bioweapons nonproliferation (e.g., falling DNA synthesis costs, easier virus assembly protocols, the history of nuclear weaponry, and strategic game theory) to grasp the implications on their own.

  The largest pandemic virus prediction efforts are offshoots of larger One Health programs focused on useful monitoring work at the animal-human interface,[15] so there would be no need to revoke any funding or break contracts: the programs could simply direct funds towards early warning systems rather than lab-based virus experimentation. Similarly, behavioral studies and public health interventions which are important for reducing the spillover of animal pathogens into human populations should continue.[16] The virus characterization experiments arguably equivalent to nuclear tests represent considerably less than 1% of virology, so impeding such experiments would be much less of an imposition on the field than the security measures governing nuclear physics.

[14] "Opportunities Exist for the National Institutes of Health To Strengthen Controls in Place To Permit and Monitor Access to Its Sensitive Data."
[15] "WSU to Lead USAID's Global Sampling Project for Discovery of Emerging Viral Zoonoses - Global Biodefense"; "STOP Spillover."
[16] Saylors et al., "Socializing One Health: An Innovative Strategy to Investigate Social and Behavioral Risks of Emerging Viral Threats.".

- Third, Congress can fix an oversight problem with current regulations, namely that funding agencies and recipients are meant to review security issues themselves:

  > "The Department of Health and Human Services (HHS) Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens is intended to guide HHS funding decisions…"
  >
  > "Funders of life sciences research and the institutions and scientists who receive those funds have a shared responsibility for oversight of DURC (dual use research of concern) and for promoting the responsible conduct and communication of such research."

  No funding agency or recipient can be expected to perform oversight for itself; that's the definition of a conflict of interest. Requiring greater transparency and review by individuals with security expertise may help prevent future well-meaning research from going awry.

Recommendation II – leverage shared strategic interests to achieve global pandemic nonproliferation

The nature of many emerging technologies places the U.S. and China at loggerheads, but our strategic interests are nearly perfectly aligned when it comes to pandemic weapons of mass destruction: both nations have little to gain and much to lose. This is an opportunity for the United States to gain leverage by offering information exchange and inviting co-leadership in global health security, and may help build diplomatic channels to address more challenging issues around other key technologies.

One way to marshal global action against pandemic virus prediction would utilize the Biological Weapons Convention (BWC), which prohibits the "development, stockpiling, acquisition, retention and production of biological agents" while "permitting the fullest possible exchange of equipment, materials, and information for peaceful purposes." Today, it's impossible to identify a credible pandemic-capable virus without allowing thousands to assemble a weapon of mass destruction by following a step-by-step protocol. There is a strong argument that Article III compels BWC signatories to block pandemic virus discovery. This may also be an opportune time to revive talks to add verification procedures.[17]

Recommendation III – require DNA synthesis screening matching or exceeding the industry standard

Most researchers who can follow a virus assembly protocol can't make their own DNA, so the fact that we can order synthetic viral DNA and have it come in the mail substantially increases the number of actors capable of assembling a pandemic weapon. California's legislature passed a bill that would require all providers of synthetic DNA and manufacturers of synthesis machines to screen orders at least as well as the International Gene Synthesis Consortium, but it was vetoed on the grounds that it should be federal legislation to avoid a regulatory patchwork.[18] Passing a federal version would exert market pressures on domestic and international providers to screen, nudging firms to engage with the NTI/WEF stakeholder discussions on a framework for universal screening as well as the SecureDNA project on implementing new advances, including in "desktop" synthesizers, that will allow automated screening for the latest threats without having to disclose customer orders or jeopardize trade secrets.[19] Similar regulations could be encouraged internationally using the BWC or other diplomatic means.

[17] Butler, "Bioweapons Treaty in Disarray as US Blocks Plans for Verification."
[18] "California Legislature - AB-70 Gene Synthesis Providers."
[19] "Biosecurity Innovation and Risk Reduction: A Global Framework for Accessible, Safe and Secure DNA Synthesis"; The SecureDNA team, "Secure DNA Project - DNA Synthesis Screening."

Recommendation IV – Build a reliable early warning system and adequate physical defenses

All rapidly growing biological threats can be reliably detected with "metagenomic" DNA sequencing of sufficient samples, suggesting a way to build a robust early warning system that could deter malevolent actors from threatening the United States with pandemic-class weapons.[20] The cost of sequencing has dropped a million-fold over the past 20 years, allowing public-private partnerships to perform sufficient wastewater sequencing of all 328 U.S. ports of entry for a few hundred billion dollars per year.

