Bulletin of the Atomic Scientists

A FRAMEWORK FOR TOMORROW'S PATHOGEN RESEARCH

FINAL REPORT

The Independent Task Force on Research with Pandemic Risks
Chairs: Ravindra Gupta, Ameenah Gurib-Fakim, Shahid Jameel, David Relman
Directors: Jesse Bloom, Filippa Lentzos

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The *Bulletin of the Atomic Scientists* equips the public, policymakers, and scientists with the information needed to reduce man-made threats to our existence. We post free articles on our website and publish a premium digital magazine. But we are much more. The *Bulletin's* website, iconic Doomsday Clock, and regular events help advance actionable ideas at a time when technology is outpacing our ability to control it. The *Bulletin* focuses on three main areas: nuclear risk, climate change, and disruptive technologies, including biosecurity and artificial intelligence. What connects these topics is a driving belief that because humans created them, we can control them.

The *Bulletin* is an independent, nonprofit 501 (c) (3) organization.

All views expressed in the *Bulletin's* publications and on its website are the sole responsibility of the author or authors.

For further information about the *Bulletin* or this Task Force, please write to the *Bulletin of the Atomic Scientists*, 1307 East 60th Street, Chicago, IL 60637, or email us at info@thebulletin.org. Visit our website, TheBulletin.org.

Preface

The *Bulletin of the Atomic Scientists* began more than 75 years ago as an emergency action by scientists who saw an immediate need for a public reckoning in the aftermath of the atomic bombings of Hiroshima and Nagasaki. The scale of the loss of life and the obliteration of these cities in the late summer of 1945 proved a wake-up call for physicists about the potential destructive power and potential uses of their science and its newfound role in waging war. Many scientists at the time anticipated that the atom bomb would be "… only the first of many dangerous presents from the Pandora's Box of modern science."

Humankind now faces additional threats and the *Bulletin* grapples with many of them, including those posed by advances in biological research. The *Bulletin* publishes influential pieces on biosafety and biosecurity, advances in genetic engineering, the role of artificial intelligence in the future of medicine, and other relevant topics.

As a not-for-profit organization the *Bulletin* is independent of government funding and influence. Its magazine is found in nearly 10,000 libraries worldwide and its website draws more than 11 million pageviews per year; nearly half of its readers are younger than 35 years of age and half reside outside the United States. In 2022, the *Bulletin* convened an independent panel of experts in biosecurity, epidemiology, virology, ethics, and other areas: the Task Force on Research with Pandemic Risks. What follows is its report.

Worldwide, there are several other important initiatives underway that align with the work of the Task Force. Each initiative calls for broader and more sustained engagement by life scientists with a broad set of stakeholders to address the risk posed by technical advances in the life sciences. The Task Force exemplifies a response to such calls. Because the Task Force is non-governmental, international, multi-disciplinary and includes members from a variety of civic institutions, the goal is to offer a perspective that complements other initiatives.

Acknowledgements

As with any 18-month project, there are many people to thank for their hard work and contributions. The task force chairs Ravindra Gupta, Ameenah Gurib-Fakim, Shahid Jameel, and David Relman were early supporters of this task force and helped recruit a wide range of leading experts to drive our effort forward. Task force members devoted considerable time to this project, by attending task force meetings, preparing and presenting briefing papers, identifying outside experts to inform the group, and joining us in Geneva and New York to bring attention to the important work of our independent panel of experts.

Co-directors Filippa Lentzos and Jesse Bloom deserve enormous gratitude for carrying out the lion's share of the effort. It is not easy to corral such a large group, and quite difficult to draft a document that earns such significant buy-in. Filippa and Jesse are world class in just about every regard, and we are so grateful for their seriousness of purpose and commitment to bringing this report to its conclusion.

Mayra Ameneiros and Becca Earnhardt served as rapporteurs throughout the process and helped organize the many insights generated throughout our months of discussion. Halley Posner served remarkably as project coordinator, making it as easy as possible for the task force to do its work. The staff of the *Bulletin* including Erik English, Matt Field, John Pope, Gayle Spinazze, Sarah Starkey and the *Bulletin*'s events coordinator January Zell each contributed in significant ways to this project.

The *Bulletin*'s Pathogens Project is supported by the Gurley Family Charitable Fund, Robert and Eleanor Meyers, the Keith D. and Arlene M. Bronstein Foundation and two anonymous donors. I am grateful for their significant investment in this effort, and the general support that allows the *Bulletin* to address the most important issues of our times.

Thank you to everyone who has allowed us the privilege of engaging in such meaningful work.

Rachel Bronson, PhD
President & CEO
February 2024

Task Force members

The Task Force is independent of the *Bulletin* and is solely responsible for the content of the report. Its members were asked to join a consensus that they endorse the general policy thrusts and judgements reached by the group, though not necessarily every finding and recommendation.

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* *The author is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this report and they do not necessarily represent the decisions, policy or views of the World Health Organization*

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‡ *The author is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this report and they do not necessarily represent the decisions, policy or views of the World Health Organization.*

Contents

A framework for tomorrow's pathogen research

Executive summary

Throughout history, viral diseases have been among humankind's greatest scourges. Many millions of people died worldwide during the 1918 influenza pandemic. Prior to initiation of the World Health Organization's smallpox eradication program and the development and widespread use of measles vaccines, it is estimated that each of these diseases caused more than two million deaths annually.

Basic scientific knowledge obtained from studying viruses has been an essential step in creating lifesaving countermeasures. Today, therapeutics and vaccines have reduced the disease burdens of COVID-19, hepatitis C, influenza, poliomyelitis, and a variety of other viral diseases. The development of these countermeasures, enabled in part by research in virology and immunology, has greatly benefited public health and will continue to do so in the future.

Most viral disease outbreaks stretching back over millennia have been caused by viruses transmitted to humans through direct or indirect contact with domesticated and wild animals. Yet modern virology research also creates new avenues for outbreaks to arise, as researchers can also become infected while collecting field specimens or performing research with viruses in the laboratory. Depending on the virus under study, an infection may spread to other workers, family members, and the wider community. These risks have existed since the early days of virology research. For example, the last cases of smallpox occurred in a small outbreak triggered by an accidental infection originating from a laboratory studying the virus in Birmingham, United Kingdom, in 1978. While biosafety has improved since the 1970s, advances in virology research also open new risks.

Recognizing the need for a focused conversation on the risks and benefits of a subset of research that could plausibly source a large outbreak, or even a pandemic, the *Bulletin* convened an independent and international panel of experts

in biosafety, biosecurity, epidemiology, ethics, genetic engineering, virology, and other areas: the Task Force on Research with Pandemic Risks.

The scope of the research examined by the Task Force included (1) research on pathogens known to be capable of causing a pandemic that under current conditions (e.g., low population immunity) could result in extensive spread beyond the current infection burden; (2) manipulation of pathogens that are not currently thought capable of pandemic spread in ways that can be anticipated to increase their capacity to cause a pandemic (e.g., by increasing virulence or transmissibility); and (3) research on pathogens with unknown characteristics.

The Task Force's report discusses the potential benefits of virology research and outlines how advances in science and technology may increase certain benefits. It then focuses on some of the potential risks of virology research, including biosafety and biosecurity, and outlines how advances in science and technology may increase some of these risks. The Task Force also examined ethical obligations to make research with pandemic risks more safe, secure, and responsible, suggesting actionable and sustainable strategies to effectively maximize the potential benefits and mitigate the foreseeable potential harms of research with known or potential pandemic pathogens, while attending to issues of equity and proportionality. The report argues for empirical studies on biosafety and biosecurity to make research with pandemic risks more safe, secure, and responsible. It also reviews the contemporary governance space for research with known or potential pandemic pathogens and argues that effective legislation, regulations, policies, and guidelines specifically regulating such research will strengthen the scientific enterprise and should be put in place and implemented without delay. It discusses challenges in building and sustaining trust in science in general and research with pandemic risks more specifically. Finally, the Task Force has issued several recommendations.

Key recommendations include:

- Research with pandemic risks should have high-probability benefits for public health.
- Where feasible, research questions about pathogens with pandemic risk should be addressed using surrogate systems, or by taking advantage of loss-of-function experiments on current human viruses.
- International protocols should be established for research on pandemic risk pathogens. Those protocols should include methods for both sample collection and laboratory work.
- Research on pandemic risk pathogens should be monitored locally, nationally and internationally. Funds should be allocated to optimize biorisk management strategies.
- Scientific journals and their editors should enforce timely data-sharing and research integrity for the manuscripts they publish.

At present, occupational health and safety governance generally adequately weighs the direct biosafety risks to the researcher in the laboratory, but there is a small subset of research on known or potential pandemic pathogens for which biosafety risks go beyond the laboratory and affect the health of significantly larger groups of humans or other animals. Indeed, if a virus has true pandemic potential, the entire world can be affected by an accident.

Navigating research with pandemic risks warrants additional precautions. The overarching aim of the Task Force on Research with Pandemic Risks is to guide the development of a safe, secure, and responsible research environment for researchers, and in so doing, to earn public trust.

"Scientists have an obligation to do no harm. They should always take into consideration the reasonably foreseeable consequences of their own activities. They should therefore: … always bear in mind the potential consequences - possibly harmful - of their research and recognize that individual good conscience does not justify ignoring the possible misuse of their scientific endeavour …"

—**IAP Statement on Biosecurity 2005**

"... [scientific] responsibility has to go beyond vocation to encompass a deeper ethical commitment based on the empathic experience of interdependence and shared humanity."

—**Charles Thorpe**

I
Introduction

Safe, secure, and responsible high-risk research.

Joseph Rotblat, a physicist who quit the Manhattan Project and later helped establish the Pugwash Conferences on Science and World Affairs, with which he shared the 1995 Nobel Peace Prize, wrote "Scientists can no longer claim that their work has nothing to do with the welfare of the individual or with state policies" (Rotblat 1999). To ignore the societal implications of their work is "immoral," he reasoned, because "… [an immoral attitude] eschews personal responsibility for the likely consequences of one's actions."

Today, it is widely recognized that scientists—especially those doing high-risk research—have a professional obligation to both consider the broader ends of their science and mitigate anticipated harmful consequences (WHO 2022).

Consequently, responsible stewardship of science today is expected to include a prominent role for scientists in developing and supporting policies (including laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, and training and education) that reflect the local, national, regional, and global communities' values, priorities, and risk-taking strategies. This stewardship entails developing and supporting ethical practices (with particular attention to issues of intent, integrity, and conflicts of interest) to ensure an effective alignment of the processes and outcomes of science with societal values, needs, and expectations. To ensure their sustainability, these practices require a commitment to public education, engagement, and empowerment.

Task Force on Research with Pandemic Risks.

The continuing coronavirus disease 2019 (COVID-19) pandemic has highlighted the potential devastating impact of a single virus. In the coming years, the human population's

encounters with high-consequence pathogens may occur more frequently (Carlson 2022; Gilbert 2022). Human-driven alterations of the natural environment and climate-driven changes in ecosystems may provide increasing opportunities for viruses to cross species barriers, including to humans. In addition, field collection and experimental manipulation of potential pandemic viruses under some circumstances can increase the risk of accidentally, inadvertently, or intentionally seeding a pandemic.

The *Bulletin of the Atomic Scientists* recognized that a multi-disciplinary, international forum was needed to consider trends and oversight of high-risk research on pathogens with a narrow focus on the potential benefits and harms of research with known or potential pandemic pathogens. In 2022, the *Bulletin* convened an independent panel of experts: the Task Force on Research with Pandemic Risks. Its aim was to foster an inclusive and broad discussion and to identify ways and means for research with pandemic risk to be managed as safely, securely, and responsibly as possible.

