Delay, Detect, Defend: Preparing for a Future in which Thousands Can Release New Pandemics

Geneva Paper 29/22

Kevin M. Esvelt

November 2022

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Geneva Centre for Security Policy

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About the author

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Executive summary

The world is demonstrably vulnerable to the introduction of a single pandemic virus with a comparatively low case fatality rate. The deliberate and simultaneous release of many pandemic viruses across travel hubs could threaten the stability of civilisation. Current trends suggest that within a decade, tens of thousands of skilled individuals will be able to access the information required for them to single-handedly cause new pandemics. Safeguarding civilisation from the catastrophic misuse of biotechnology requires delaying the development and misuse of pandemic-class agents while building systems capable of reliably detecting threats and preventing nearly all infections.

Key takeaways

Background

- We don't yet know of any credible viruses that could cause new pandemics, but ongoing research projects aim to publicly identify them.
- Identifying a sequenced virus as pandemic-capable will allow >1,000 individuals to assemble it.
- One person with a list of such viruses could simultaneously ignite multiple pandemics.
- Viruses can spread faster than vaccines or antivirals can be distributed.
- Pandemic agents are more lethal than nuclear devices and will be accessible to terrorists.

Delay

- A pandemic test-ban treaty will delay proliferation without slowing beneficial advances.
- Liability and insurance for catastrophic outcomes will compensate for negative externalities.
- Secure and universal DNA synthesis screening can reduce unauthorised access by >100-fold.

Detect

- Untargeted sequencing can reliably detect all exponentially spreading biological threats

Defend

Goal: eliminate the virus while providing food, water, power, law enforcement, and healthcare

- Develop and distribute pandemic-proof protective equipment for all essential workers
  - Comfortable, stylish, durable powered respirators must be proven to work reliably
- Foster resilient supply chains, local production, and behavioural outbreak control
  - Strengthen systems and offer individualised early warning to block transmission
- Develop and install germicidal low-wavelength lights, which appear to be harmless to humans
  - Overhead fixtures can reduce airborne and surface pathogens by >90 per cent in seconds

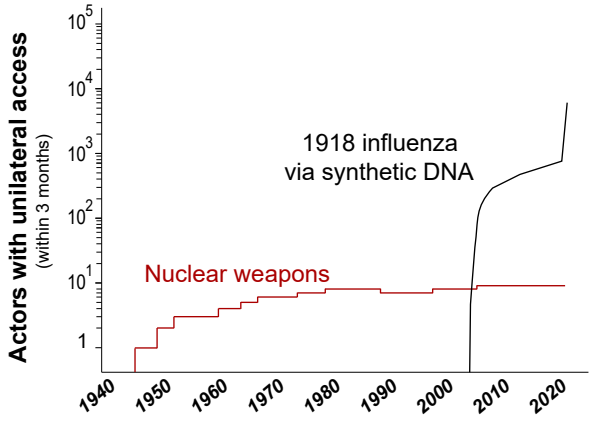
I. Introduction

Relative to nuclear weapons, pandemic-class agents are comparably lethal and will be far more accessible

The international community has gone to immense lengths to prevent non-state actors from acquiring nuclear weapons. However, COVID-19 has demonstrated that even relatively mild pandemic viruses can kill more people than any nuclear device. While pandemic-class agents would be strategically useless to nation-states due to their slow spread and indiscriminate lethality, they might be acquired and deliberately released by terrorists.

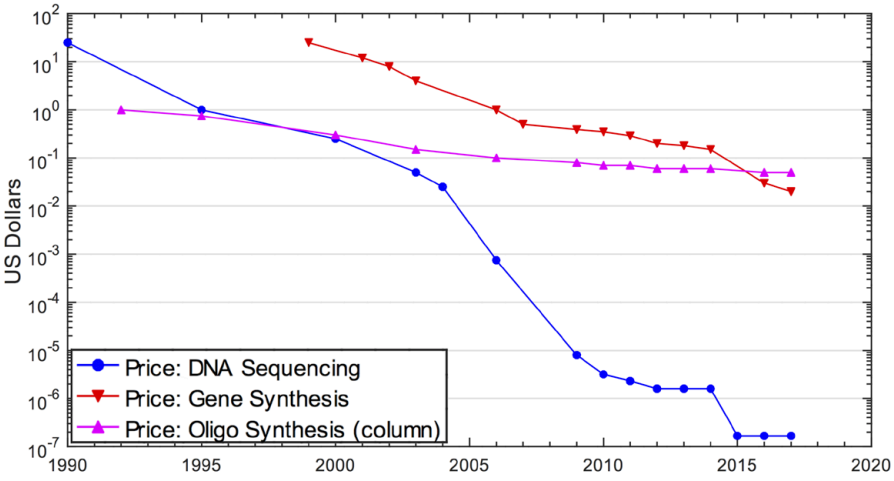
Numerous independent advances in virology and biotechnology, none of which is obviously threatening on its own, have recently combined to render many viruses accessible to skilled individuals at a low cost. Step-by-step assembly protocols capable of producing infectious viruses from a genome sequence and standard laboratory reagents are widely available[1], with particularly detailed and reliable instructions for influenzaviruses and coronaviruses, the families responsible for the last five respiratory pandemics[2]. Such protocols, which are intended to obviate the requirement for "tacit knowledge" to successfully perform the experiment, have become increasingly common. The recent democratisation of biotechnology suggests that they have broadly succeeded: the typical advance made in a cutting-edge laboratory by individuals with doctorates has required just one year to be reproduced in other laboratories, three years to be adapted for use in other contexts, five years to be reproduced by undergraduates and individuals with moderate skills, and 12-13 years to become accessible to high school students and others with low skills and resources[3].

Figure 1: Proliferation of nuclear weapons and of pandemic 1918 influenza virus



The 1918 pandemic influenza virus became accessible to more individuals than possessed the authority to launch nuclear weapons as soon as its genome sequence was published. It is unlikely to cause a pandemic today due to preexisting immunity to H1N1 strains.

Figure 2: Price per base of DNA sequencing and synthesis, circa 2017[4]



Today, perhaps 30,000 individuals with doctorates currently possess the skills to follow the most straightforward virus assembly protocols: the United States has awarded approximately 2500 doctorates in virology in the past 20 years[5]; at least three times as many scientists in more common disciplines such as synthetic biology, bioengineering, and biomedicine also work with viruses and can follow such protocols, and the United States trains approximately one-third of such scientists worldwide[6]. No clinical samples are required: due to exponentially falling sequencing costs, most virus genome sequences are shared publicly soon after discovery, allowing them to be assembled from commercially available synthetic DNA, which is now widely available at a low and exponentially falling cost (see graph)[7]. While members of the International Gene Synthesis Consortium, an industry group concerned about the prospect of misuse, screen customers and DNA synthesis orders for hazards at considerable expense, it is easy to find non-members that presumably do not[8].

While sequenced viruses are widely accessible, pandemic proliferation and misuse cannot yet occur because we lack key knowledge: there are still no credible examples of viruses likely to cause new pandemics. As soon as someone identifies a single capable virus and shares its complete genome sequence, many thousands of people will immediately be able to generate infectious samples that could start a new pandemic. A list of many such viruses would allow a suitably skilled and resourced individual to ignite more pandemics simultaneously than would naturally occur in a century.

This future appears bleak and frightening. There is a natural temptation to reject it, and search for reasons to believe that the life sciences, which

have given us cures for so many diseases, could not possibly pose a threat comparable to nuclear weapons. As a biologist and biotechnologist, I find the temptation to disbelieve nearly overwhelming. If human actions could never yield globally catastrophic consequences, then faster, more open science would always be the right decision. Yet the highest tenet of science is our reverence for the truth. Nuclear weapons and climate change have already proven that we do not live in such an idyllic world, and it would be irresponsible of us to pretend otherwise.

The primary reason that no terrorist has ever gained access to a nuclear device – or even the fissile materials required to create one – is that people of many nations recognized the proliferation threat and worked together to forestall it[9]. The resulting nuclear security measures did not prevent us from reaping the benefits of nuclear power: the International Atomic Energy Agency estimates that between 1971 and 2018, nuclear power plants prevented the emission of 74 gigatonnes of carbon dioxide, and continue to prevent an additional two gigatons per year[10]. Today, it's unlikely that a naive observer would single out nuclear physics as an unusually unhealthy or unproductive field even though it has operated under security restrictions for many decades, and although working in climate science may be less comfortable now that the field has been politicised, accurate projections are arguably more important than ever.

Biology is no different. We can rationally assess the potential for misuse and take appropriate countermeasures without impeding beneficial advances; in fact, we have already done so. The advent of recombinant DNA in the 1970's – i.e. the ability to cut and splice genes – provoked widespread concern that "there was an atomic bomb hidden away in modern biology"[11]. "Scientists were concerned that unfettered pursuit of this research might engender unforeseen and damaging consequences for human health and Earth's ecosystems[12]," leading them to declare a moratorium on their own research. Only after intense discussions at the famous Asilomar conference of 1975 did they correctly conclude that recombinant DNA within carefully chosen laboratory-adapted constructs posed no risk of spreading on its own[13].