Once the threat is known, targeted detection could provide greater sensitivity at all sampling sites, allowing rapid diagnostics to pinpoint exactly where the virus(es) can be found. Biomedical countermeasures may not be achievable for every threat (see HIV vaccines), let alone in a reasonable timeframe, but an American who is physically protected from infection is a safe American. If we develop comfortable and highly reliable personal protective equipment, at least as protective as current unattractive and uncomfortable $1000-market-price powered air purifying respirators, and provide it to our most essential workers, the United States will be able to keep food distribution systems moving, the water flowing, the lights on, and the hospitals open in the teeth of a 30% lethality pandemic until it burns out within our borders. While recent divisions over pandemic policy have sowed doubt about our ability to pull together, I am confident that Americans will rally to defend our nation and protect one another if confronted with a high-lethality threat or a clear attack by a malevolent actor. But we will suffer terribly and needlessly if we do not invest in defenses. For useful investments, see the Apollo Program on Biodefense and the White House's American Pandemic Preparedness Plan.[21]

Recommendation V – Amend the 2002 Bioterrorism Response Act to update the Select Agent program

The Federal Select Agent & Toxin Program (FSAP) is unique in regulating all research in the United States, not just federally-funded entities, and additionally impacts the export control list. However, it is updated slowly, doesn't include most viruses that might be pandemic-capable, and the Act was last amended before we developed techniques such as virus chimerism, directed evolution, ancestral protein reconstruction, and machine learning approaches that can generate new threats from existing ones.

Congress could update FSAP to 1) cover anything that uses pieces of Select Agents to builds hazards that wouldn't currently be covered but are just as dangerous, 2) automatically add any virus with a single experimental result indicating that it may be pandemic-capable[22], and 3) immediately lift all restrictions on any Select Agent confirmed to be actively spreading in order to enable research on countermeasures. In addition to reducing accident risks and requiring background checks of anyone working with a virus that may be capable of causing a pandemic, these rules would disincentivize researchers from performing experiments to determine whether their favorite virus is a weapon of mass destruction, as doing so would render it a Select Agent.

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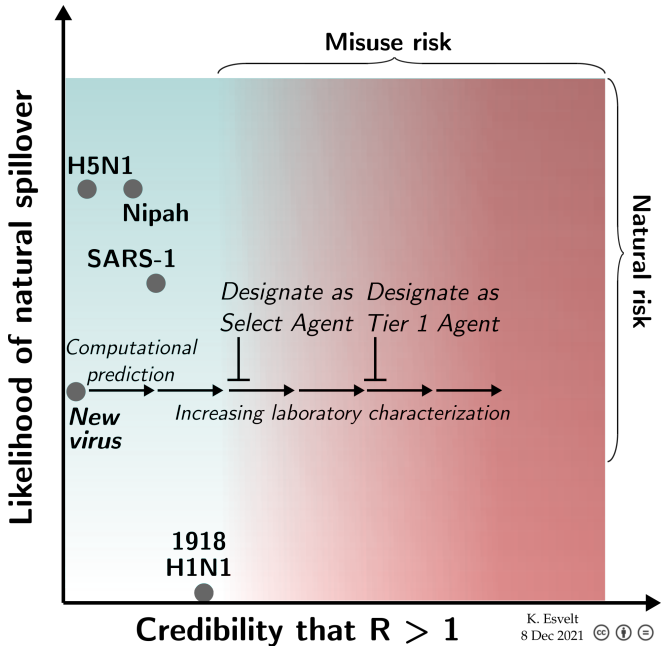
[20] The Nucleic Acid Observatory Consortium, "A Global Nucleic Acid Observatory for Biodefense and Planetary Health."
[21] "The Apollo Program for Biodefense - Winning the Race Against Biological Threats - Bipartisan Commission on Biodefense"; "American Pandemic Preparedness: Transforming Our Capabilities."
[22] **Defining pandemic-capable:** Any virus that normally circulates in a population (R~1) will cause a pandemic when introduced into a more susceptible population that lacks pre-existing immunity (R>1). This is why pandemics typically arise from viruses that spill over from other species, which spread rapidly before becoming endemic. Therefore, a virus is a credible pandemic threat if its components:

- are functionally equivalent to those of an endemic human virus of the same family
- are not recognized by the adaptive immune systems of most humans



Assessing pandemic risks. Pandemics may result from natural spillover, laboratory accidents, or deliberate misuse of viruses identified as credibly pandemic-capable (R>1). Designating viruses as Select Agents upon obtaining the first experimental evidence indicative of pandemic potential could preserve the hypothesized benefits of virus discovery for "universal" virus family vaccine and broad-spectrum antiviral development while reducing accident risks and deterring characterization experiments that would otherwise result in the proliferation of credible weapons of mass destruction.

This testimony reflects the personal opinions and technical expertise of Dr. Kevin M. Esvelt.
He is currently a professor at MIT, but does not speak on behalf of the Institute on this occasion.

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