The remit of the Task Force was to focus on the risks and benefits of a subset of research that could plausibly source a large outbreak, or even a pandemic, due to accidental or inadvertent actions during the conduct of experiments, or that results in information that could be misused by a malicious actor. The accidental and inadvertent risks generally concern biosafety whereas the malicious actor risk generally concerns biosecurity, though these boundaries are approximate (Evans, Lipsitch, and Levinson 2015). The Task Force's scope included (1) research on pathogens known to be capable of causing a pandemic that under current conditions (e.g., low population immunity) could result in extensive spread beyond the current infection burden, (2) manipulation of pathogens that are not currently thought capable of pandemic spread in ways that can be anticipated to increase their capacity to cause a pandemic (e.g., by increasing virulence or transmissibility), and (3) research on pathogens with unknown characteristics. The Task Force was to critically review the handling of such pathogens throughout the research lifecycle, from collection in the field and transportation to sites for research, to characterization, cultivation, and manipulation in the laboratory, to disposal at the end of research.* Taking its lead from the US National Science Advisory Board on Biosecurity (NSABB), the Task Force understood enhanced potential pandemic pathogen research to include (NSABB 2023):

"… research that is *reasonably anticipated* to enhance the transmissibility and/or virulence of any pathogen … such that the resulting pathogen is *reasonably anticipated* to exhibit the following characteristics that meet the definition of a PPP [potential pandemic pathogen]:

- Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or
- Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans, and
- Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security" (italics added for emphasis).

Like the NSABB, the Task Force took *reasonably anticipated* to mean a non-trivial probability assessment by individuals with relevant scientific expertise. It does not require high confidence that

* *Discussion around risks in virology and microbiology have sometimes included the term "gain of function," which was the phrase applied to controversial research that modified H5N1 influenza A virus to transmit among domestic ferrets in the laboratory (**LINK**). However, this term when used generically lacks specificity in capturing risks, since formally speaking "gain of function" can just mean introducing any new trait into an entity (a virus in this case). For instance, modifying a non-transmissible oncolytic virus used for cancer treatment to improve infection of cancer cells would technically involve a gain of function by this virus, but in practice such research would likely be beneficial for public health with little risk.*

the outcome will definitely occur. This wording, however, does exclude research for which experts would anticipate the outcome to be technically possible but highly unlikely. In the case of newly discovered pathogens that are not yet well characterized, it is often particularly challenging to assess how individual experiments (such as serial passaging in human cells or introducing features or genes from similar pathogens) might alter transmissibility or virulence. Thus, when these biological properties cannot be anticipated for newly discovered pathogens, it should be assumed that the pathogen is a potential pandemic pathogen (and therefore managed at the corresponding biosafety level) when its taxonomically close relatives include pathogens with those characteristics.

Virologists conduct research with potential pandemic pathogens mainly to increase knowledge about these pathogens, improve surveillance, and to inform the design of diagnostics, vaccines, and therapeutics. However, the risks associated with *enhanced* potential pandemic pathogen research can be exceptionally high, and probabilities of harm increase with the number of such studies undertaken (Klotz and Sylvester 2012).

There has been considerable progress in the ability of virologists to rapidly detect and sequence the genomes of viruses, including those that could potentially harm humans, other animals, plants, or the environment (although the ability to predict function from sequence alone remains limited). At the same time, the ability to generate fully replication-competent viruses, or to re-construct extinct pathogens based solely on their genetic sequence has improved. Large poxviruses, which have long genomes, (Noyce, Lederman and Evans 2018) and viruses with short genomes (e.g., influenza A virus, polioviruses, and betacoronaviruses can be created using synthetic DNA (Tran et al. 2020; Xie et al. 2020). Generating some of these viruses from synthetic DNA is undertaken by many, reasonably resourced virology laboratories, and the accessibility and efficiency of these techniques is likely to continue to increase.

The intersection of these advances has increased the capacity of scientists to identify the genome sequences of potentially high-risk viruses, and then generate the actual pathogen in the laboratory from knowledge of the sequences, including modified versions. This capacity has yielded benefits. For instance, it has enabled the engineering of attenuated viruses for vaccines (Trimpert 2021) and helped in the development of countermeasures that are harder for viruses to escape by acquiring resistance (Starr 2021). Further, some experiments are safer because of using attenuated viruses in place of wild-type viruses. Experiments with attenuated viruses can be performed at lower biosafety levels, which accelerates research progress. Moreover, these capabilities can reduce the need for collection of replicative ("live") virus samples from the field, since one of the main reasons to acquire live samples from nature is to obtain virus isolates for countermeasure development. These viruses can now also be generated using reverse "on-demand" genetic systems, which enable rescue of wild-type viruses from synthesized nucleic acids in high or maximum containment based only on sequences that were determined using inactivated natural samples, i.e., samples that do not contain "live" viruses anymore and that do not necessarily have to be transported across country borders (Beitzel 2021). However, this increased capacity has also increased the ability of scientists to create and work with viruses that could accidentally or intentionally cause harm, in some cases with potentially devastating global consequences.

Because research with potential pandemic pathogens will never be risk-free, navigating in this high-risk research space warrants additional precautions, including traffic signals (e.g., red lights identifying research that should not be undertaken and yellow lights identifying research that requires caution and close oversight), guardrails (e.g., introducing enhanced biorisk

management), speed bumps (e.g., ensuring additional multi-disciplinary review of some research or imposing temporary moratoriums), and lamp posts (e.g., illuminating safer directions for research and including proportional oversight to protect the well-being of humans, other animals, plants, and the environment).

The overarching aim is to create a safe, secure, and responsible research environment for researchers, and in so doing, to earn public trust.

Work of the Task Force.

The *Bulletin* established a year-long Task Force on Research with Pandemic Risks comprising 28 international experts across fields such as anthropology, bacteriology, bioengineering, biorisk management, biotechnology, epidemiology, ethics, global governance and policy, infectious disease, law, political science, security studies, sociology, synthetic biology, as well as virology. Task Force members joined in their individual capacities and not on behalf of the institutions at or for which they work. A list of Task Force co-chairs, directors, members, rapporteurs, and *Bulletin* staff involved in the project is found in Appendix I.

The Task Force convened online six times from October 2022 to October 2023. In addition, the *Bulletin* and the Task Force met in Geneva, Switzerland, on April 19-21, 2023. The meeting in Geneva also included policy leaders, journalists, scientists, and nongovernmental organization leaders. To further enhance engagement, deliberations were live-streamed and recorded (Bulletin 2023).

This report is the result of the Task Force's deliberations. The Task Force is independent of the *Bulletin* and is solely responsible for the content of the report. Its members were asked to join a consensus signifying that they endorse "the general policy thrust and judgements reached by the group, though not necessarily every finding and recommendation." Each Task Force member had the option of putting forward an additional or a dissenting view, although the goal was always consensus-building.

Structure of the report.

The report includes several sections. Section II introduces virology research and its key potential benefits and outlines how advances in science and technology potentially increase certain benefits. Section III focuses on some of the risks of virology research, including biosafety and biosecurity, and outlines how advances in science and technology potentially increase some of these risks. Section IV focuses on ethical obligations to make research with pandemic risks more safe, secure, and responsible. It also suggests actionable and sustainable strategies to effectively maximize the potential benefits and mitigate the foreseeable potential harms of research with known or potential pandemic pathogens, while attending to issues of equity and proportionality. Section V argues for empirical studies on biosafety and biosecurity to make research with pandemic risks more safe, secure, and responsible. Section VI reviews the contemporary governance space for research with known or potential pandemic pathogens and argues that effective legislation, regulations, policies, and guidelines specifically regulating such research will strengthen the scientific enterprise and should be put in place without delay. Section VII discusses challenges in building and sustaining trust in science in general and research with pandemic risks more specifically. The Task Force's recommendations follow in Section VIII of the report.

II

The benefits of virology research: Reasons for hope

Infectious disease agents include bacteria, viruses, fungi, and parasites; all have had major impacts on public health and welfare. Viruses are among the simplest of these agents and for this reason are more amenable to generation from synthetic DNA given knowledge of a sequence. Viruses can also be highly transmissible and cause rapidly growing outbreaks.

Throughout history, viral diseases have been among humankind's greatest scourges. It is estimated that at least 17 million people died worldwide over a period of two years during the 1918 influenza pandemic (Spreeuwenberg et al. 2018). Viral diseases such as smallpox and measles have also been major causes of death (Michaud 2009). Prior to initiation of the World Health Organization's (WHO's) smallpox eradication program in 1967, it is estimated that smallpox caused over two million deaths annually (Fenner 1993). Likewise, prior to the development and widespread use of measles vaccines, it is estimated that measles caused more than two million deaths of children annually. By 2021, the WHO reported an estimated 128,000 deaths per year from measles, a major decrease primarily due to vaccination (WHO n.d.a; WHO 2023).

In multiple instances, basic scientific knowledge obtained from studying viruses has been an essential step in creating lifesaving countermeasures. Today, disease burdens due to influenza, COVID-19, poliomyelitis, and hepatitis C are reduced through the use of therapeutics and vaccines, developed in part by leveraging basic research to gain detailed virologic knowledge. Antiviral drugs now also play a central role in treating HIV/AIDS and reducing transmission, raising the prospect for the first time that the world may bring a viral pandemic under control without a vaccine.

The development of COVID-19 vaccines provides an important example of how modern scientific research can rapidly yield benefits for public health. Within a year of the publication

of the SARS-CoV-2 genome sequence, several companies produced vaccines that during the first year of use are estimated to have prevented approximately 14–20 million deaths worldwide (Watson et al. 2022). Scientists were able to develop these vaccines rapidly thanks to the convergence of multiple scientific advances accumulated from decades of prior research, including basic research into the properties of betacoronavirus spike proteins and methods to stabilize them for use in vaccines, development of assays for antibody-based neutralization of betacoronaviruses, and new vaccine technologies (e.g., mRNA-based platforms). Another important example is the research that has gone into first developing, and then adapting, trivalent oral poliomyelitis vaccines to monovalent oral poliomyelitis vaccines when trivalent vaccines were proven less effective in providing an immune response to poliovirus types 1 and 3. When the number of type 2 vaccine-derived polioviruses increased in the 2020s, further research led to the development of a new and more stable oral polio vaccine (Wilkinson et al. 2023; Bandyopadhyah 2015).

The development of vaccines, enabled in part by research in virology and immunology, has greatly benefited public health and will continue to do so in the future.

III

The risks of virology research: Reasons for caution

Biosafety risks.

Most viral disease outbreaks stretching back over millennia have been caused by viruses transmitted to humans through direct or indirect contact with other animals. Although most of these infections result in dead-end transmission chains, occasionally a virus will be, or evolve to be, transmissible enough to spread widely in the human population, causing a large outbreak, an epidemic, or even a pandemic.

Researchers can become infected while collecting field specimens (Amman et al. 2015) or performing research with viruses in the laboratory (Byers and Harding 2006). Infections of individual researchers may spread to other workers, family members, and the wider community. Additionally, a containment breach may result in the accidental release of a pathogen directly into the environment, leading to potential viral spread in the geographical area surrounding the laboratory.

Examples of scientists becoming infected in the laboratory date back to the early days of virology research (Young 2023). For instance, in 1933, the initial isolation of human influenza A virus in the laboratory involved a complicated chain of events thought to include infection of the scientist Wilson Smith with the virus that he and his colleagues had initially inoculated into ferrets (Evans 1966). The last human cases of smallpox involved an infection originating from a Birmingham, United Kingdom, laboratory in 1978 after the virus had been eliminated in nature (Rimmer 2018). After the severe acute respiratory syndrome (SARS) outbreak was mostly contained in 2003, laboratory infections of researchers in three different locations—Singapore, mainland China, and Taiwan, with further transmission to others in mainland China—led the WHO to highlight laboratory accidents alongside natural zoonotic infections as potential sources for the re-emergence of the etiological agent, severe acute respiratory syndrome coronavirus (SARS-CoV) (WHO 2004). From 1979 to 2015,

more than 2,300 laboratory-acquired infections across all biosafety levels were reported in the literature (Byers and Harding 2006), a figure of over 100 per year that probably reflects significant underreporting (Kimman, Smit, and Klein 2008). Focusing purely on accidents in modern laboratories, more than 300 laboratory-acquired infections and eight deaths were reported worldwide in the first two decades of this century, which reflects how modern practices and containment may reduce risks, but cannot eliminate them completely (Blacksell et al. 2023). There is no equivalent reporting of fieldwork accidents, or sufficient historical data to study the impact of improved biosafety procedures on these trends.