As nuclear fears receded with the end of the Cold War and the conclusions of Asilomar were confirmed, fears of "Andromeda strains" faded[14], while assertions that "Nature is the greatest bioterrorist" – that humanity cannot match nature's ability to generate novel agents capable of spreading on their own in the wild – became a cliché[15]. This claim may have been accurate as recently as a decade ago, but is now tenuous at best. For example, in 2013 I discovered CRISPR-based gene drive, a technology widely viewed to be capable of spreading genomic alterations made in laboratory organisms to entire wild species[16]. Gene drive systems, which can cause populations to collapse if not go extinct[17], hold tremendous promise for eradicating diseases such as malaria and schistosomiasis, but the technology is accessible to

individual researchers, who in principle are now capable of single-handedly altering Earth's ecosystems. The remarkable acceleration of new advances in biotechnology over the past decade strongly suggests that other methods of building agents capable of exponential spread are also possible. Add ongoing attempts to deliberately engineer lethal viruses to become highly transmissible[18], and asserting that humanity will *not* develop novel methods of engineering new pandemic-class agents appears to be dangerously overconfident[19].

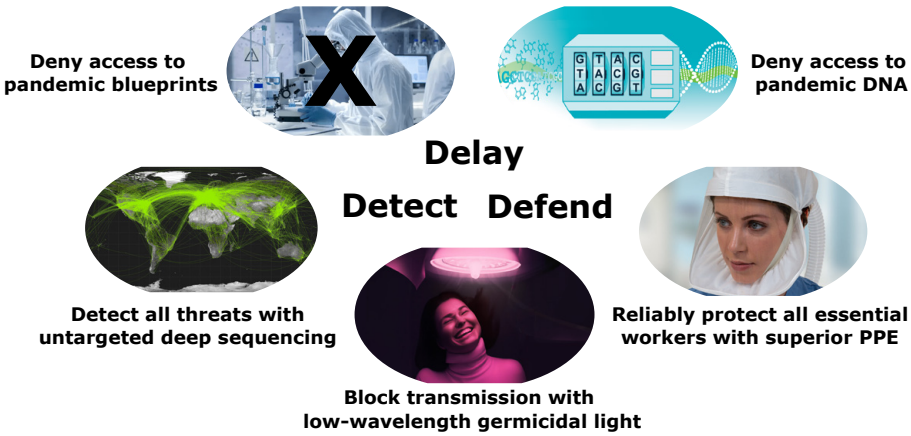
Nor does catastrophic misuse require novelty. Animal viruses manifestly do not spill over to cause pandemics in multiple airports simultaneously, and certainly not in groups, but once enough of them are identified, thousands of people will be capable of causing both[20]. If current trends continue, many such viruses will be made public: well-intentioned researchers at one agency currently seek to identify animal viruses capable of causing new pandemics, share their genome sequences with the world, and publish them in a list rank-ordered by threat level[21]. The security implications, which apparently went unrecognised by the relevant agency, its scientists, and even national security experts for over a dozen years, are ghastly.

A credible list of pandemic-capable viruses would in principle allow anyone capable of assembling those agents to seed so many outbreaks that even the harshest and most comprehensive of lockdowns by today's nations would struggle to contain them all. With some natural viruses exhibiting the transmissibility of early variants of SARS-CoV-2 and a lethality rate exceeding 30 per cent[22], such an event could precipitate the greatest catastrophe in the history of humanity. Even the best-prepared nations lack sufficient protective equipment for most key personnel, and vaccines and other medical countermeasures could not plausibly be manufactured and distributed in any time frame shorter than months, if they could be developed at all[23]. If essential workers are unwilling or unable to maintain food, water, and power distribution networks, societies will collapse.

This outcome is not inevitable, however, or even especially likely. But the same is true of a large-scale nuclear exchange, and of four degrees of climate warming: we cannot tolerate a tiny chance of any of them actually occurring. On this basis alone, we should approach the mitigation of global catastrophic biological risk with the same degree of seriousness as we do nuclear non-proliferation and climate change mitigation.

Below, I propose a set of interventions that, taken together, could plausibly solve this immense problem while negligibly impacting the lifesaving work of my colleagues in the life sciences. Technologies capable of effectively immunising nations against even adversarial releases of pandemic-class agents are now within our reach, and the price tag is a tiny fraction of existing defence budgets, let alone the cost of mitigating climate change. By delaying proliferation while we construct reliable systems for threat detection and defence, we can safeguard the international community from biological catastrophe.

Figure 3: Delay, Detect, Defend



II. Adversaries

The world has never faced non-state actors capable of killing millions

Strategies aiming to delay the identification and deliberate release of pandemic-class agents can benefit from understanding who is most likely to misuse biology to catastrophic effect.

Powerful nations share an overriding strategic interest in preventing the proliferation of pandemic-class agents. Such agents cannot be reliably targeted and are of negligible tactical utility, but their accessibility and destructive power pose a major security risk. Even if superior targeting becomes possible, the slow spread and obvious nature of selective harm would severely limit their usefulness to powerful nations. Still, the existence of the Soviet Union's large-scale biological weapons program demonstrates that states may pursue such research against their own interests[24]. More importantly, while few if any nations harbour offensive bioweapons programmes involving pandemic-class agents, their peaceful biomedical, public health, and biodefence agencies can and do inadvertently fund life sciences research facilitating the proliferation of such agents. Examples include the United States[25], European Union[26], China[27], Japan[28], and Germany[29].

Rogue states may be interested in acquiring pandemic-class agents for deterrence, but because it is easy to fake data indicating that a novel virus is pandemic-capable, such a deterrent may not be taken seriously until it is independently verified. However, these states are capable of assembling and threatening to release any agents for which credible blueprints are already available. Like powerful nations, rogue states have a strategic interest in preventing other actors from accessing pandemic-class agents.

Extremists are non-state actors who value pandemic-class agents for their potential to coerce whatever or whoever they wish to target. Having less to lose than rogue states, they may be more willing to openly make threats and trade knowledge with others, but are similarly constrained by their inability to credibly claim to possess novel pandemic-class agents. They also have no interest in disseminating blueprints.

Zealots are unique among adversaries in being uninterested in coercion or deterrence; they seek pandemic-class agents in order to use them. Historical examples include omnicidal cultists such as Aum Shinrikyo[30], single-minded terrorists who will grasp at any means to kill their enemies[31], radicals who seek to bring down our current civilisation[32], deep ecologists aiming to dramatically reduce the human population[33], the

small fraction of nihilistic or mentally disturbed mass shooters skilled and disciplined enough to undergo suitable training in the life sciences[34], and some of those who see no future for their own value system and way of life[35]. Most zealots are not capable of novel research, but a few may possess or deliberately acquire the skills needed to assemble pandemic-class agents from blueprints.

Numerically, fewer than a dozen powerful nations have funded research seeking to identify pandemic-class agents[36]. There are only a handful of rogue states, but many thousands of extremists and zealots (see Table 1). The existence of Seiichi Endo of Aum Shinrikyo, a graduate-trained virologist who joined the cult in 1987, initiated its biological weapons program in 1990, and was active until his arrest in 1995 – including a reported attempt to obtain Ebola virus[37] – strongly suggests that zealots with the technical skills, resources, and intent to commit mass murder may also exist today. Any modern individual with Endo's educational background and resources could almost certainly obtain Ebola virus by assembling it from synthetic DNA using established protocols; many other viruses are equally accessible[38]. Modern-day equivalents of historical mass murderers such as the Unabomber – a Harvard graduate and former Berkeley mathematics professor who sought to bring down industrial civilisation and wrote of "the immense power of biotechnology"[39] – would likely seek training in virology. The potential for so many extremists and zealots to gain access to pandemic-class agents once suitable viruses are credibly identified underscores the importance of denying them access to critical information and materials for as long as possible.

Table 1: Anticipated level of interest in the study of credible pandemic-class agents

	# Interested*	R&D capacity	Credibility**	Motivation	Can be deterred?
Powerful nations	< 15	High	High	Knowledge	Yes
Rogue states	< 10	Moderate	None	Deterrence	Yes
Extremists	> 1,000	Limited / varies	None	Coercion	Somewhat
Zealots	> 1,000	None / varies	None	Mass death	No

* *Interest by powerful nations may be well-meaning, intended to support science and combat natural pandemics*

** *The ability to identify a pandemic-capable agent and be believed*

III. Delay

When an attack cannot be blocked and deterrence is not feasible, delay and denial are the only defences

SARS-CoV-2 and its variants have proven that the world would struggle to contain a new pandemic agent, even one only introduced at a single site distant from a travel hub. Any agent deliberately released in airports would spread considerably faster. Therefore, we must delay proliferation and forestall deliberate misuse by restricting access to the information and physical materials required to build pandemic-class agents until reliable methods of containing pandemic viruses are available throughout the world.

A. Information denial: known hazards

Even unblockable threats require blueprints

The basic principles governing atomic and thermonuclear weapons are widely known, but exact blueprints and details about enrichment processes are closely held and difficult to reproduce. The higher the barriers to rogue states and especially to non-state groups seeking to develop the weapons, the better. The same is true for pandemics: scientists should not perform and openly publish experiments that would credibly identify pandemic-class agents because doing so would unavoidably hand blueprints to rogue states, extremists, and zealots who may not be able to identify such agents on their own. Nations should similarly hesitate to identify pandemic-class pathogens even if they think they can keep the results out of the public domain. First, it would be extremely difficult to privately utilize the information for protective purposes. Second, any such classified programmes would appear to be weapons-related if any indication of their existence became known. Finally, even highly classified information can seldom be protected forever.

Only a small group of experiments can increase our confidence that a virus is capable of causing a new pandemic. For animal viruses, they include measuring the ability of its entry protein to mediate infection of relevant primary human cells, the growth of the virus or a chimera in such cells, and viral transmission between animal models. If enough of the measured values approach those of an endemic human virus of the same family – which must be highly transmissible due to its ability to circulate even though much of the population is immune from prior exposure – then the animal virus is likely pandemic-capable. For human viruses engineered in ways that would not occur in nature, experiments measuring the extent to which they can evade innate, antibody, and T-cell immunity could similarly identify those that are pandemic-capable.