Occupational health and safety governance generally adequately weighs the direct biosafety risks to the researcher in the laboratory, but there is a small subset of research on known or potential pandemic pathogens for which biosafety risks go beyond the laboratory and affect the health of significantly larger groups of humans or other animals. Indeed, if a virus has true pandemic potential, the entire world can be affected by an accident. When the conduct of scientific research risks significant harm to large numbers of people, and especially when it is debatable whether the potential research benefits are commensurate with the research risks, additional oversight, beyond occupational health and safety, is essential (Evans, Lipsitch, and Levinson 2015).

Biosecurity risks (including dual-use risks).

Based on prior experience, most disease outbreaks are unintentional; they are not the result of a deliberate act of crime, terrorism, or war. There are scenarios, however, of intentional misuse that could cause disease outbreaks.

Although uncommon, the risks of an intentional disease outbreak caused by malicious actors (including states; terrorist and extremist groups; and individuals) may be increasing. Key concerns include (1) increased access to powerful techniques in the life sciences, including an increase in the capabilities of individuals outside traditional research institutions (Jackson et al. 2019); (2) the lack of biosecurity norms in the biotechnology industry that could be exploited by a malicious actor; (3) pathogens or other related material being stolen from a laboratory or scientists going "rogue"; (4) laboratory insiders using their knowledge, skills, and access to intentionally cause harm; and (5) scientific knowledge and methods generated to understand and manipulate the biological and epidemiological properties of pathogens for use in public health being repurposed by malicious actors to intentionally cause harm.

Analysis of laboratory crimes over the past 25 years shows that most of these are motivated by economic or emotional factors, rather than ideological ones and that such acts are surprisingly common. Examples of criminal acts include stealing equipment or laboratory animals from containment space to sell on the black market (for the value of the items stolen, rather than the value of any associated pathogens) and violence perpetrated because of fraught interpersonal relationships (Carus 2002). Examples of bioterrorism include the 2001 "Amerithrax" attacks in the United States and earlier attacks by the Rajneeshee (1984) and Aum Shinrikyo (1995) cults.

Research with known and potential pandemic pathogens also carries risks to peace and international security. Increases in the number of laboratories, the prevalence of associated infrastructure, and the ranks of researchers working with high-risk pathogens may contribute to a perception that the risks of intentional misuse are increasing. This may provide a country with justification to initiate or expand a biological warfare program—of which there have historically been several—in breach of the Biological Weapons Convention (Lentzos 2016; Inglesby and Relman 2016; Wheelis, Rózsa, and Dando 2006; Guillemin 2005). There are also

allegations of contemporary programs in several countries (Lentzos and McLeish 2021; Lentzos and Jakob 2022; Lentzos and Jakob 2023).

Advances in science and technology that potentially increase risks.

Recent advances in science and technology have increased the ability to rapidly identify and sequence the genomes of new viruses. Significant and accelerating advances are also being made in abilities to synthesize, modify, and manipulate genes, genomes, and biological systems through synthetic biology and genome editing, since viruses were first generated from cloned or synthesized forms of their genomes (Cello, Paul, and Wimmer 2002; Racaniello and Baltimore 1981). As more laboratories develop and engage in these technologies, the frequency of accidental releases of laboratory-grown and laboratory-modified pathogens could rise.

Furthermore, if the intent were there, individuals or groups could exploit the identification of genes and DNA sequences associated with pathogenicity, transmissibility, host range, evasion of countermeasures, and other properties to attempt to enhance known and potential pandemic pathogens and render them even more harmful (Fink et al. 2004). The last decade has seen much progress in understanding how small modifications (e.g., individual mutations) can increase host range (Starr et al. 2022), escape protective immunity (Starr et al. 2021), or escape drugs (Flynn et al. 2022). Such advances have been valuable for anticipating short-term viral evolution (Cao et al. 2023) and informing vaccine strain selection or drug design, but they also increase the potential for making targeted modifications to viruses that could change their properties and make them more harmful—although it should be recognized that such modifications may produce viruses that are less fit to survive in the real world. Although it is now possible to re-construct many known viruses from a sequence, it remains beyond current scientific knowledge to design an entirely novel pathogenic virus from scratch.

There is increasing concern that artificial intelligence (AI) and machine learning could be used to predict and design enhancements of pathogens that make them even more harmful or to identify and manipulate key genetic components affecting their transmission and/or disease-causing properties. However, currently there are no data showing this to be the case. At the present time, the risk that AI could allow for the design of new pathogens is hypothetical and uncertain. For efficient AI training, large and high-quality datasets are paramount, and it is questionable whether there are sufficient data to enable meaningful training of models that can predict how mutations affect complex traits such as transmissibility. Currently AI and machine learning can only augment *in silico* analyses of pathogen sequences or proteins. For any risk to be actualized, the sequences must be converted into actual pathogens.

Another concern is that large language models (LLMs) like ChatGPT may make it easier for non-experts to access dual-use knowledge, thereby lowering barriers to intentional misuse even if they do not enable effective design of new pathogens (Sandbrink 2023). In this sense, these models could help increase the number of people with conceptual access to techniques that currently require specialized training.

All told, there are many uncertainties in how AI and machine learning might affect research on known and potential pandemic pathogens. All concerns should be taken seriously, while neither minimizing nor exaggerating the risks (including hypothetical risks).

IV

Ethical obligations to make research with pandemic risk more safe, secure, and responsible

The benefits of pathogen research are significant because it has dramatically improved the well-being of humans, other animals, and the environment—and has the potential to continue to do so in the future. However, the potential harms of research with potential pandemic pathogens are no less significant as these could affect entire populations.

This reality underscores the need for actionable and sustainable strategies and mechanisms to effectively maximize the potential benefits of research with potential pandemic pathogens and eliminate or mitigate the foreseeable potential harms, while attending to issues of equity and proportionality.

Ethical obligation to ensure high-probability benefits for public health.

Research with pandemic risks should have high-probability benefits for public health.

We acknowledge that the public health benefits of research with known and potential pandemic pathogens are difficult to assess as these would typically unfold over long time scales, with much uncertainty and with uneven distribution around the world. Moreover, these benefits depend upon disputed technical details about the research in question. As a result, claimed public health benefits are often vague or underspecified, complicating a comparison to risks.

In some instances, scientists may overstate the potential benefits of research. For example, supporters of the H5N1 influenza A virus enhancement research have claimed benefits for surveillance and vaccine design, notwithstanding that research had previously identified many of the mutations those studies determined to be important for transmission by safer methods without increasing the transmissibility of the actual H5N1 influenza A virus (Lipsitch 2016). Consequently, although such research certainly has increased human knowledge, it is fair to ask if

the public health benefits of that knowledge are commensurate with the risk of a pandemic that could be caused by the accidental (or otherwise) release of a mammalian-transmissible H5N1 influenza virus.

Underpinning public health benefits assessments is the idea that the expected benefits of human pathogen research are greater if pathogens (and the specific variants under study) are circulating in humans and domestic animals. Conversely, the expected benefits are smaller if pathogens are solely found in wildlife or are extinct or enhanced variants of current pathogens that are not currently circulating. In turn, this is considered more beneficial than research on pathogens that are not expected to naturally evolve (for example, highly chimeric pathogens or pathogens modified with genes from other organisms). Specific frameworks have been proposed to make these types of assessments (Casagrande and Greene 2022). Taking the example of re-constructing the 1918 pandemic H1N1 influenza A virus, a qualitative assessment might rate the public health benefits of that research as lower than the public health benefits of research on today's H5N1 avian influenza A strains because the 1918 strain is not currently circulating in humans or domestic animals and is unlikely to re-appear unless the re-constructed virus itself is released. On the other hand, understanding the characteristics that made historical pandemic viruses virulent or transmissible may provide insights that enable us to predict whether pathogens currently circulating in animals are potential human pandemic risks. Where feasible, these questions should be addressed using surrogate systems or by taking advantage of loss-of-function experiments on current human viruses (Johnson 2021; Yen 2011).

There are many types of research designed to mitigate the risk of pandemics, with enhancing the properties of potential pandemic agents being just one of these. Other approaches include studies of virus components using noninfectious or safe constructs (see Box 1) as well as non-virologic approaches such as countermeasure development, which is often not dependent on any knowledge of the specific phenotypes studied in enhanced potential pandemic pathogen research (e.g., transmissibility), or improvements in health care. However, it is important to note that in many cases countermeasures may need to be tested with actual live pathogens.

Moreover, a pandemic would result in a risk to lives even if the probability of an accident is low, and a risk to the lives of others cannot be justified purely by the promise of increased scientific knowledge. This highlights the need to review studies for risk to bystanders (non-participants) resulting from enhanced potential pandemic pathogen research (Eyal et al. 2019).

Once reviewers complete a systematic public health benefit assessment for proposed research with known and potential pathogens, they will still need to make judgements on how to evaluate the risks of a study, including any residual risk.

Ethical obligation to minimize risk of harm by using less-risky alternatives, where appropriate.

Biological risk assessments tend to be limited in scope to biosafety issues and a risk to laboratory personnel and their communities. For research with pandemic risk, from which the potential for harm extends to the entire human population, a more elaborate risk assessment is required.

As WHO sets out, researchers and their institutions have an obligation to use less-risky research when this would be equally beneficial (WHO 2022). When the potential benefits from a study that involves an enhanced potential pandemic pathogen could be achieved by other less-risky means, the lower-risk research design should be the choice. This analysis is consistent with the types of decisions routinely made by individual researchers and funding agencies, when they aim to choose an investment of time and money that optimizes the likely gain from the study rather than abstractly weighing doing

versus not doing a study (Lipsitch 2018; Lipsitch and Inglesby 2014). Incentives, both positive and negative, need to be devised and promulgated, mindful of local sensitivities, to encourage the weighing of risk, along with time and money, in deciding on research design.

A significant percentage of the risk from virological research arises from the possibility of accidents or misuse of the pathogens themselves instead of the information gleaned from the research. Consequently, incorporating a virus into laboratory research increases exposure risk, even under the strictest biorisk management operating procedures. Whether the risks of the research are tolerable is a function of the value of the outcomes. The answer will be dependent on several factors, such as the type of virus under study (its infectivity, transmissibility, and virulence as well as the availability of countermeasures), the type of experiment (*in silico*, *in vitro* or *in vivo*), the amount and concentration of the handled virus, the biosafety level of the laboratory where the research is conducted, the level of training and standard operating procedures of laboratory staff, and the implemented oversight (e.g., institutional biosafety committees, animal-care-and-use committees, and dual-use committees). To reduce risk, it is prudent to evaluate whether incorporating potential pandemic viruses into the research is necessary: (1) scientifically (i.e., whether researchers could replace viruses with so-called "surrogate systems" to yield the same types and qualities of answers to questions) and (2) pragmatically (i.e., whether the virology community, including funding agencies, promotion committees, and publishers, will take research using surrogates seriously).

In the past, promising results obtained with surrogate systems (see Box 1) have not always withstood validation with the viruses they are intended to represent. These failures have led to concerns on the part of virologists, scientific journals, and funding agencies that virology research without using actual replication-competent viruses is subpar or incomplete. Researchers have quickly learned that successful publication of their results is often dependent on including replication-competent virus research because reviewers and editors almost inevitably request it, even if it is technically not necessary and does not contribute to the utility of the study. Consequently, studies with replication-competent viruses are often held in high regard, even if the use of a surrogate system would yield equally robust and scientifically useful results. The broader scientific community (in particular, journals, their staff, and reviewers) determines whether a study is deemed a success, which has a direct impact on the professional fate of researchers. The preference for research using replication-competent viruses thus drives a reliance on risky virus research. One path forward to overall less-risky research is for the scientific community to commit to using surrogate systems when feasible.

Examining whether surrogate systems yield equally robust and scientifically useful results has several advantages. It appropriately considers whether the extra knowledge gained from doing riskier research justifies extra risk. It appropriately weighs the fact that riskier research is necessarily more expensive than safer alternatives due to the extra biosafety and biosecurity controls needed. Such an analysis might well suggest that investing funds in safer alternatives could result in more generalizable knowledge and avoid the small sample sizes often used in expensive research on high-risk viruses (Linster et al. 2014; Herfst et al. 2018). At the same time, it is important to recognize that often there will not be a surrogate system that can effectively answer the question at hand.

Considering the best alternative to research with pandemic risks obviates arguments about the risk of "not doing" a set of studies, or the opportunity costs of a road not travelled. While it is true that the benefits of basic biomedical research may be long term and its value not immediately evident, some argue that not doing a study foregoes the

unknowable potential benefits of that study. However, the same is true of the alternative study. Factoring in unknowable potential benefits is therefore an argument for doing science in general, rather than a point in favor of specifically doing risky research or foregoing all risky research.

Surrogate systems

Over recent decades, researchers have developed numerous surrogate systems for conducting research in the absence of replicating target viruses. These systems exist to simplify the complex virus-host system and allow focus on different aspects of it. They reduce risks for laboratory workers and publics and avoid the need to perform research in high- or maximum-containment laboratories. They can overcome the need for unavailable resources (e.g., target viruses and access to containment laboratories). In some cases, surrogates enable studying aspects of a virus lifecycle that can be dissected better with these systems than with infectious viruses. On the other hand, some findings obtained with surrogate systems may not always reflect the biological reality of the fully replicating virus. The potential pros and cons of surrogate systems can be seen in several examples:

Pseudotypes (Cui and Huang 2023; Radoshitzky et al. 2018; Steeds et al. 2020)

Pseudotypes are created by expressing a viral entry protein on the surface of a virion that packages a reporter gene but lacks the full complement of viral genes needed to undergo multicycle growth and are thus unlikely to cause disease. Pseudotypes can be modified to incorporate the surface proteins of the viruses they are intended to represent (e.g., Nipah virus) instead of their own (e.g., HIV-1) surface proteins. Since the surface proteins of many viruses determine which cells and organs they infect and are the main targets of antibodies, pseudotypes can be used to study and develop medical countermeasures for the earliest events in viral infection. Importantly, these studies can be done at lower biosafety levels with minimal risk. However, for various technical reasons, pseudotype systems only work for some target viruses with surface proteins amenable for pseudotyping and, because the "geometry" of pseudotypes is not identical to particles of target viruses, results sometimes need to be confirmed with the actual target viruses. Thus, pseudotype research cannot always completely replace research with the bona fide pathogen but can instead reduce it. It is a suitable method for addressing many questions of biological and public-health relevance.

VLPs/trVLPs/biologically contained particles (Hoenen et al. 2011; Halfmann et al. 2008; Wenigenrath et al. 2010)

Virus-like particles (VLPs) are replication-incompetent particles produced by the co-expression of certain viral structural proteins. They can be used in a similar manner as pseudotypes and have the advantage of correct particle "geometry." Virus-like particles can be turned into transcriptionally active virus-like particles (trVLPs), i.e., target virus particles that contain

truncated target virus genomes and behave like replicative entities in cells continuously producing virus components *in trans* (that is, provided by the researcher in various ways rather than from the truncated genomes). In the extreme, transcriptionally active virius-like particles can be turned into "biologically contained viruses." This is achieved by introducing virus genomes that lack one or a few viral genes into cells that produce the missing genes. Transcriptionally-active-virus-like particles and biologically contained particles "behave" like true viruses but cannot replicate and cause disease in organisms because they lack critical components. Few such systems exist due to often formidable technical challenges and safety concerns of developing them (e.g., possible recombination and thereby creation of fully infectious viruses). Thus, research with these systems may be less risky than research with target viruses but is not considered risk-free.

Minigenomes (Hannemann 2020; Hoenen et al. 2011)

Minigenomes are target viral genomes typically devoid of most genes. They contain viral genomic regions required for replication and/or transcription. Researchers manipulate cells so they provide the minimal replication/transcription proteins of a virus *in trans*, thereby resulting in minigenome replication. If a reporter gene is incorporated, the process will result in its transcription and translation, as well. These systems can be used to identify candidate medical countermeasures targeting, for instance, proteins that viruses use to replicate (viral polymerases) or the functions of an infected host cell (host factors) on which a virus depends for that process. However, the challenge of developing minigenomes increases with the complexity of the target virus and is crucially dependent on the knowledge of replication and transcription signals of the viral genome, which often are not known (and not easily determined) for target viruses. In addition, the minimal genome replication complexes represented by minigenomes do not capture all aspects of the viral life cycle.

Recombinant viruses (Gross et al. 2018; Fathi, Dahlke, and Addo 2019)

Another approach to decrease, but not abolish, risk is to create recombinant viruses that express target virus proteins instead of their own proteins. A classic example is vesicular stomatitis Indiana virus (VSIV) manipulated to express the Ebola virus glycoprotein instead of its own glycoprotein. VSIV infects insects, cattle, horses, and pigs and, rarely, leads to mild influenza-like disease in humans, whereas Ebola virus often causes fatal illness in humans. Researchers can use recombinant versions of VSIV expressing the surface proteins of a target virus to study cell entry processes similar to pseudotypes but in a fully replicative background. Recombinant VSIV expressing Ebola virus glycoprotein ("rVSV-ZEBOV-GP") is currently considered sufficiently safe to be used as a vaccine against Ebola virus disease and is approved for this purpose by the European Union and the US Food and Drug Administration. However, such recombinant viruses are not necessarily attenuated, and their cell and host tropism depend on the incorporated protein. Therefore, these viruses may pose unknown risks. In addition, special regulatory approval may be necessary because their creation could be considered research of concern due to the incorporation of components of a potentially pandemic pathogen into a less dangerous background, leading to the possibility that a previously benign virus becomes a risky one.

Alternatively, researchers could render target viruses less risky by, for instance, by serially passaging the target virus in cell cultures and/or animals to select a weakened (attenuated)

strain. However, creating attenuated viruses necessarily starts with replication of the target virus (and hence is "risky" to a degree). Also, any manipulation or selection includes inherent (even if minimal) "gain-of-function" risks (or at least the perception thereof), as it cannot be strictly assumed that any mutations resulting from serial passage will only result in attenuated viruses (although this is usually the case if the passage is done in common cell lines). In addition, there are concerns about the potential for reversion of attenuated viruses to wild-type viruses. The development of attenuated viruses is in some cases possible by rational approaches if reverse genetics systems are available that enable deleting or modifying known viral pathogenicity factors, or by recoding strategies that are known to confer attenuation (e.g., codon-pair deoptimization (Cai et al. 2020)). This would reduce the risk since it omits starting with replication of the authentic target virus.

Gene synthesis and protein expression

If the genomic sequence of a target virus is at least partially known, its genes can still be synthesized individually from known sequence fragments and their encoded proteins can be expressed in tissue culture. This approach enables the study of individual virus components and, to a degree, identification of candidate medical countermeasures that bind them or their cellular or viral interaction partners. However, many viral proteins do not fold or function correctly in the absence of other proteins that often have not been identified. Many viral proteins may not show the same (sub-)cellular localization compared to their localization within infected cells, and this approach often does not identify medical countermeasures that are active enough during target virus infections, during which exponential replication of viral protein components overcomes the fixed concentration of the countermeasure. Moreover, viral proteins may act in complex ways, or require the presence of other viral proteins to reveal their true function. Artifacts of over-expression systems are also a confounder.

***In silico* analyses (Versini et al. 2024; Gutnik et al. 2023; Ismi, Pulungan, and Afiahayati 2022)**

In silico (computer simulation) methods, including those based on AI, have made great strides forward in predicting structures of target virus components (e.g., AlphaFold 2 and RoseTTAFold). However, while these methods often work well for predicting structures of isolated (e.g., secreted) virus proteins, they often yield suboptimal results for proteins that require interacting partners for correct folding. Thus, these methods become less useful with increasing virus complexity. Moreover, these systems may not yet accurately predict the folding of proteins with disordered regions, or domains that do not fit well with the known structures within a database. Furthermore, the function of a protein is often dependent on a complex cellular environment that cannot currently be modelled using in *silico* methods.

While virus surrogate systems are an important component of virological research, none of them is universally applicable to all viruses or experimental research questions. Importantly, due to caveats and limitations of each surrogate system, the results obtained with these systems often need to be confirmed using actual virus research and some of these systems may themselves pose novel risks or concerns. It should be noted that for many viruses, particularly those that have not been intensively studied before, researchers have not established surrogate systems yet or cannot establish them for functional/biological reasons. Therefore, there are often circumstances in which there is no alternative to studies involving authentic viruses.

Nonetheless, funding agencies and journal editors are responsible for advocating for less risky experiments and must be vigilant when funding recipients or reviewers propose live pathogen experiments with unpredictable outcomes. Of particular concern are situations in which potentially risky experiments are proposed and decided upon in private without external oversight (e.g., between only funder and funding recipient or journal editor and author). Having a decision-making policy that draws in external expertise and oversight in these events would more strongly protect funders, publishers, researchers, and publics.

Ethical obligation to correct inequities in benefit-sharing and research burdens.

The benefits of scientific research often accrue differently across the range of stakeholders. For researchers and their institutions, publication, grant funding, professional advancement, and prestige are powerful incentives and benefits of successful research. For journals and funders, publishing and supporting successful research can represent high impact and strong returns on investments.

Public health benefits or benefits to particular communities, if they do transpire, are often delayed or only become apparent in the longer term. In the present setting, inequities in access and purchasing power have often led to earlier and larger public health benefits from the fruits of research for wealthier countries and for wealthier residents within those countries. This often contrasts with the risks. Pandemics, by definition, have widespread geographic impact and have often caused considerably greater harm to those already at economic and social disadvantage, both within countries and across the globe (Murray et al. 2006). Parties involved in caring for patients and managing the downstream consequences of potential outbreaks resulting from accidental, inadvertent, or intentional releases—public health authorities, clinicians, and other front-line workers—also do not benefit directly from research with known and potential pandemic pathogens and are not usually consulted as part of harm-benefit assessments. There is, therefore, often a mismatch between those who bear the risk (e.g., communities directly or economically affected by a biosafety incident) and those who might benefit from the products of the research.

Researchers and their institutions play an important role in harm–benefit assessments. They likely have the earliest and clearest insight into whether their particular research raises biosafety and biosecurity risks. When it does, researchers and institutions are usually best positioned to propose mitigation strategies or to find alternative lower-risk paths for pursuing their research. However, with research with known and potential pandemic pathogens, for which the stakes are higher and the inequities in the harm–benefit distribution across stakeholders greater, researchers and

their institutions should not be the only ones conducting harm–benefit assessments; a broader range of stakeholder groups should be involved in consultation.

Ethical obligation to respect prohibitions on research when there is not a proportionate harm–benefit ratio.

The most concerning research is that which could result in (1) uncontained community spread of a novel pathogen or variant of a pathogen among humans, other animals, plants, or the environment and cause harm, or (2) uncontained community spread of a novel pathogen that was already transmissible and capable of epidemic or pandemic spread but has been made more harmful. This could be the result of accidental, inadvertent, or intentional release of the known or potential pandemic pathogen. An independent and transparent review of risks and potential benefits of this kind of research should occur at national/federal levels, and, given that the risks are global, may also warrant review at the international level (Steinbruner et al. 2007). This level of review should not only precede the work but occur at regular intervals as new data are collected and new experiments are proposed.

Research with pandemic risks should proceed only when the research community and relevant oversight bodies can (1) demonstrate that the research would be conducted safely, securely, and responsibly; (2) demonstrate that no alternative and safer research could reach the same public health ends; and (3) provide adequate assurances of substantial benefits expected in the near term with a plausible plan for equitable global distribution of these benefits.