Box 1: Examples of key experiments that can increase our confidence that a virus is pandemic-capable

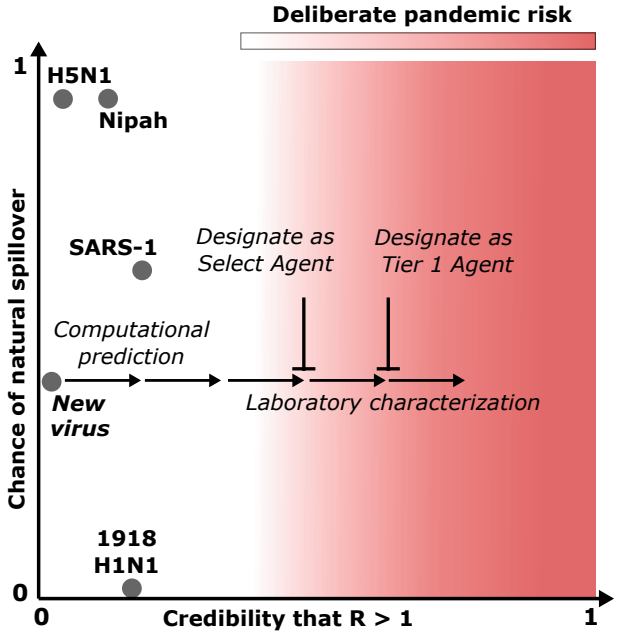
1. Quantify the growth of a zoonotic virus or viral backbone in relevant human primary cells
2. Quantify the transmissibility of a zoonotic virus in a relevant animal model
3. Quantify the extent to which an engineered human virus evades preexisting humoral immunity
4. Quantify the extent to which an engineered human virus evades preexisting cellular immunity
5. Quantify the extent to which an engineered human virus evades preexisting innate immunity

These pandemic virus identification experiments are the virological equivalents of nuclear testing: until they are credibly performed, no one will believe that an actor could use an agent to kill millions. Because computational approaches cannot yet predict pandemic capability and will struggle to do so in the absence of datasets generated by these types of experiments, preventing them from being conducted and the results from being published can effectively delay the dissemination of information sufficient to cause pandemics.

In nuclear physics, the proliferative consequences of discovering a much more accessible path to nuclear weapons would be immediately obvious to the inventors, who would never consider publicly sharing the information. Security concerns are less salient in the current culture of the life sciences, as evidenced by the number of projects explicitly intending to create[40], identify[41], and publicly share a list of viruses ranked by apparent threat level[42]. Even if identifying a pandemic-capable virus in nature allowed us to perfectly prevent that pathogen from spilling over into humans, there are thought to be over a hundred times as many pandemic-capable viruses at any given time as there are severe natural pandemics in a typical century, making it highly unlikely that any identified virus will go on to cause a natural pandemic[43]. Since a single zealot can assemble and release any pandemic viruses that have been identified by others, including many at once, a mere 1 per cent annual risk that each identified virus will be deliberately released predicts that credible pandemic virus identification will kill a hundred people for every person it might save (Box 1).

Now that the COVID-19 pandemic has demonstrated that pandemics are still able to kill more people than any nuclear detonation, and any identification of such an agent would clearly give access to many zealots who cannot be deterred, nations can take steps to change norms and incentives. To prevent proliferation, policymakers can reform or halt existing programmes supporting such research, block the sharing of complete genome sequences of new viruses in favor of omitting critical pieces required for assembly but not research into countermeasures, disincentivise laboratories from performing the relevant experiments through regulation, or ban them outright. For example, nations might automatically apply the most stringent available regulatory status to any virus that tests positive in a single pandemic identification experiment – such as the Select Agent list in the United States – so any laboratory performing such an experiment would risk greatly increasing its own research costs. Functional equivalents of listed agents generated through recombination with other agents, by applying directed evolution, or through the use of computational design tools should be similarly regulated.

Figure 4: Deliberate pandemic risk



Box 2: What is the likelihood that a zealot will release a pandemic-class agent in a given year?

Misuse is a function of the distribution of zealots with some nonzero level of intent, the requisite skills, comparatively inexpensive laboratory resources, and knowledge of which agents could cause pandemics. As of this writing, it doesn't matter how many zealots have the necessary skills and resources – there is currently no information in the public domain permitting them to reliably ignite a new pandemic*.

As soon as someone credibly identifies and publicises a pandemic-capable virus, many zealots will hear of it, so the expected rate will jump from zero to something higher. The number of zealots and their odds of success are difficult to quantify, but the existence of historical zealot mass murderers such as Seiichi Endo – whose modern equivalents would unquestionably possess the necessary skills and resources to assemble and release a publicly known self-spreading virus – suggests the number is not trivial. Add other historical zealots such as Ted Kaczynski, whose modern equivalent would likely seek training to harness what he called "the immense power of biotechnology" to bring down the industrial system, and a 1 per cent chance per year appears to be a quite conservative estimate. Because such an attack could be released in multiple travel hubs simultaneously, it could not be contained with current tools: as in the old security aphorism, any system demonstrably vulnerable to accidents is helpless against a deliberate attack.

If a second pandemic strain were validated and put into the public domain, the odds of a deliberate pandemic would approximately double, for however many zealots are out there trying to start a pandemic, and however capable they may be, they would reasonably attempt to assemble and release the second virus in parallel, with a similar probability of success. At some point, the zealots' capacity to build agents in parallel will be exhausted, so the odds would not continue to scale with the number of strains – but even if some strains are already in the public domain, it is still worth trying to prevent new ones from being added.

* The virus responsible for smallpox is minimally accessible due to size and difficulty of assembly and a vaccine stockpile of 300 million doses stands ready to extinguish any attempts, acquired immunity to SARS-CoV-2 is cross-protective against SARS-CoV-1, and most of the population has been exposed to circulating influenza strains that are protective against 1918 influenza virus, which in any case killed most victims through secondary bacterial infections that today would be treatable with antibiotics.

Even more importantly, nations can make it clear that those whose actions directly lead to major catastrophes may be held liable, including actions that permit misuse by others. Today, the negative externalities of actions with a small but nontrivial chance of causing catastrophe are seldom factored into decision-making. Indeed, there are no quantitative risk-benefit analyses of pandemic virus identification research at all. Introducing generalized catastrophe liability with a high threshold, such as ten million or more global deaths, and requiring institutions to purchase insurance will ensure that rare yet devastating negative externalities are evaluated by professional risk analysts and priced into operating costs. While no reinsurance market could cover the full cost of a major pandemic, the value of the insurance might be capped at a large fraction of the reinsurer's assets and still obtain most of the benefits[44].

Internationally, the Biological Weapons Convention prohibits "assisting others in acquiring biological weapons", although it explicitly encourages "the fullest possible exchange of information" in Article X. Nations could invoke Article VI's procedures for alleging violations to determine whether the latter includes giving tens of thousands of individuals access to agents permitting them to kill millions single-handedly, but given the expansiveness of Article X and the lack of verification measures, it would be more effective to forge a new agreement narrowly targeting the identification and associated proliferation of pandemic-class agents.

A pandemic test-ban treaty modelled after the Nuclear Test Ban Treaty would explicitly ban the dissemination of results from the handful of experiments capable of substantially increasing our confidence that a natural or synthetic virus can cause a new pandemic. Crucially, blocking these experiments would not impede vaccine or antiviral therapeutics research; they are only useful to assess pandemic capability, and whatever the benefits of targeted spillover prevention efforts may be, they do not appear to outweigh the expected harms of misuse (see Box 1) given that many more pandemic viruses exist in nature than will spill over. Unlike nuclear testing, which generates an unfalsifiable seismological signature, the results of pandemic virus identification experiments are easily faked, so any data presented by rogue actors seeking to threaten others will be doubted until independently verified. To successfully block proliferation, the treaty need only prevent reputable but security-naive parties from performing the experiments and disclosing the results.

Recommendation 1: Automatically apply safety and access control regulations as soon as a single pandemic virus identification test indicates potential pandemic capability. Any functional equivalents generated by a design process that uses a regulated agent as input should be similarly regulated.

Recommendation 2: Make anyone disclosing a pandemic-class agent or a method of increasing harm from such an agent liable in the event of sufficiently catastrophic damages, including from misuse by others. Extend this liability between nations where possible. Require that all private and public general liability insurance cover catastrophe liability, causing professional risk analysts to create numerical risk assessments in order to price rare but catastrophic negative externalities into the annual operating costs of institutions, including those performing research relevant to pandemic-class agents.

Recommendation 3: Enact a new pandemic test-ban treaty to forbid pandemic virus identification experiments worldwide. Redirect funds supporting such research to a “1-10-100k” plan: empower communities at high risk of zoonotic spillovers to sequence the responsible agent within 1 day of detecting an epidemic, and within 10 days, manufacture 100,000 rapid diagnostic tests and 100,000 nucleic acid vaccine candidates for use in a combined Phase 1+2 ring vaccination trial to contain the outbreak.