V

Research on biorisk management to make research with pandemic risk more safe, secure, and responsible

There are significant differences across laboratories and countries in the measures adopted to manage biorisks (Koblentz et al. 2023). Limited data exist to support whether these differences result in a measurable improvement in safety and security or whether resources are being wasted on unnecessary and costly equipment (Ritterson and Casagrande 2017). Historically, biosafety and biosecurity improvements have always added on to existing equipment, procedures, or administration because there were no data suggesting which specific improvements were particularly effective.

As data to inform biorisk management are lacking, the frequency and consequences of accidents are unknown; well-informed key decisions cannot be made in the absence of adequate evidence. Similarly, it is difficult to understand the means by which outsiders are most likely to gain access to a laboratory or how they could misuse pathogens. If robust data were available, stakeholders could identify which biorisk management measures were truly worth the investment, enabling stakeholders to spend only what is needed on safety and security and the rest on research.

Research on biorisk management is urgently needed to improve efforts at eliminating and mitigating associated risks (Palmer, Fukuyama, and Relman 2015). Such research could generate useful knowledge to (1) prevent laboratory accidents and mistakes (as the research community generates real data on which practices are safe, which are risky, and under which conditions) and (2) reduce the chance that malicious actors can access known and potential pandemic pathogens. Research data could inform changes to a protocol, policies for access control, the movement of equipment within a laboratory, the training received by key personnel, or a redesign of a risky experimental approach. Biosafety and biosecurity studies could help inform where new laboratories of various types should be built.

Naturally, proper biosecurity and biosafety precautions entail more than sound laboratory infrastructure and practices. Context matters. What works in one setting or country may not fit with practices or available resources elsewhere and running simulations, while valuable, may not consider the full spectrum of possibility regarding safety and security risks. Psychosocial and behavioral research may also shed important light on how different actors (e.g., laboratory workers) interact with laboratory infrastructure and respond to governance structures and policies.

Research to improve biosafety management.

The WHO's *Laboratory Biosafety Manual* informs best practices for safely handling biological agents in laboratories and covers a range of topics, including personal protective equipment, biosafety cabinets, risk assessment, decontamination, and waste management (WHO 2020). Originally published in 1983, it is now in its fourth edition. The *Laboratory Biosafety Manual* is viewed by the scientific and practitioner community as the gold standard for biosafety and it is in wide use.

Nonetheless, accidents occur and there is considerable benefit in better understanding the causes. For example, recently published research demonstrates how frequently snap-cap microcentrifuge tubes, which are commonly used to store and mix biological samples, splash when opened (Wyneken et al. 2023a). The frequency of splashes from these tubes no matter how they are opened suggests that laboratories should substitute these or take additional measures to reduce splashing and immediately implement these solutions to reduce risk. A laboratory simulator in which researchers are observed manipulating small volumes of fluid and running mock assays could be used to compile data on the frequency of spills, splashes, and accidents. Researchers are completing the first studies of this type (Wyneken et al. 2023b; Wyneken et al. 2023a), which may begin to answer key questions such as: How often do researchers spill? What factors (e.g., training and experience) reduce this? Importantly, this initial research has demonstrated that studies done by volunteers in mock laboratories replicate similar accident rates in real clinical laboratories that were conducting blinded studies of error. A critical finding of this research is that even experienced laboratory researchers often do not know when or where a spill occurred. This underscores the often-repeated advice of biosafety professionals to decontaminate the entire workspace after every experiment, not just after a spill.

Additionally, researchers are collecting data on the frequency, size, and pattern of contamination of the biological laboratory worker; this critical first step will guide studies on how best to reduce risk from contamination. Data generated by biosafety research can also boost compliance with safer but inconvenient practices.

More generally, basic data are lacking for how researchers in laboratories are exposed to infectious material through spills, splashes, and contamination. Unlike in other industries, in which mechanical failures alone can cause catastrophe, in biological laboratories, researchers initiate or exacerbate most accidents; for example, researchers may spill infectious material and/or respond inappropriately by violating quarantine or contaminating themselves during cleanup.

In clinical settings, accidental infections often occur when protective gear (e.g., gloves, masks, coats, etc.) is removed after sterile procedures (Mumma et al. 2018). It is suspected, but unproven, that many instances of infection or contamination in laboratory settings happen in a similar manner. Studies that document how frequently laboratory researchers contaminate their hands when taking off gloves (or breach their gloves during research) could improve practices and procedures. For examples, studies that compare the use of a single pair of gloves with the use of two overlapping pairs of gloves

could demonstrate the effectiveness of one or the other strategy to either solidify or negate the use of two overlapping pairs of gloves. Similarly, studies on when respiratory protection should be worn and what type of protection is needed under different conditions could usefully guide practices and procedures. For example, a variety of routine procedures, including centrifugation and flow cytometry or cell sorting, can generate and expose laboratory workers to aerosols if the proper containment is not used or if the device is not confined to a biosafety hood. In general, if protective gear works well in most situations but not when careless or inexperienced researchers wear and/or remove it, additional investments in training and oversight/proficiency testing would be warranted.

Research to improve biosecurity management.

Failures in biosecurity can occur when leadership is inadequate, oversight institutions do not have the needed expertise or proper means to assess their effectiveness, or organizational structures and risk management processes are slow to recognize consequential advances in science and technology (Palmer, Fukuyama, and Relman 2015).

Biosecurity is challenging to investigate empirically, but observational research and controlled studies can be very useful. Observational studies in training laboratories can measure the frequency of similar failures (e.g., unauthorized access, failure to report worrisome behavior, or database security glitches). Controlled studies can also measure both the rate of non-compliance with a rule and the rate at which researchers hide their non-compliance. Without a significant effort, studies could gather more biosecurity data generated in the day-to-day conduct of research or training.

A research agenda should also seek to examine the extent to which releasing information about research with potential pandemic pathogens may create so-called "information hazards (Relman 2014)." Malicious actors may misuse published information and therefore researchers, funders, and journals should consider whether information controls are appropriate.

In summary: There is an evident need to improve current efforts at eliminating and mitigating biosafety and biosecurity risks.

Researchers and their institutions, as well as funders and governments, should fund studies that will provide robust empirical evidence about the nature of biosafety and biosecurity challenges and the effectiveness of potential mitigation strategies. Such data would enable more effective risk reduction practices. Biorisk management data could inform harm–benefit studies to determine exactly how laboratories working with known and potential pandemic pathogens, including in research with pandemic risks, should be organized and managed without unnecessarily diverting funding that could be invested in the research itself. Not only will this improve biorisk management, but using new evidence to eliminate wasteful measures would make laboratories more efficient and sustainable. At the same time, biorisk management practices should be reviewed to eliminate those without evidence of added value or to replace more burdensome practices with less burdensome ones.

VI

Responsible and sustainable governance to make research with pandemic risk more safe, secure, and responsible

International standards and guidance set overarching global benchmarks, and there are many with relevance to biorisk assessment.

The contemporary governance space for research with potential pandemic pathogens.

Recently, WHO developed a *Global guidance framework for the responsible use of the life sciences*, which, among other things, lays out a set of values and principles for responsible science. Published in 2022 and fundamentally anchored in a clear commitment to use the knowledge, material, and skills of basic and applied life sciences for the common good, the framework's overarching aim is to make life better for humans and other animals, and to protect and promote the planet's biodiversity, ecosystems, and environments. Promoting health, safety, and security, should, in turn, contribute to peace. In practice, this means using appropriate biosafety and biosecurity measures to prevent life sciences knowledge from causing harm, and it means preserving biodiversity where possible, to promote health, safety, and security and as an intrinsic value.

Of critical importance to the pursuit of health, safety, and security is a commitment to responsible stewardship of science. As detailed in WHO's guidance framework, this entails a commitment to rigorous, evidence-based life science, to exercising caution to minimize risks, and to identifying and managing the reasonably foreseeable, potentially harmful consequences of life sciences research that could result from accidental, inadvertent, or intentional actions. Of particular relevance to research with pandemic risks, the responsible stewardship of science also involves a commitment to identify whether risks are proportionate to the potential benefits of the research, whether less-risky forms of research could be equally beneficial, and whether modifying the research design or the dissemination and publication plans as the

research proceeds or after the research has been completed is advisable.

Other prominent international standards and guidance with relevance to biorisk assessment include the International Organization for Standardization's *ISO 35001: Biorisk management for laboratories and other related organisations*, which outlines a process to identify, assess, control, and monitor the risks associated with hazardous biological materials, and the World Organisation for Animal Health (WOAH) *Guidelines for responsible conduct in veterinary research*, which provides advice to the veterinary community on identifying, assessing, and managing dual-use research.

Additionally, there are several international organizations and networks that support strengthening biorisk management (e.g., the International Federation of Biosafety Associations (IFBA), the American Biological Safety Association (ABSA) International, and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International). Professional accreditation and certification in biosafety and biosecurity-related activities are critical to ensuring that practitioners and researchers are proficient and up-to-date on international biosafety and biosecurity standards.

While research regarding medical countermeasures and surveillance of known and potential pandemic pathogens may be an international priority, ensuring that this research occurs at the appropriate biosafety level is critical. The European Research Infrastructure on Highly Pathogenic Agents (ERINHA), for example, provides maximum containment support for research that has undergone a comprehensive application process to ensure scientific feasibility and meets ethical standards and the organization's research priorities.

Ensuring that known and potential pandemic pathogens are secured and that research is monitored is a key function of international biorisk oversight. The WHO's Advisory Committee on Variola Virus Research (ACVVR) is a prime example of the role of international research oversight and laboratory inspections to ensure that previously pandemic pathogens do not re-emerge while allowing approved research plans to fill critical knowledge gaps on orthopoxviruses. AAALAC International conducts on-site visits as part of its laboratory accreditation process, which includes an assessment of transportation and arrangements when new animals are introduced to an existing herd as well as laboratory physical security.

Capacity-building and knowledge-sharing also form a crucial part of strengthening international biorisk management. The Global Health Security Agenda partnership of more than 70 countries and non-governmental organizations focuses its biosafety and biosecurity work on community-building, information-sharing, and resource hub functions. The primary focus of the group is providing expertise and resources for addressing country-level gaps identified in WHO assessments of country capacities to prevent, detect, and respond rapidly to public health risks (WHO n.d.b). The International Experts Group of Biosafety and Biosecurity Regulators (IEGBBR) is a group of biosafety and biosecurity regulatory representatives from 11 member countries who share practical knowledge on developing national-level oversight and regulatory standards for biorisk management, encouraging a global complementary approach to developing a regulatory framework. The Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet) provides training opportunities and workshops for laboratory workers, focused primarily on the care and handling of animals in a maximum-containment laboratory environment.

At the national level, a mix of legislation, regulations, policies, and guidelines aimed at assessing and managing biological risks apply to researchers and their institutions. Widely recognized and adapted to a broad range of national contexts, gold standards for working

safely with biological agents include: (1) the US Centers for Disease Control and Prevention's *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*; (2) the US National Institutes of Health's *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*; (3) the United Kingdom's health and safety laws and guidance on biological agents including the Advisory Committee on Dangerous Pathogen's *Management and operation of microbiological containment laboratories*; and (4) the European Union's legislation on the contained use and deliberate release of genetically modified organisms.

There is limited guidance, internationally or nationally, focused specifically on review and oversight of potential pandemic pathogens. The US policies for oversight of dual-use research of concern and the potential pandemic pathogen care and oversight (P3CO) policy framework are the leading standards. But each nation needs to consider resource availability, sensitivities, and public health priorities in creating policies that are appropriate for the local context.

In the US policies, dual-use research of concern is defined as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security (US Government 2012; Fink 2004)." Review is limited to research involving one or more of the 15 listed agents considered to pose the greatest risk of intentional misuse with most significant potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence. Review is further limited to research with the listed categories that aims to produce, or is reasonably anticipated to produce, one or more of the following effects:

- Enhance the harmful consequences of the agent.
- Disrupt immunity or the effectiveness of an immunization against the agent without clinical or agricultural justification.
- Confer resistance to the agent to clinically or agriculturally useful prophylactic or therapeutic interventions or facilitates its ability to evade detection methodologies.
- Increase the stability, transmissibility, or the ability to disseminate the agent.
- Alter the host range.
- Enhance susceptibility of a host population to the agent.
- Generate or reconstitute an eradicated or extinct agent.

The US potential pandemic pathogen care and oversight framework (HHS 2017) outlines a review and reporting process aimed at limiting the possibility of accidental, inadvertent, or intentional release of a pathogen capable of causing widespread harm to public health from US federally funded research. It provides a list of criteria for guiding funding decisions by the Department of Health and Human Services on proposed research that involves, or is reasonably anticipated to involve, the creation, transfer, or use of enhanced potential pandemic pathogens. Included in the list is a requirement that researchers demonstrate "… [t]here are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk … ." Since the policy's implementation in 2017, the federal agency has reviewed three research projects, all of which were approved, though one project was ultimately modified so that it did not involve potential pandemic pathogens (NIH n.d.). The department has not released details on its process for deciding whether research projects should undergo review, nor has it specified the nature of the review or the deliberations leading to the approval of these projects. Many have criticized this lack of transparency, and the framework is currently under review (Inglesby et al. 2023).

In March 2023, the National Science Advisory Board on Biosecurity (NSABB), a US federal advisory committee that addresses issues related to biosecurity and dual-use research, published its recommendations on how to develop a more comprehensive and integrated framework for oversight of pathogen research that may pose significant biosafety or biosecurity risks (NSABB 2023). The US Government issued a request for information on potential changes to the dual-use research of concern and potential pandemic pathogen care and oversight policies in September 2023.

In summary: Effective legislation, regulations, policies, and guidelines specifically regulating research with pandemic risks will strengthen the scientific enterprise and should be put in place without delay. Greater clarity about work that does not require special oversight would reduce uncertainty among researchers and streamline the research process.

In the meantime, informal governance through professional norms, codes of ethics, standard operating procedures, and other practices associated with self-governance should be harnessed to provide norm-setting standards and raise awareness of the need for enhanced harm–benefit assessments for this kind of research. At present, it is broadly accepted that science should be conducted in a way that avoids subjecting populations, human research participants, or laboratory workers to undue risks or causing unnecessary suffering to experimental animals. It should become a similar article of scientific ethos that exceptional public health benefits unachievable by safer means are necessary to justify any undertaking that could increase the risk of an accidental, inadvertent, or intentional pandemic.

Education and training are also important components of informal governance. They not only raise awareness but can provide important how-to tools for assessing and documenting biorisks in a way that is accessible to co-workers and to internal and external auditors as well as tools to identify and implement measures and practices to minimize the impact of biorisks. We should aspire towards a state in which concern for minimizing population-level risks of accidental pathogen releases or misuse of research results is as automatic and universal to researchers as current norms about ensuring proper treatment of human research participants and reducing, replacing, and refining the use of nonhuman animals in research.

Stanford University's *The Biorisk Management Casebook: Insights Into Contemporary Practices* provides a series of concrete examples of how biorisk frameworks from around the world have been implemented in practice (Greene et al. 2023). These case studies, and others like them, can enable scientists and their institutions to learn from one another about what works and under which circumstances.

Key to the success of more informal tools and mechanisms is that they are properly and sustainably resourced and institutionally recognized, valued, incentivized, and rewarded.

VII
Trust-building

Across academia, industry, and governments, many scientists work in service of publics. An important part of that work, often unrecognized, is enabling oversight and advisory bodies that deliberate over the risks and potential benefits of new research and technology. The role of scientists, including the nature of their research, how it is regulated, and how that research has or has not benefited the common good, is not well communicated. In the prevailing climate of misinformation and disinformation, it is more important than ever for members of the scientific community to think deeply about who they need to engage and how to earn trust (see Box 2). Many scientists see themselves as well-intentioned purveyors and defenders of scientific truths. However, without thoughtful communication and trust-building, scientists often further alienate those who do not trust science and its practitioners. This can in turn fuel extremist narratives or conspiracy theories rather than build bridges and encourage more moderate and informed viewpoints on polarizing scientific issues.

Research that could risk the emergence of novel pathogens and the prediction and quantification of that risk can be controversial even among scientists. The responsibility to educate stakeholders (including publics) about policies and practices for safe and secure research and to improve these policies and practices can seem to be a time-consuming distraction from scientific research. It can also introduce the risk of potential harassment. Adequate resources to support scientists in anticipating future problems and deciding how, when, and what information to share with publics are often not available (Mejlgaard et al. 2020). In the worst-case scenario, scientific controversies can lead to long-lasting mistrust in scientists and associated institutions, as well as governments.

The first step for scientific organizations and institutions to earn the trust of publics and other

stakeholders will be to ensure that pathogen research is safe, secure, and responsible (as delineated in previous sections of this report and its recommendations).

Aspiring to trustworthiness.

Responsible science entails an obligation towards public engagement (WHO 2022), and research with pandemic risks requires extra attentiveness to communication. This is important because lack of trust in science and scientists can have grave consequences. A 2023 Pew Research Center survey found significant loss of public confidence in scientists among Americans in general, with only about 11 percent of Republicans and 37 percent of Democrats showing a great deal of confidence in scientists to act in the best interests of publics (Kennedy and Tyson 2023). One study from Yale University of excess deaths in Florida and Ohio found they were 43 percent higher in April-December 2021 among Republican voters compared to Democratic voters (Wallace, Goldsmith-Pinkham, and Schwartz 2023). A Pew Research Center study found a similar trend: Counties that voted Republican reported less trust in medical science and substantially more pandemic deaths than those that voted Democrat in the presidential elections of 2020 (Hope-Hailey 2014; Jones 2022). One interpretation of these studies is that the consequences of low confidence in science and scientists not only harmed those who do not trust science but also harmed their communities.

A lack of scientific literacy is often cited as a reason why many do not trust scientists. For instance, a 2021 survey of more than 2,000 adults in the United Kingdom found that those with extremely negative attitudes towards genetic technologies tended to have low textbook knowledge but high confidence in their own understanding (Fonseca et al. 2023). This highlights the need for science communication to address the gap between what people objectively know and what they believe they know. Conversely, many people do trust other scientific technologies without understanding them. For example, people receive medical treatments without understanding how they work (presumably because they trust the intent of medical doctors). This suggests that scientific literacy, or a knowledge deficit, may not be the primary determinant of whether an individual trusts scientists to act in the best interests of publics.

What has been observed more recently is a lack of trust in the process, motivations, and politics surrounding emerging areas of science. This is an important reason for scientists (from diverse backgrounds) to demonstrate that they are honest purveyors of knowledge who care about people's perspectives and concerns. Moreover, it is vital that scientists speaking to publics are transparent about reasonable perceived influences and conflicts of interest.

There are generally agreed-upon characteristics of trustworthy leaders that are important when communicating complex science to publics: (1) competency, including knowledge, skill and ability; (2) virtues, including wisdom, justice, compassion, courage, integrity, honesty, empathy, and selflessness; (3) consistency, i.e., reliability and predictability in approach; and (4) engagement, including being respectful of others and their knowledge and perspectives in a non-conceited and non-elitist manner, and being connected with the community impacted by their research by directly and clearly communicating challenges, motivations, and solutions (Mayer, Davis, and Schoorman 1995).

Scientists must embrace the above values to facilitate safe, secure, and responsible research leading to technologies that promote the common good. Ethical considerations must be incorporated into research design along with a commitment to minimize potential risks to health, safety, and security. Key elements of managing risk and enhancing trust include developing biorisk prevention and management systems and practices; defining and identifying

high-risk research; and ensuring that there is appropriate scrutiny and oversight to effectively mitigate potential harms as well as transparency with regards to associated risks. All of this behooves the research community to institutionalize effective and trustworthy communication with policymakers and journalists.

In highly competitive research fields, including pathogen discovery and manipulation, there is no incentive to share data or research plans prior to publication since this could cause researchers to lose their competitive edge. This challenge is heightened when there is unequal capacity, funding, or resource allocation and distribution of benefits (such as, publications and recognition or profits from products developed because of the collaboration). One specific problem is data-sharing. Scientists who collect novel pathogens may be disadvantaged and lose their head start if they share these discoveries with collaborators or other scientists with more resources and ability to publish in prestigious journals. Under these circumstances, journals, databases, and funding agencies have powerful roles and obligations to enforce timely data sharing, research integrity, and equitable outcomes.

Attentiveness to trust-building will require engaging experts in science communication and policymaking to reshape how scientists carrying out research with pandemic risks should interact with different publics, groups, journalists, other scientists, and policymakers.

Additional reading for building trust

World Health Organization (WHO) 2022 *Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research.* World Health Organization. **LINK**

Cochrane Convenes. 2022. *Preparing for and responding to global health emergencies.* Cochrane Convenes. **LINK** and Cochrane Convenes. 2023. *How to communicate scientific uncertainty: A Lifeology and Cochrane collaboration.* Cochrane Convenes. **LINK**

The National Academies of Sciences, Engineering, and Medicine (NASEM). 2015. *Trust and Confidence at the Interfaces of the Life Sciences and Society: Does the Public Trust Science? A Workshop Summary.* **LINK**

Pamuk Z. 2021. *Politics and Expertise: How to Use Science in a Democratic Society.* Princeton, NJ: Princeton University Press. **LINK**

VIII
Findings and recommendations

- When there is potential for harm to large numbers of people as a result of research with pandemic risks (i.e., research with known and enhanced potential pandemic pathogens and pathogens with unknown risk), and especially where it is questionable whether those at risk will benefit from the research, additional oversight, beyond occupational health and safety, is essential, as is a more elaborate risk assessment than is currently performed for research lacking these risks.

- Research with pandemic risks should have high-probability benefits for public health.

- Researchers and their institutions have an obligation to identify whether the risks from research with known and potential pandemic pathogens are proportionate to the potential benefits of the research and whether less-risky forms of research could be equally beneficial. When the potential benefits could be achieved by other less-risky means (e.g. surrogate systems), the research design of choice should be the less-risky one. Regulators, policymakers, publishers, and scientific editors should evaluate in that context the extent to which they can encourage pathogen research to use the safest means suitable, while not encouraging risky experiments for experimentation's sake.

- For research with pandemic risks in which the stakes are higher and inequities in harm–benefit distribution across stakeholders are greater, researchers and their institutions should not be the only ones conducting harm–benefit assessments; a broader range of stakeholder groups should be consulted in the harm–benefit assessments.

- Research with pandemic risks should proceed only when the research community and relevant oversight bodies can (1) demonstrate that the research would be conducted safely, securely, and responsibly; (2) demonstrate

that no alternative and safer research could reach the same public-health ends; and (3) provide adequate assurances of substantial benefits expected in the near term with a plausible plan for equitable global distribution of these benefits.

- Regular reporting to national authorities of significant biorisk management incidents should be required by all institutions conducting research with pandemic risks.

- Funders and governments should increase funding for research that will provide robust empirical evidence about the nature of biosafety and biosecurity challenges and the effectiveness of potential biorisk management strategies for research on known and potential pandemic pathogens.