B. Information denial: novel hazards

Avoid publicising any potentially accessible threat to civilisation without a reliable plan to obviate it before potential adversaries can exploit the vulnerability

The identification of natural pandemic-capable viruses and of mutants with enhanced transmissibility generated through so-called "gain-of-function" research pose the most serious near-term catastrophic proliferation risks[45], but future "dual-use" biotechnologies are also likely to generate novel pandemic-class agents. The current culture of the life sciences encourages disclosure, so any identification of these technologies as hazardous after their development will likely result in attempts to "warn the world", thereby making the threat credible and triggering immediate proliferation. For

example, the high-profile assembly of horsepox virus was widely described in both the scientific literature[46] and mass media[47] as a way for malevolent actors to acquire infectious samples of smallpox, with still worse possibilities discussed openly[48]. As long as the culture of the life sciences continues to encourage public disclosure as the optimal course of action in all cases - a view sharply at odds with best practices in cyber security, in which newly identified threats should not be made public until an effective patch or countermeasure is readily available, as well as in physical security, in which the Secret Service does not publicly discuss the best ways to assassinate the US President - then training biologists to recognise dual-use research will do more harm than good.

Instead, nations can require external security reviews of requests for proposals by funders to increase the chance that catastrophic hazards will be identified before development, when mitigation is still feasible. Rather than updating existing checklists of research categories that could be reverse-engineered into recipes for weaponization, articulating simpler principles can help discourage or de-risk catastrophically dual-use experiments before they are performed, as well as distinguish studies relevant to pandemic-class agents from more conventional dual-use experiments more analogous to chemical weapons. A simplified framework for potentially catastrophic dual-use research in the life sciences might ask just two questions:

- Could this research allow a nucleic acid to spread exponentially across much of the world?
- Could this research cause an exponentially spreading nucleic acid to inflict greater harm?

The first question determines whether the technology might be used to create a pandemic-class agent, and therefore the scale of the potential misuse. The second determines the severity of the harm. This framework can also assist technology developers in determining how best to proceed.

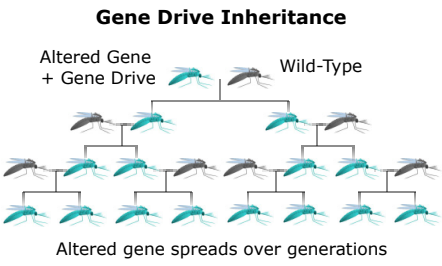
The least hazardous type of pandemic-class agent clearly favours defence: it is slow, easily detected, and readily countered using already-existing technology. An example is CRISPR-based gene drive[49], which uses recurrent genome editing to exponentially spread an engineered trait through a wild species. The technology could be used to help eradicate diseases such as malaria and schistosomiasis, but could also crash populations of keystone species or cause ubiquitous organisms to more efficiently vector pathogens. Upon first conceiving of the technology, I refrained from disclosing it to anyone until confident that it favoured defence: it takes many generations to spread, has an unmistakable genomic signature, and can be reliably overwritten using an “immunising reversal” gene drive system. The first experiment testing CRISPR-based gene drive in the laboratory confirmed that overwriting was effective, and we only reported the outcome because reversal worked[50].

In the middle are those pandemic-class agents analogous to most exploits in cyber security: those for which a countermeasure appears to be technically feasible, but is not yet available. For example, a novel agent that spreads more slowly than HIV would qualify, because a vaccine - if successfully developed - could be distributed far more quickly than the pathogen could spread. As is standard in cyber security, researchers who discover such a biological threat should avoid publicly revealing its existence while privately developing a means of neutralising it, ideally by contacting funders with a record of support for mitigating catastrophic biological risks.

The most hazardous type of pandemic-class agent is one for which population-scale countermeasures cannot be developed and distributed with any current or near-future technology. Like nuclear missiles, such agents are effectively unblockable if they are deliberately released. Researchers who stumble across such a technology can only refrain from disclosure and pursue safer alternatives in an attempt to satisfy the rationale for the original line of research, thereby discouraging independent re-discovery.

In each of these cases, the world benefits when risks are privately identified before public disclosure, ideally in advance of laboratory development, underscoring the importance of external security reviews. Under no circumstances should health or development agencies be allowed to review their own proposals for security concerns, or to appoint (and dismiss) their own oversight boards, as is currently true of the US National Institutes of Health. In addition to funder reviews, policies encouraging early-stage peer review of proposals in high-risk fields would likely accelerate beneficial research while improving the chance that potentially harmful advances will be identified before they occur. To begin establishing norms of caution and early review surrounding exponentially spreading biotechnologies, the World Health Organization could establish a research registry for gene drive[51] and similar defence-favouring technologies capable of autonomous spread.

Figure 5: Security implications of access to gene drive and to pandemic agents



Gene drive	Favours defence
Slow	Takes generations to spread
Detectable	Sensitive detection by sequencing
Blockable	Immunizing reversal drive overwrites
SARS-CoV-2	**Favours offence**
Fast	Omicron infected >26% in 100 days
~Subtle	Can transmit without symptoms
~Unblockable	World largely failed to block spread

Changing norms across the life sciences will not be easy. The simplest and most effective action would require the editors of the highest-profile

journals to issue a joint statement acknowledging that whatever its origin, COVID-19 has demonstrated that civilisation is vulnerable to pandemic agents that were not deliberately released, and that any system vulnerable to accidents is helpless against a deliberate attack. Accordingly, they will not under any circumstances publish research that could be deliberately misused to catastrophic effect, including upholding any decision made by another journal that previously evaluated the paper and judged it too risky to publish. As previous efforts arguably failed due to scepticism over the accessibility of viruses and the world's vulnerability to pandemics, now is the time to try again. Such a statement would do much to reshape the current harmful incentives governing academic research[52], substantially delaying the public identification of engineered pandemic-class agents.

Recommendation 4: Ensure independent oversight of life science research in all leading nations: require security experts to review requests for proposals, mandate numerical cost-benefit models of proposals alleged to pose catastrophic risks, encourage early-stage peer review, establish research registries for all experiments involving gene drive systems or other exponentially spreading biotechnologies, and make institutions and journals liable for the consequences of any catastrophic misuse.

Recommendation 5: Convene high-profile journal editors to agree upon a joint statement that they will never knowingly publish any manuscript posing even a small chance of catastrophic misuse.

C. Physical denial

All biological engineering requires custom DNA synthesis

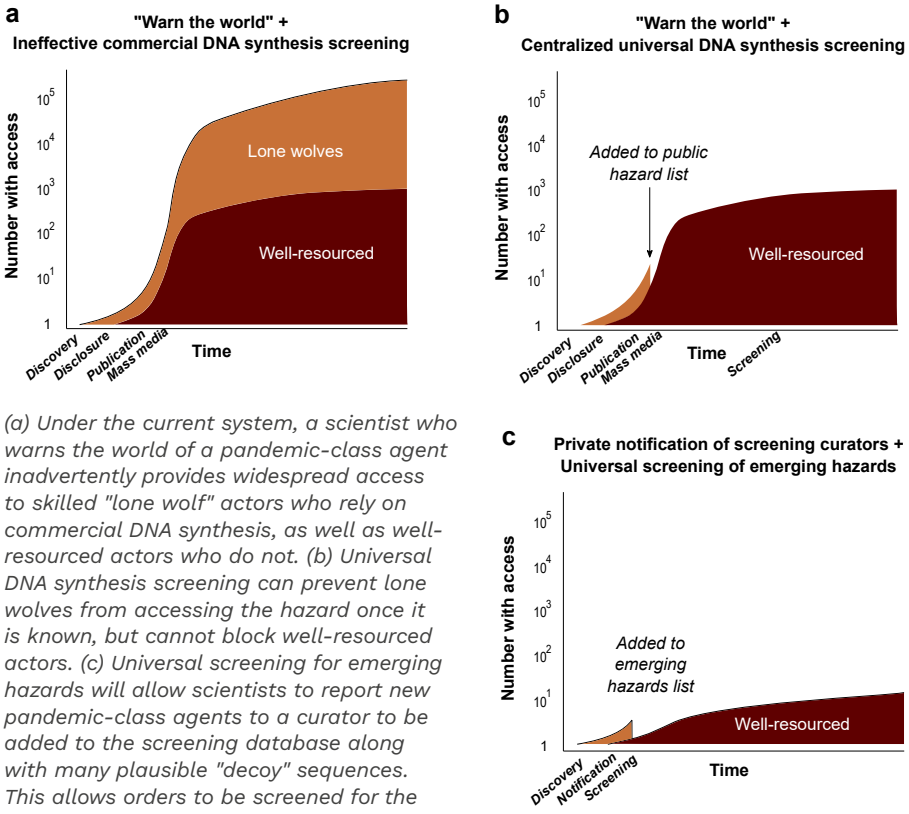
Virus assembly protocols enable infectious viruses to be generated from a string of nucleic acids matching the genome sequence of the virus in question[53]. This string can be generated through DNA synthesis. The price of gene-length synthetic DNA has fallen by a factor of a thousand since the first synthetic poliovirus was generated in 2002[54]. DNA constructs of length sufficient to generate infectious 1918 influenza virus can now be obtained for US$1,500; coronaviruses cost approximately US$2,000, but typically must be enzymatically stitched together by hand prior to virus generation, limiting (for now) the number of capable individuals to those also skilled at

modern biotechnology[55]. The laboratory equipment and reagents required for these tasks can typically be obtained for less than US$50,000.