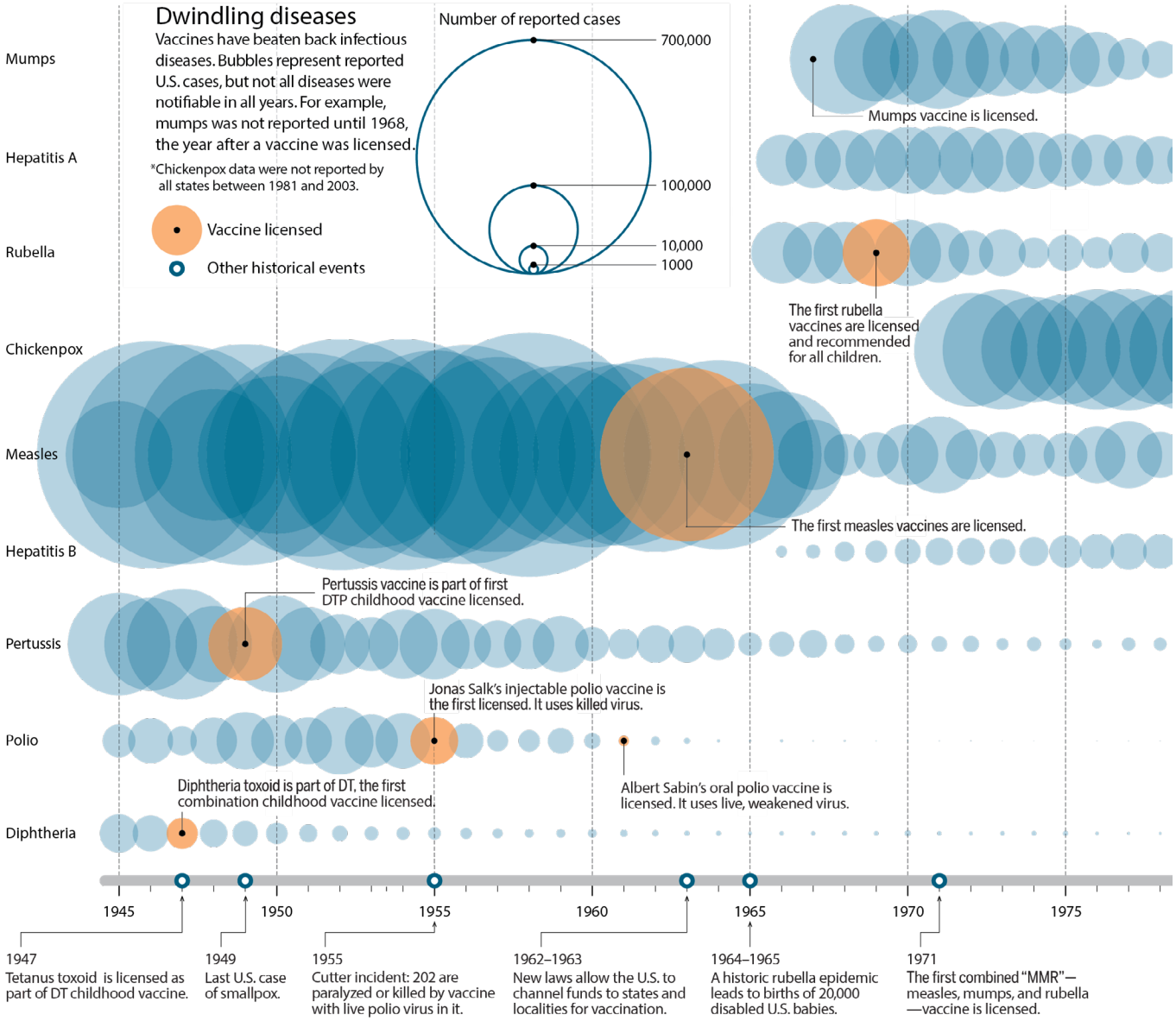
- Scientific journals and their editors should enforce timely data-sharing and research integrity for the manuscripts they publish.

- Effective legislation, regulations, policies, and guidelines specifically regulating research with pandemic risks will strengthen the scientific enterprise. These formal governance measures should be put in place without delay. Meanwhile, informal governance through professional norms, codes of ethics, standard operating procedures, and other practices associated with self-governance, should be harnessed to provide norm-setting standards and raise awareness of the need for enhanced harm–benefit assessments of research with known and potential pandemic pathogens.

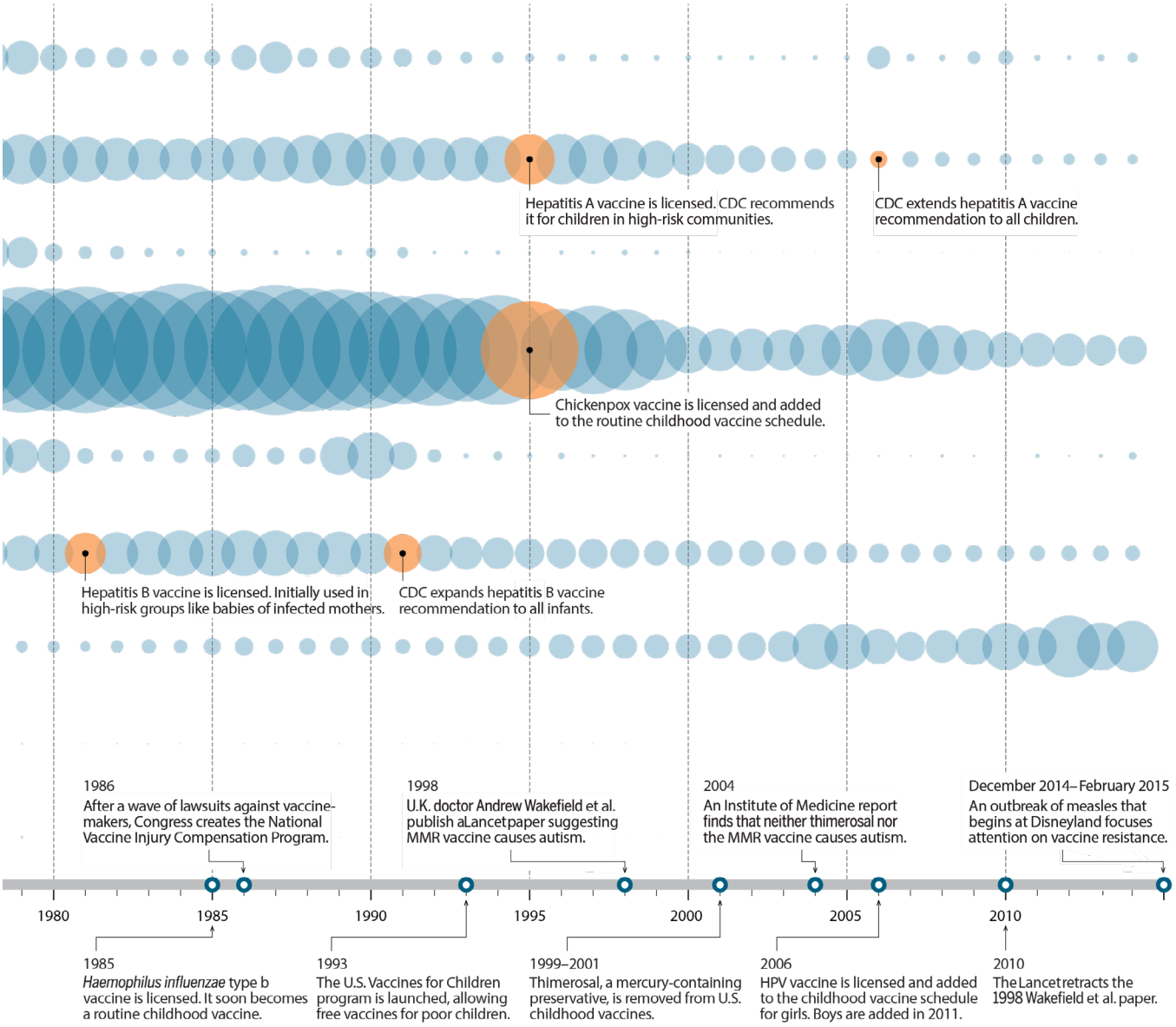
- International and national standards for fieldwork biosafety should be developed and implemented.

- Trust in the scientific method is important for societal acceptance of the fruits of science, and research with known and potential pandemic pathogens requires extra attentiveness to effective communication and trust-building. Science communication and public engagement related to research with pandemic risks should be funded and institutionalized.

Appendix



(Graphic) J. You/*Science* (Data) Centers for Disease Control and Prevention



(Graphic) J. You/*Science* (Data) Centers for Disease Control and Prevention

Task Force

Chairs

Ravindra Gupta
Professor, Clinical Microbiology, Cambridge Institute for Therapeutic Immunology and Infectious Diseases

Gupta is professor of clinical microbiology at Cambridge University. Gupta has worked in HIV drug resistance both at molecular and population levels, and his work led to change in WHO treatment guidelines for HIV. He led the study demonstrating HIV cure in the 'London Patient' – the world's only living HIV cure. During the COVID-19 pandemic, Gupta has deployed his expertise in RNA virus genetics and biology to report early evidence for immune escape of SARS-CoV-2 within an individual. More recently Gupta defined the replication advantage of the Delta variant and the tropism shift and immune escape of Omicron. Gupta has advised the UK government on COVID-19 through SAGE and NERVTAG and in 2020 appeared in the list of 100 most influential people by TIME.

Ameenah Gurib-Fakim
Former President, Republic of Mauritius

Gurib-Fakim served as the 6th and first female president of the Republic of Mauritius (2015-2018). Prior to that, she has been the managing director of the Centre International de Développement Pharmaceutique (CIDP) Research and Innovation as well as Professor of Organic Chemistry with an endowed chair at the University of Mauritius. Since 2001, she has served successively as Dean of the Faculty of Science and Pro Vice Chancellor. She has also worked at the Mauritius Research Council as Manager for Research. Ms Gurib-Fakim earned a BSc in Chemistry from the University of Surrey and a PhD from the University of Exeter, UK.

Shahid Jameel
Sultan Qaboos bin Said Fellow, Oxford Centre for Islamic Studies

Jameel is the Sultan Qaboos bin Said Fellow at Oxford Centre for Islamic Studies and Research Fellow, Green Templeton College, University of Oxford. He serves as the Principal Investigator for the Centre's project on Science, Technology and Environment in Muslim Societies. Previously he was the director of the Trivedi School of Biosciences at Ashoka University. He was formerly head of the scientific advisory group to the Indian SARS-CoV-2 Genomics Consortia. Jameel is an elected fellow of all the three major Indian science academies. The Council of Scientific and Industrial Research, awarded him the Shanti Swarup Bhatnagar Prize for Science and Technology, one of the highest Indian science awards, for his contributions to Medical Sciences in 2000.

David Relman
Thomas C. and Joan M. Merigan professor in medicine and professor, Microbiology & Immunology, Stanford University and chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System

Relman is the Thomas C. and Joan M. Merigan professor in medicine and a professor of microbiology & immunology at Stanford University and chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System. He is senior fellow at the Center for International Security and Cooperation at Stanford and previously served as the Center's science co-director. His current research examines diversity, stability, resilience in the human microbiome. Relman served as president of the Infectious Diseases Society of America and as chair of the Forum on Microbial Threats at the US National Academies of Science and is currently a member of the Defense Science Board for the US Department of Defense and the Science and Security Board of the *Bulletin of the Atomic Scientists*. He was elected to the National Academy of Medicine in 2011 and the American Academy of Arts & Sciences in 2022.

Directors

Jesse Bloom
Professor, Fred Hutchinson Cancer Research Center; Investigator, Howard Hughes Medical Institute

Bloom is a professor at the Fred Hutchinson Cancer Center and an Investigator of the Howard Hughes Medical Institute. His lab uses a combination of experiments and computation to study the evolution of viruses such as influenza and SARS-CoV-2. A major focus of his research is to use high-throughput approaches to define which viral mutations can affect sensitivity to antibodies. The goal is to use these insights to better understand viral evolution and design vaccines.

Filippa Lentzos
Associate Professor, Science & International Security, King's College London

Lentzos is a reader (associate professor) in Science & International Security at King's College London, where she is jointly appointed in the Department of War Studies and the Department of Global Health & Social Medicine. She is also an Associate Senior Researcher at the Stockholm International Peace Research Institute (SIPRI), and a Non-Resident Scholar at the James Martin Center for Nonproliferation Studies (CNS). Lentzos serves as the Chair of the WHO Technical Advisory Group on Responsible Use of the Life Science and Dual use Research (TAG RULS DUR), a member of the UK Biosecurity Leadership Council, a member of the WHO Health Security Interface – Technical Advisory Group (HSI-TAG), and as the NGO Coordinator for the Biological Weapons Convention.