Members of the International Gene Synthesis Consortium, an industry group, screen DNA synthesis orders for hazards and check backgrounds and permissions before delivering potentially dangerous sequences[56]. However, the process is voluntary and there is no ongoing verification to ensure that providers continue meeting the industry standard[57]. While the consortium supplies an estimated 80% of the global market, other providers presumably do not screen orders due to the cost of paying human experts to look at ambiguous orders thrown up by screening software, which is notorious for generating false alarms[58]. Worse, next-generation "benchtop" synthesis devices threaten to transition the market from large centralised providers that can be induced to screen orders and customers to a decentralised network of devices that may struggle to accomplish either type of screening. Any device that stores a copy of its screening criteria on the device itself is inherently vulnerable to these criteria being extracted and published, thereby giving every malicious actor infinite attempts to bypass them. In addition, the most reliable hardware security methods cannot be applied to local criteria that must be updated to detect newly identified agents. Therefore, any DNA synthesis machine that does not require a secure network connection to an external, regularly updated screening system in order to function will serve as a perpetual source of agents with nuclear-level lethality.

There are promising developments on the horizon: a joint Nuclear Threat Initiative/World Economic Forum project has been convening stakeholders to define new standards for customer screening[59], while the international SecureDNA project, a joint collaboration between European, Chinese, and US academics and software developers, is building a fully automated and cryptographically secure screening system with a negligible false-alarm rate[60]. SecureDNA, which will be operated by a neutral Swiss foundation, will be offered as a free centralised service to synthesis providers and device manufacturers throughout the world. By sending cryptographically uninterpretable orders to a remote screening service, it can protect networked benchtop devices without order information leaving the device, thereby protecting trade secrets. SecureDNA can also screen for emerging hazards without disclosing threats that are not yet public, a capability that will become increasingly important as biotechnology advances. For example, inviting scientists to disclose threats to authorised screening system curators rather than attempting to warn the world could simultaneously crowdsource threat identification while minimising the number of actors who learn about each vulnerability.

Figure 6: DNA synthesis screening and access to pandemic-class agents



(a) Under the current system, a scientist who warns the world of a pandemic-class agent inadvertently provides widespread access to skilled "lone wolf" actors who rely on commercial DNA synthesis, as well as well-resourced actors who do not. (b) Universal DNA synthesis screening can prevent lone wolves from accessing the hazard once it is known, but cannot block well-resourced actors. (c) Universal screening for emerging hazards will allow scientists to report new pandemic-class agents to a curator to be added to the screening database along with many plausible "decoy" sequences. This allows orders to be screened for the threat without disclosing its existence, and lightly discourages new experiments involving the hazard or decoys by requiring scientists who do not already work with the relevant sequences to inform their biosafety committee before they can obtain the DNA.

Recommendation 6: Require all DNA synthesis requests placed or fulfilled within national boundaries to undergo screening for hazards as soon as a screening system is freely available. Two years after such a system becomes available, require that all devices capable of DNA synthesis or gene assembly incorporate built-in screening that can be immediately updated to account for new hazards and does not store screen criteria on the device itself.

D. Deterrence

Attacks that cannot be blocked might be deterred – unless the adversary is a zealot

Powerful nations, rogue states, and extremists with access to pandemic-class agents can be deterred from threatening others in several different ways. Firstly, the Biological Weapons Convention has created strong norms that could be strengthened by a pre-commitment to oppose any actors who threaten to use pandemic-class agents, declaring them – in what may be the most appropriate use of the term – *hostis humani generis*[61], i.e. an enemy of all humankind. Secondly, while a pre-commitment to retaliation could theoretically help deter use, it could easily be exploited using false-flag attacks to set nations against one another. Instead, nations can foster and highlight "genetic attribution", microbial forensics, and traditional human and signal intelligence methods capable of swiftly identifying those responsible for design, manufacturing, and release[62]. Finally, defences can be advertised as soon as they become available in order to deter misuse, as the United States has done with its stockpile of smallpox vaccines. Since adequate defences are unlikely to be available for all of humanity in the near-term or even medium-term future, it is especially important for prepared nations to deter enemies from using biological agents that would also strike the poor and vulnerable.

Zealots cannot be deterred except by credibly advertising that all possible methods of attack accessible to them will fail. Until the world develops reliable methods of detecting and containing pandemic-class events, intelligence agencies should closely monitor extremists with potential omnicidal tendencies and their connections to individuals with the technical skills to assemble pandemic-class agents.

Box 3: Extremist beliefs potentially associated with zealots who may release pandemic-class agents:

1. Ecology: humanity is a plague upon the natural world that should be forcibly controlled
2. Apocalypse: the mass death of civilians is required to bring about societal renewal or heaven on earth
3. Technology: industrial society must fall to prevent future advances incompatible with human dignity
4. Hatred: no price is too high when it comes to destroying the enemy
5. Pain: the world is so full of suffering that it would be best if future people are never born
6. Despair: a world without <disappearing cultural group, belief, or way of life> does not deserve to exist

Recommendation 7: Identify all extremist groups with ideologies suggesting that mass civilian casualties, the collapse of civilisation, or the extinction of humanity would be a tolerable or desirable outcome. Apply human and signal intelligence methods to detect and monitor all connections between affiliates of such groups and individuals with the technical skills to assemble pandemic-class agents.

IV. Detection

Exponentially growing threats are exponentially easier to contain when detected early

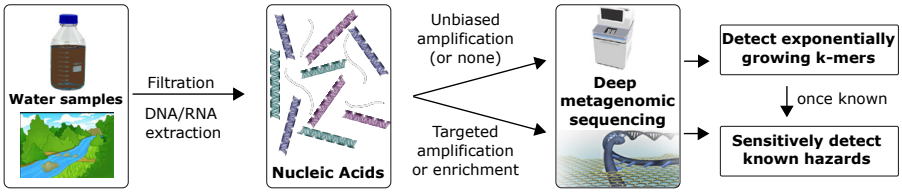
A. Reliable detection

Everything biological is made of nucleic acids, and all pandemics spread exponentially, so detecting exponentially increasing nucleic acids can provide reliable early warning

All pandemic-class agents are encoded by nucleic acids and exhibit exponential growth on some timescale. Therefore, any system capable of detecting exponentially growing patterns of nucleic acid fragments should be capable of reliably detecting any and all catastrophic biothreats, including stealthy agents analogous to HIV that might otherwise infect most of humanity before exhibiting any visible clinical effects[63]. A nucleic acid observatory that performs untargeted metagenomic sequencing of all nucleic acids across relevant human and natural ecosystems would serve as a reliable early warning system, one that neither adversaries nor natural pandemics could evade.

Building such an observatory appears to be extremely affordable relative to traditional defense budgets. In the United States, a system performing untargeted metagenomic sequencing of wastewater[64] from all 328 ports of entry could likely be operated for under a billion dollars a year at-cost; systems in smaller nations would be less expensive[65]. A basic global version would monitor numerous air traffic hubs throughout the world by sequencing wastewater or air filters from aircraft and airports, or possibly clinical samples from flight crews, for as little as tens of millions of dollars a year. With the bulk of the expense arising from the sequencing itself, the cost is expected to continue falling faster than Moore's Law.

Figure 7: Reliably detecting subtle threats



A nucleic acid observatory could perform untargeted metagenomic sequencing of wastewater or air filters from travel hubs and samples from natural waterways. Searching for sequences that grow exponentially at a single site or appear across multiple monitoring sites can reliably detect any agent undergoing exponential growth – a pattern characteristic of all pandemic-class threats – even in the absence of clinical evidence.

A single nucleic acid observatory monitoring site can only detect a pathogen when the frequency of the sequence fragments in question has detectably risen in an exponential pattern, but a network of sites can detect the same pattern of sequence fragments as it first becomes visible at multiple locations. By monitoring their busiest global air traffic hubs and sharing results with one another, nations can detect subtle pandemic agents that might otherwise spread to most of humanity as early as possible. Observatories can subsequently expand to sequence waterways in order to detect gene drive systems and other agents capable of spreading through the environment.

B. Sensitive detection

Targeted amplification can map the extent to which a known threat has spread

Methods that use probes to target specific sequences from known agents are considerably more sensitive than untargeted sequencing. These targeted methods range from simple polymerase chain reaction (PCR) and sequencing to selectively pulling down nucleic acids with oligo probes[66] to novel CRISPR-based diagnostics[67]. Because adversaries may learn which sequences are targeted and engineer agents to evade detection – or use agents that were previously unknown – targeted amplification cannot be the primary method of detection, but it can be applied to search for existing hazards and be swiftly updated when a new threat is detected in the clinic or by untargeted methods. For example, nations are already establishing targeted wastewater monitoring systems for public health applications[68], which can be swiftly adapted to detect newly discovered agents in order to map the extent of their spread throughout the world.

Recommendation 8: Contribute to a global early warning system capable of reliably detecting pandemic-class agents. Perform daily untargeted metagenomic sequencing of wastewater at major air traffic hubs, including sewage from arriving flights, to continuously monitor all pathogens. Explore the possibility of performing similar sequencing of air filters. Share the results internationally to hasten the early detection of adversarially-designed pandemic-class agents that may not be clinically detectable. Ensure that targeted monitoring systems can map the spread of any newly identified agent within days.

V. Defence

The only reliable way to defend against a pandemic-class agent is to prevent infection

Conventional pandemic defence relies on medical countermeasures. For example, over two-thirds of funds requested by the American Pandemic Preparedness Plan (AP3) were to be allocated to biomedicine[69]. Given that we still lack vaccines capable of protecting against natural viruses such as HIV, it is safe to assume that it will not be possible to block the effects of some pandemic-class agents with any form of medical countermeasure.

Worse, even though an effective nucleic acid vaccine can now be designed within 24 hours of sequencing the genome of a pandemic-class agent[70], the testing, approval, manufacturing, and especially distribution process will not be able to match the speed of viral spread. The AP3 and G7 plans call for a vaccine within 100 days of sequencing the genome of an emerging pandemic virus[71], but 100 days after the omicron variant was sequenced in South Africa on 11 November 2021, it had infected a quarter of the United States[72] and as much as half of Europe[73]. Pandemic-class agents deliberately released in multiple airports would spread considerably more rapidly.

Broad-spectrum vaccines and antivirals that function against entire families of viruses are highly desirable and should be developed and stockpiled if at all possible, but they are also unreliable: any great power, most rogue states, and even unusually competent extremists or zealots are capable of engineering pandemic-class agents to resist or evade publicly known medical countermeasures. The unreliability of medical countermeasures should not prevent nations from investing in rapid nucleic acid vaccine production facilities worldwide, preparing to immediately launch combined Phase 1+2 ring vaccination trials in response to outbreaks, and supporting research into receptor decoys[74] and therapeutic interfering particles[75] capable of slowing the spread of a virus. But none of these constitutes a reliable defence against agents anticipated to become accessible to individual zealots. Reliably preventing harm from pandemic-class agents requires looking beyond biomedicine.

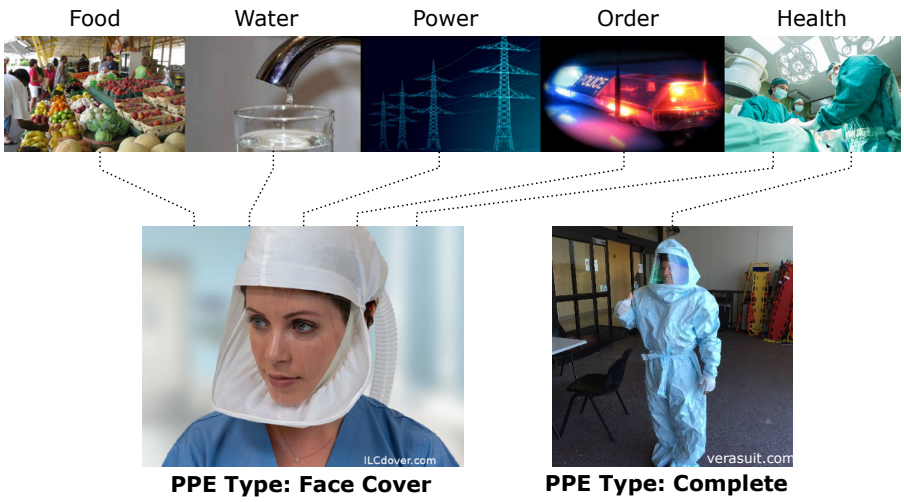
A. Active defence: equipment

Protecting essential workers from pandemic-class agents can immunise society against biological catastrophe

The best way to ensure food, water, power, law enforcement, and healthcare will continue to be distributed during a 90% lethality pandemic is to equip the workers who provide those services with sufficiently protective equipment. Cost-effective pandemic-proof personal protective equipment (P4E) has yet to be developed, but likely does not require fundamental advances. It is equipment that, when worn by an untrained person, completely blocks external access to all human cells that could be subverted and used to replicate a pandemic-class agent, harm the wearer, or both.

Equipment is only protective if worn, so P4E must be exceedingly comfortable, ideally even stylish, and leave most or all the wearer's face visible to permit normal social interaction. Essential workers wearing it must be willing to do their jobs during a high-lethality pandemic. In a world containing viruses such as measles, which typically infects more than 90% of vulnerable individuals exposed to a single case[76], spreads readily through ventilation systems[77], and can infect people who arrive up to two hours after the index case has departed[78], this is a tall order.

Figure 8: Safeguarding essential workers with pandemic-proof protective equipment (P4E)



Any society that can continue distribution of food, water, power, order, and healthcare remains intact. Identifying all essential workers and providing them with sufficiently protective equipment can preserve civilisational stability in the face of any overt human-targeted biological threat, provided that workers are confident that the equipment will protect them during a high-lethality pandemic.

Standard P4E for most essential workers in areas other than healthcare should optimize for protection against the explosive spread of respiratory viruses. Such equipment would likely take the form of an improved powered air-purifying respirator (PAPR), which uses a battery-powered air pump to deliver sterilized air to a mask covering the user's nose and mouth. The goal is to ensure that all air touching the wearer's mucus membranes has been filtered or otherwise sterilized to remove harmful particles, while simultaneously preventing the wearer from accidental self-infection after touching a contaminated surface. P4E should still function even if worn improperly or the user lifts part of the mask off their face in order to adjust the fit, and must be compatible with hydration and liquid nutrient delivery to enable long-term use.

Estimates of infectious doses are highly imprecise, but if measles patients emit >100 infectious units per minute that linger for >100 minutes[79], anyone sharing a small room might be exposed to as much as 10,000 units. Extremely effective HEPA filters are least so for measles-sized particles, so correctly wearing a HEPA-filtered PAPR in perfect condition would reduce this exposure to 1-6 units; adding germicidal LEDs would offer full protection. But if the PAPR is covered in an agent that is also surface-transmitted, the wearer takes off the P4E while touching its exterior, then rubs a now-exposed mucus membrane, they could become infected. Preventing this outcome will require a design enabling safe doffing and sterilization of the PAPR before re-use. Some healthcare workers will require additional protection from fluid-transmitted agents such as Ebola. Commercial providers already offer suitable apparel for this purpose[80] that might benefit from making the gown component reusable.

P4E may be designed, developed, and manufactured by nonprofits or by for-profits seeking to serve the immunocompromised, but governments may be the only buyers capable of purchasing enough to guard populations against pandemic-class agents. There is no silver bullet against catastrophic biological threats, but the combination of a reliable early warning system with sufficiently protective and trusted P4E in the hands of essential workers can render nations virtually immune to pandemic-class agents – if the supply and distribution chain can provide all necessary materials and services.

Recommendation 9: Support the development of pandemic-proof personal protective equipment (P4E) designed to reliably prevent infection by all respiratory pathogens, to be used by the immunocompromised, the elderly, and healthcare workers. Further develop versions for healthcare workers that also guard against fluid-mediated infections.

B. Active defense: resilient production

Resilience requires identifying and protecting essential workers and hardening supply chains

Ensuring that the most vital workers who must interact with other people can be given access to P4E within days requires defining precisely who they are. The daily distribution of food, water, energy, and law enforcement are the bare essentials of society[81]. In the United States, food and water production (2.7%), warehousing and distribution (1.2%), energy (0.4%), and police and national guards (0.3%) comprise 4.6% of the total population[82]. Adding healthcare (5%) and critical manufacturing (0.6%) adds up to just over 10% of the population requiring access to P4E, although some of these may work in isolation. Other categories of workers defined as essential bring the total to 16.5%[83], but since this includes financial services – a notably remote-friendly occupation – and amounts to a third of the workforce, the 10% figure may be more accurate. Nations should carefully identify their essential workers, convey the importance of their role in a catastrophe, and develop and test plans to distribute stockpiles of P4E immediately upon receiving early warning.

Because some pandemic-class agents such as HIV may exhibit long infectious periods, and much of the global supply chain may shut down during a pandemic-class event, there is a major risk that vital and effectively irreplaceable equipment for the distribution of food, water, energy, and healthcare will fail during an extended pandemic. Nations should perform network vulnerability analysis[84], identify local sources of these items, and create strategic stockpiles as needed. They should identify systems that could be effectively operated remotely and install engineering controls to protect workers by keeping them isolated from others while performing vital tasks.

Recommendation 10: Identify all essential workers, convey the importance of their roles and the plan to protect them at all costs, maintain robust production lines for the manufacture of pandemic-proof personal protective equipment, generate sufficient stockpiles, and arrange for its swift delivery to essential workers when needed. Additionally, identify and arrange for the stockpiling and delivery of essential components for key equipment required for the provision of food, water, energy, law enforcement, and possibly healthcare that will no longer be available when global supply chains break down.

C. Active defense: diagnostics + personalized early warning

Knowing how many connections have been infected can change behavior and prevent others from being exposed

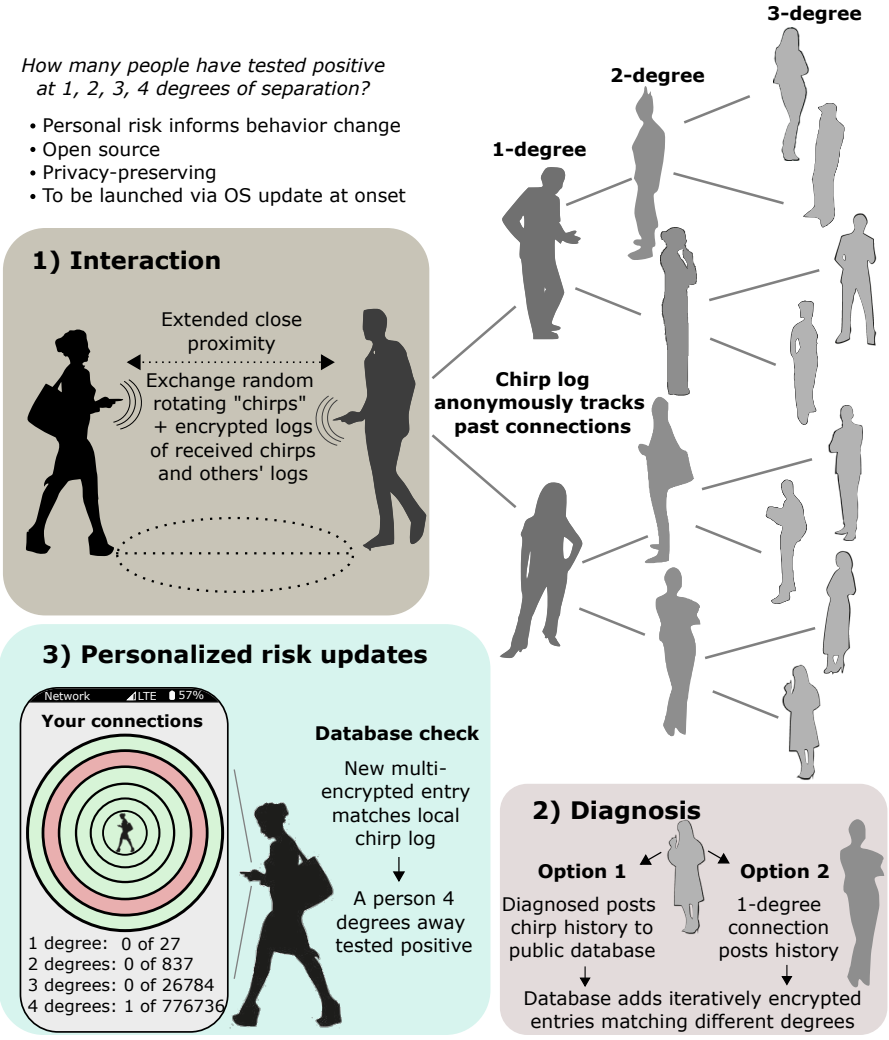
Covid-19 demonstrated that swiftly identifying the infected can help curtail the spread of a pandemic agent by encouraging self-isolation and behavioral changes by close contacts, which could include donning P4E. In principle, most pandemic-class agents could be controlled if the entire population is tested daily using a rapid, sensitive, and specific diagnostic, but only if the test is sensitive before the individual is maximally contagious and most of the infected are willing to self-isolate, neither of which is guaranteed. The challenge is to develop, manufacture, and distribute diagnostics faster than an exponentially growing biological agent seeded at a dozen sites can spread. This may be achievable for some pandemic-class agents using rapid antigen tests and especially CRISPR-based diagnostics[85] and other methodologies developed during Covid-19. Ensuring that these rapid diagnostics will be available to everyone in an afflicted region within days of identifying a new pathogen will be essential to containment. General methods of reliably detecting signs of acute infection with any viral or bacterial pathogen through physiological biomarkers may offer a version that could be prepared in advance, but such tests would not be specific, nor effective against all threats.

If daily testing of everyone in an afflicted region is not possible, as is likely in much of the world, the utility of each positive diagnostic test can be magnified with contact tracing, especially bidirectional tracing, to identify and isolate those exposed[86]. Exposure notification systems based on smartphone proximity[87] as determined by Bluetooth[88] and/or ultrasound[89] can supplement human tracers. However, even the best test-and-trace systems will likely fail when confronted with fast-replicating agents such as influenza virus, which is often transmitted just ~2.5 days after infection[90].

A more effective way to curtail the spread of all pathogens would preemptively warn individuals to alter their behaviour as soon as they are personally at increased risk of infection. For example, people could be notified when the first friend-of-a-friend-of-a-friend has been infected, or even provided with information on the fraction of individuals infected at one, two, three, four, and five degrees of connection away from them. This would spur preemptive behaviour changes to reduce exposure at a population level, but only for those actually at risk, eliminating the need for lockdowns at low frequencies[91].

Crucially, connection-based methods need not require individuals to report their own positive tests, instead allowing them to anonymously report that a first-degree contact was infected without specifying which one, albeit at some risk of false reports. Such a system consequently becomes effective

Figure 9: Personalized Early Warning



when only a small fraction of the population has opted in. A centralised app, NOVID[92], pioneered many of these capabilities, but decentralised versions are also possible. Because connection-based warning systems can be built and kept inactive until there is a pandemic emergency, and then only recording information relevant to social connections in encrypted and unusable form in each user's device, there is no need to trade privacy for protection until confronted with a threat – and with advances in cryptographic implementations, possibly not even then[93].

Recommendation 11: Ensure rapid diagnostic tests will be available soon after identification of a new threat to enable daily testing if necessary. Incorporate a connection-based early warning system into major smartphone operating systems, to be activated only when the next pandemic is identified, in order to provide individualised risk evaluations to all smartphone users.

D. Passive defense: transmission-blocking infrastructure

Safe pathogen-killing light and better ventilation can block transmission without requiring human action

Active defences will be most effective during high-lethality pandemics, when the fear of infection could otherwise disrupt essential services to the point of collapse, but they require willing adoption. SARS-CoV-2 has highlighted the need for passive defences capable of containing more subtle agents that may not be recognized as a serious threat by much of the population. The 36 million casualties of the ongoing HIV epidemic[94] underscore the harm that can be inflicted by extremely subtle pathogens.

Passive defences automatically prevent infections while people go about their day-to-day lives. Crucially, any passive defence capable of substantially impeding the spread of a novel pandemic agent would also suppress or outright eliminate many or even most endemic human viruses and pathogenic bacteria. Since economic losses from common infectious diseases in the United States reached an estimated ~$300 billion in 2017[95], or about $2,000 per worker, employers will be strongly incentivized to install any defences capable of reducing these losses in a cost-effective manner as soon as they have been developed.

Traditional passive defences, which use ventilation and occasionally upper-room germicidal irradiation to modestly reduce transmission[96], do not obviously meet this bar. Aircraft, which boast over 20 air exchanges per hour when the ventilation system is active, offered considerably greater safety from SARS-CoV-2 infection than other indoor environments[97]. While effective, upgrading ventilation to the level of aircraft – let alone higher – is expensive and often noisy, especially if air must be forced through a HEPA filter. Germicidal ultraviolet light, which can now be generated efficiently by LEDs, offers a somewhat lower-cost alternative: placing such lights in upward-pointing fixtures in rooms with high ceilings can eliminate aerosolized pathogens without harming humans[98]. Improving germicidal surface coatings and exploring better methods of hand sanitization, and especially promoting social customs that can block transmission, are worth pursuing. However, such interventions will struggle to completely block the

transmission of highly infectious agents in crowded indoor areas, especially those with low ceilings.

"Low-wavelength light" between 200 and 230 nanometers may provide a solution[99]. Like higher wavelengths in the ultraviolet spectrum, such light can effectively kill viruses and bacteria in aerosols and on surfaces. Unlike higher wavelengths, it cannot penetrate the outermost layer of human eyes and skin[100]. Light below 230nm is absorbed increasingly efficiently by proteins, which constitute 60% of the dry mass of eukaryotic cells. The outer surface of human skin is composed of a layer of protein; the tear film covering the eyes is also rich in protein[101]. As a result, humans tolerate levels of 222nm light hundreds or thousands of times greater than doses of higher wavelengths that cause skin damage and irritation[102]. Due to its dramatically greater biological safety relative to germicidal UV-C, "low-wave" light – which is somewhat misleadingly termed "far-UVC" and deserves a more accurate moniker – could constitute an extraordinarily effective pandemic defence.

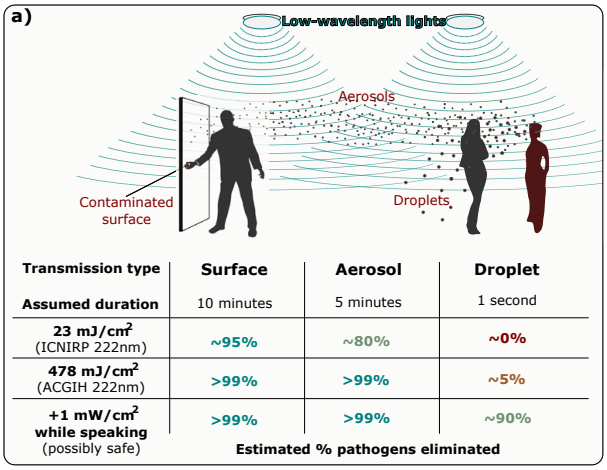
Every 1-2 mJ/cm^2 of 222nm light reduces the concentration of airborne or surface-associated infectious pathogens by approximately 90%[103]. Studies of eye safety in rats suggest that exposure to 3,500 mJ/cm^2 causes no visible effects[104], and eyes receive at most 5.8% of the maximum amount delivered by an overhead lamp[105]. Much higher levels are tolerated by human skin, with 18,000 mJ/cm^2 causing only a slight bronzing – which can be removed by applying and removing tape – and no observable DNA damage in replicating cells[106]. Hairless mice prone to skin cancer that were subjected to 396 mJ/cm^2 for five days per week over the course of 66 weeks exhibited no effects[107]. While very high levels of such wavelengths can generate ozone, new catalysts[108] and should be able to keep levels well below those known to be safe.

These studies collectively suggest that low-wave light is exceptionally safe, but they are sufficiently few in number that the American Conference of Governmental Industrial Hygienists (ACGIH) cautiously set its Threshold Limit Value for overhead exposure of 222nm light to skin at just 478 mJ/cm^2 per day, nearly 20 times below the highest acute dose delivered to a human volunteer without apparent ill effect[109]. The International Committee on Non-Ionizing Radiation Protection (ICNIRP) has declined to adjust its limits until multiple new safety studies are performed. Developing low-wave light as a passive defence will require a coordinated plan of research and development focused on safety, efficacy, and efficient generation, most likely by newly developed LEDs.

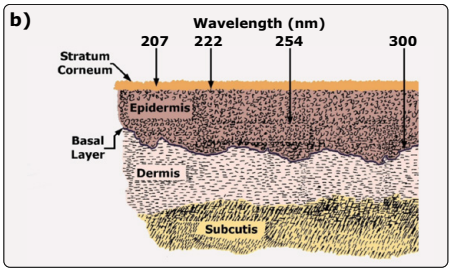
The most immediate priority is to determine the level that would be safe if low-wavelength fixtures were installed in every building, then raise the international exposure limits accordingly. In addition to rigorously testing both peak and chronic exposure to eyes and skin at suitably high levels in animals and human volunteers, future studies must examine any changes

in the human skin microbiome and effects on animals with open wounds, which lack the layers of protein and non-replicating cells that normally shield eyes and skin. To identify and assess all potential risks, field experts should issue an open call for suggestions and concerns from the general public, identify knowledge gaps, then design suitable experiments while avoiding conflicts of interest. Funders who recognize that 200-230nm light represents one of our best potential defences against catastrophic biological threats can then sponsor labs around the world to perform these pre-registered experiments in replicate. ICNIRP and ACGIH, as nonprofit groups that strive to avoid all conflicts of interest, can then evaluate the resulting data and set their guidelines to the appropriate level.

Figure 10: Low-wavelength light eliminates pathogens without penetrating skin or eyes



a) Estimated elimination of pathogens for various durations of illumination of surfaces, aerosols, and respiratory droplets. b) Wavelengths below 230nm are efficiently absorbed by proteins, making them unable to penetrate the outer layer of cells in the skin. c) Low wavelengths are similarly unable to penetrate the outer layer of the cornea. Images adapted from refs[110].



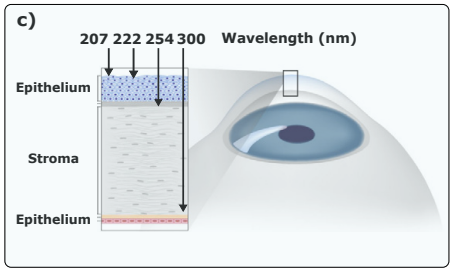
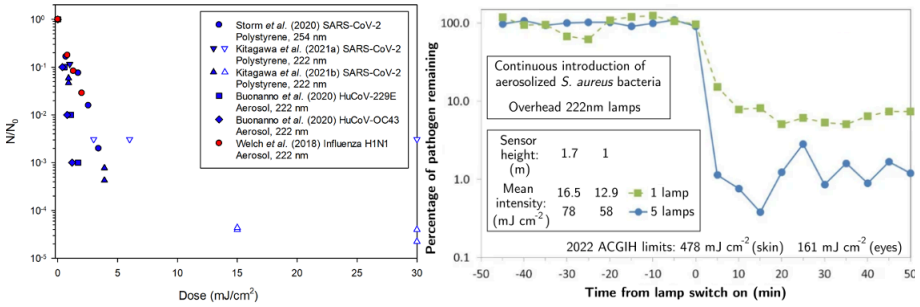


Figure 11: Demonstrated efficacy of 222 nanometer light at eliminating pathogens



Images adapted from from refs[111].

In parallel, experiments can examine epidemiological efficacy. Low-wave light is clearly germicidal, but the extent to which it can block transmission in animals and especially in human populations remains untested. As a first test, performing classical animal transmission studies in mice, hamsters, guinea pigs, or ferrets with and without low-wave light could directly measure efficacy against different pathogens and modes of transmission. More directly relevant studies can be performed in the United States by partnering with institutions that operate at multiple locations. Installing KrCl excimer lamps or LEDs in compliance with the ACGIH limits, randomly choosing half of the locations to turn them on, and then testing occupants for infection by all known human pathogens over the course of a year could quantify transmission-blocking effects on employee health and estimate employer cost savings. These tests would be maximally informative in comparatively isolated environments, such as long-haul commercial or military ships, which can best mimic the effects of widespread installation. As KrCl fixtures cost $10-20,000 per 100 square meters (~1000 sq. ft) per year at current market prices, such lamps may suppress the spread of common pathogens enough to justify widespread installation. Had they been sufficiently ubiquitous, low-wavelength lamps might even have prevented the spread of SARS-CoV-2 without other interventions.

However, ubiquitous KrCl excimer lamps alone would likely fail to contain a novel pandemic agent as contagious as measles, which probably requires a method of safely eliminating microbes from the air between people engaged in conversation. Delivering 1 mJ/cm^2 per second, which would suffice for short-range aerosols if not necessarily larger respiratory droplets, adds up to 28,800 mJ/cm^2 over 8 hours, which future studies may demonstrate is safe. But even if not, such levels are only required when people are actively speaking. Most people speak ~16,000 words per day at ~2.5 words per second, or for ~6400 seconds per 17-hour day[112]. Many words are spoken

outdoors, to devices, or at home, so fixtures in shared buildings that are only activated upon detecting conversation, coughs, or sneezes could plausibly prevent almost all transmission between conversation partners without exceeding future safety limits. And while current KrCl excimer lamps cannot switch on and off in response to detected coughs, sneezes, or other enunciations, nor can they easily reach the intensities needed to inactivate most pathogens within a second, LEDs installed in the overhead fixtures of buildings could plausibly do both at much lower cost. 200-230nm LEDs already exist[113], but their efficiency will need to rise by at least a factor of 50, as has occurred for other types of LEDs, to be market-competitive.

If demonstrated to be safe enough to increase exposure guidelines, there is evidence sufficient to convince employers to install it to prevent lost productivity and sick days, and the public supports widespread use in shared-occupancy buildings, low-wave light might prevent most infections by normal human pathogens while providing a powerful passive defence against future pandemics.

Recommendation 12: Support the development of low-wavelength germicidal light sources, including filtered 207nm KrBr and 222nm KrCl lamps and especially 200-230nm LEDs, and encourage the installation of germicidal lights and improved ventilation to passively reduce transmission in buildings. If determined to be sufficiently safe at high levels, such lights should yield large economic benefits by preventing productivity losses resulting from infectious disease transmission in public spaces.

VI. Conclusion

For 77 years, the international community has successfully kept nuclear weapons from falling into the hands of non-state actors. The anticipated proliferation of access to pandemic-class agents will far exceed the worst-case nuclear proliferation scenario. If current trends continue for the next decade, tens of thousands of individuals will obtain the power to single-handedly kill millions. Every rogue state will gain a credible deterrent, extremist groups will acquire agents permitting them to credibly blackmail the world, and zealots will be able to release every pandemic-class agent that they can assemble across travel hubs. If those agents are sufficiently harmful, many regions of the world will experience civilisational collapse.

As of this writing, humanity has not yet credibly identified any viruses capable of causing new pandemics. A coordinated effort can delay proliferation while we leverage new technologies to reliably detect and defend ourselves against the worst biological threats. Nations can cease funding efforts to identify pandemic-capable viruses – which are expected to kill a hundred times as many people as they save because the vast majority of viral threats circulating in animals will stay there, never spilling over into humans – and disincentivize researchers from performing the relevant experiments with regulations, publication policy changes, catastrophe liability insurance, and a pandemic test-ban treaty. They can dramatically limit unauthorised access by requiring all DNA synthesis to be screened for hazards once a freely available screening system becomes available, as is arguably required under Article IV of the Biological Weapons Convention[114], and eventually require screening to be incorporated into all synthesis and assembly devices.

Enacting these delaying policies will cost governments nothing and impact scientific progress negligibly, if at all. Early warning systems based on untargeted metagenomic sequencing of aircraft and airport wastewater and air filters, as well as flight crews and possibly hospital patients[115], can reliably detect all exponentially growing biological threats in humans and the environment for a couple of billion dollars a year. Detecting all threats circulating in commercial air travellers might only cost in the hundreds of millions or even tens of millions per year, thereby ensuring that all subtle HIV-like pandemics will be detected before too many people are infected. Forewarned essential workers can be sent comfortable protective equipment in advance, enabling them to stay safe while providing the general population with food, water, power, healthcare, and law enforcement. Stockpiling enough for essential workers comprising 1/7 of the population and arranging for its distribution as soon as a future pandemic agent is detected should cost less than $300 per person. If safety and efficacy studies of low-wavelength light proceed as hoped, employers will

pay to install fixtures in workplaces in order to mostly eliminate illness-related productivity losses by preventing most infections. Combined with basic preparations on the part of nations, these measures will allow us to reliably detect and eliminate emerging pandemic-class agents before they can inflict widespread harm.

We can build a civilisation that is virtually immune to the catastrophic misuse of biology. The question is no longer what to do, nor how to do it, but whether we can jointly acknowledge that the nascent proliferation of pandemic-class agents represents a profound threat to our future.

In the 1970s, when the public viewed the potential risks from recombinant DNA as the next atomic bomb[116], acknowledging our peril would not have been difficult. Thirty years later, norms had shifted so dramatically that the editor-in-chief of *Science* publicly decried the White House's request that a manuscript sharing the genome sequence of a virus that killed over 50 million people be subjected to a security review[117]. Most scientists defer to these new norms when they consider security issues, and policymakers defer to them. But these "new" norms originated nearly two decades ago: after the fear of nuclear weapons had faded; before the great acceleration of biotechnology that gave us the power to unilaterally edit virtually any gene in any genome, and spread alterations to entire species[118]. Before synthetic DNA became a thousandfold cheaper, the cost of sequencing fell by a millionfold[119], scientists shared the genome sequences of half a million new viruses, and detailed step-by-step protocols gave many thousands of people the ability to assemble infectious samples.

Policies and norms, like technology, must change.

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