Members

Anurag Agrawal
Dean, BioSciences & Health Research, Trivedi School of Biosciences, Ashoka University

Agrawal is Dean, BioSciences and Health Research, Trivedi School of Biosciences, Ashoka University, India, and former director of the Institute of Genomics and Integrative Biology, a national laboratory of CSIR, India. His primary research is in respiratory biology and broader interests are in a new vision of health and healthcare seen through the lenses of emerging technologies. He serves on numerous national and global advisory groups, recently chairing the World Health Organization technical advisory group for viral evolution, the Lancet-Financial Times commission for governing digital health futures, and serving on the pandemic preparedness subgroup at the Global Partnership for Artificial Intelligence.

Nisreen AL-Hmoud
Director, Biosafety and Biosecurity Centre, Royal Scientific Society of Jordan

AL-Hmoud has served as the director of the Biosafety and Biosecurity Centre at the Royal Scientific Society of Jordan since October 2015. As a scientist, Dr. AL-Hmoud is motivated to provide research that focuses on the public good; her research emphasis is the preservation of human health and biodiversity. During the last fifteen years, Dr. AL-Hmoud has dedicated her research to the development of scientific capacity in the fields of water & food safety and security and evaluation of environmental risks for scientists, government agencies, local communities and non-governmental organizations in Jordan and in the Middle East and North Africa region. Dr. AL-Hmoud is actively contributing to biorisk management capacity building programs nationally and regionally.

Françoise Baylis
Distinguished Research Professor Emerita, Dalhousie University

Baylis, CM, ONS, PhD, FRSC, FISC is distinguished research professor emerita, Dalhousie University, Canada. Baylis is a philosopher whose innovative work at the intersection of policy and practice, aims to move the limits of mainstream bioethics and to develop more effective ways to understand and tackle global public policy challenges. Baylis is the author of Altered Inheritance: CRISPR and the Ethics of Human Genome Editing, which won the 2020 PROSE Award in Clinical Medicine. In 2021, she was a member of WHO working groups on a global guidance framework for the responsible use of life sciences. That same year she was elected to the Governing Board of the International Science Council. In 2022, Baylis was awarded the Killam Prize for the Humanities, and in 2023, she received the Canada Council for the Arts Molson Prize in Humanities—these are Canada's most distinguished awards for humanities scholars

Agnes Binagwaho
Retired Founding Vice Chancellor of the University of Global Health Equity

Binagwaho, MD, M(Ped), PhD, is the retired vice chancellor and co-founder of the University of Global Health Equity, an initiative of Partners in Health. She previously worked as the executive secretary of Rwanda's National AIDS Control Commission, permanent secretary of the Ministry of Health, and Minister of Health. She is a professor of pediatrics at UGHE, a senior lecturer at Harvard Medical School, and an adjunct clinical professor at Dartmouth. She is a member of the U.S. National Academy of Medicine, the African Academy of Sciences and the World Academy of Sciences. She was named among the 100 Most Influential African Women for 2020 and 2021 and is a recipient of the 2022 L'Oréal-UNESCO Awards for Women in Science.

Sylvie Briand
Executive Head, Global Preparedness Monitoring Board Secretariat

Briand is the Executive Head of the Global Preparedness Monitoring Board Secretariat at the World Health Organization (GPMB/WHE), where she advances global efforts to prevent and control existing and emerging infectious diseases by increasing access to evidence-based interventions; fostering impactful innovation; and leveraging technical, operational and strategic partnerships. The scope of GIH includes COVID-19 but also other dangerous pathogens. Since 2001, Dr Briand has been actively involved in the detection, preparedness and response to global threats, leading the scientific and strategic component of the WHO response (avian and pandemic influenza, Ebola, Zika, Plague, yellow fever, cholera, MERS).

Rocco Casagrande
Founder & Chair of the Board, Gryphon Scientific

Casagrande is a founder and chair of the board of Gryphon Scientific, a life sciences consultancy. With a degree from Cornell in biology and chemistry and an MIT PhD in biology, Dr. Casagrande applies quantitative and systematic analysis to tackle daunting problems to manage scientific risks. The work of Dr. Casagrande and his team have formed the basis of the US Government's and WHO's policies on biosecurity and biosafety, including the US policy on the oversight on research on pathogens with pandemic potential and the design and operations of high containment laboratories. Currently, Dr. Casagrande is focused on generating data to inform biorisk management and improve biosafety in containment laboratories.

Alina Chan
Scientific Advisor and Viral Vector Engineer, Broad Institute of MIT & Harvard

Chan is a scientific advisor and viral vector engineer at the Broad Institute of MIT & Harvard. Dr. Chan is a Broad Ignite fellow and a recent Human Frontier Science Program fellow with a background in medical genetics, synthetic biology, and genetic engineering. Her research has been focused on creating next generation vectors for human gene therapy. During the pandemic, Dr. Chan began to investigate problems relevant to finding the origin of the SARS-CoV-2 virus and spearheaded the development of the COVID-19 CoV Genetics (covidcg.org) browser for scientists worldwide to rapidly track virus lineages and mutations by locations and date ranges of interest.

George Gao
Professor, Institute of Microbiology, CAS

Gao is a member (academician) of the Chinese Academy of Sciences (CAS), international member of the U.S. National Academy of Sciences (NAS) and foreign membership of the U.K. Royal Society (RS). He is a professor at Institute of Microbiology at CAS. Gao obtained his DPhil degree from Oxford University, UK and did his postdoc work in both Oxford University and Harvard University. His research focus is on pathogen microbiology and immunology. Gao is a leading scientist in the field of virology and immunology in China and worldwide, and he has long been engaged in the research of transmission of pathogenic microorganisms.

Asha George
Executive Director, Bipartisan Commission on Biodefense

George is the executive director of the Bipartisan Commission on Biodefense and a member of the Bulletin's Science and Security Board. George served in the US House of Representatives as a senior professional staffer and subcommittee staff director at the House Committee on Homeland Security in the 110th and 111th Congress. George also served on active duty in the US Army as a military intelligence officer and a paratrooper. She is a decorated Desert Storm Veteran. She holds a BA in Natural Sciences from Johns Hopkins University, a MS in Public Health from the University of North Carolina at Chapel Hill, and a Doctorate in Public Health from the University of Hawaii at Manoa. She is also a graduate of the Harvard University National Preparedness Leadership Initiative.

David Heymann
Professor, Infectious Disease Epidemiology, LSHTM

Heymann is a medical epidemiologist and professor of Infectious Disease Epidemiology at LSHTM. He was previously chair of Public Health England and led the Centre on Global Health Security at Chatham House (London). In 2003, he headed the WHO global response to SARS. Heymann was a member of the CDC (Atlanta) team to investigate the first Ebola outbreak in DRC. He has published over 250 peer reviewed articles and book chapters, is editor of the Control of Communicable Diseases Manual, and is an elected member of the UK Academy of Medical Sciences and the US National Academy of Medicine. In 2009 he was named an Honorary Commander of the Most Excellent Order of the British Empire for services to global health.

Clare Jolly
Professor of Virus Cell Biology, University College London

Jolly is a professor at University College London. Her research is focused on the cell biology of virus infection and virus-host interactions. Specifically, her lab seeks to understand how pandemic HIV-1 and SARS-CoV-2 hijack host cells to successfully replicate while avoiding antiviral defences. During the pandemic, Jolly applied her expertise in working with HIV-1 at high-containment and pivoted to SARS-CoV-2 research. Working with a team of UK and international collaborators, her group discovered mechanism of innate immune sensing of SARS-CoV-2 by human cells, and showed how the Alpha variant evolved enhanced innate immune evasion, linking adaptation to host with variant dominance, and genotype to phenotype. Jolly obtained her BSc (Hons) and PhD from the University of Melbourne, Australia.

Thomas Kariuki
Chief Executive Officer, Science for Africa Foundation

Kariuki is Founding Director and Chief Executive Officer for the Science for Africa Foundation, established in 2021 to support, strengthen and promote science and innovation in Africa. A long-time advocate involved in the global effort to develop vaccines, drugs, and diagnostics for poverty related diseases, he is a prolific science leader whose experience in science diplomacy has enabled the mobilisation of support and hundreds of millions in USD funding from global funders and African governments for science and innovation programmes in Africa.

Jens Kuhn
Principal Scientists and Director of Virology Contractor, NIH/NIAID/Integrated Research Facility at Fort Detrick

Kuhn is a principal at Tunnell Government Services (TGS), Bethesda, MD, USA, tasked as one of two Principal Scientists and the Director of Virology (contractor) at the NIH/NIAID/DCR/Integrated Research Facility at Fort Detrick (IRF-Frederick), a biosafety level 4 (BSL-4) facility in Frederick, MD, USA. Dr. Kuhn specializes in highly virulent viral human and animal pathogens. He is the author of "Filoviruses: A Compendium of 40 Years of Epidemiological, Clinical, and Laboratory Studies" (Vienna: Springer, 2008) and co-author of "The Soviet Biological Weapons Program—A History" (Cambridge: Harvard University Press, 2012), and he has studied and worked in Germany, Italy, Malta, Russia, South Africa, and South Korea.

Poh Lian Lim
Director of the High-Level Isolation Unit, National Centre for Infectious Diseases Singapore

Lim is Director of the High-Level Isolation Unit, National Centre for Infectious Diseases Singapore, Head of the Travellers' Health and Vaccination Clinic, Tan Tock Seng Hospital, and Senior Consultant with the Ministry of Health Singapore. Dr Lim's extensive clinical and public health experience is in the areas of outbreak preparedness and response, emerging and novel pathogens, travel medicine, and vaccines. She has served on WHO's GOARN Steering Committee and the UN Secretary General's Global Health Crises taskforce, chaired the WHO Technical Advisory Group for the Health Security Interface, and currently chairs the Independent Allocation of Vaccines Group for the COVAX Facility.

W. Ian Lipkin
John Snow Professor of Epidemiology, Columbia University; Director, Global Alliance for Preventing Pandemics

Lipkin is the director for the Center of Infection and Immunity and John Snow Professor of Epidemiology with the Mailman School of Public Health at Columbia University, director for the Global Alliance for Preventing Pandemics (GAPP), and director of the Center for Solutions for ME/CFS. He is internationally recognized for global public health contributions by being at the forefront of outbreak response and through the innovative methods developed for infectious diseases diagnosis, surveillance, and discovery. Lipkin consulted on COVID-19 protocols for the 2020 Democratic National Convention and the 2021 Academy Awards and served as scientific advisor to the film "Contagion".

Marc Lipsitch
Founding Director, Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health

Lipsitch is professor of epidemiology and founding director of the Center for Communicable Dynamics at Harvard T.H. Chan School of Public Health. He speaks in his academic capacity, but for the record is also part-time detailed to the US CDC where he is senior advisor for the Center for Forecasting and Outbreak Analytics. His research focuses broadly on the impact of medical and public health interventions on pathogen populations and the consequences of these changes for human health. Lipsitch received a BA from Yale and a DPhil from the University of Oxford, followed by postdoctoral work in biology at Emory University and a period as a visiting scientist at CDC. He is a member of the American Academy of Microbiology and the US National Academy of Medicine.

Sandra López-Vergès
Health Researcher V, Head of the Department of Research in Virology and Biotechnology, Gorgas Memorial Institute for Health Studies, Panama city, Panama;. Sistema Nacional de Investigación (SNI), Secretaria Nacional de Ciencia, Tecnología e Innovación (SENACYT), Panama city, Panama

López-Vergès is a Senior Health Researcher V, Head of the Department of Research in Virology and Biotechnology, Gorgas Memorial Institute for Health Studies, Panama city, Panama;. Sistema Nacional de Investigación (SNI), Secretaria Nacional de Ciencia, Tecnología e Innovación (SENACYT), Panama city, Panama. Her research focuses on understanding the virological and immunological factors shaping the emergence of viruses and the severity of diseases associated with viral infection in humans. To answer these questions her research integrates clinical, virological, cellular, molecular and immunological approaches and a continued collaboration with researchers from other fields like medicine, epidemiology, entomology and statistics. The ultimate goal is to identify biomarkers of infection or disease severity that will be used to guide clinical management of patients, as well as to develop new effective treatments and vaccines.

Suzet McKinney
Principal & Director, Life Sciences, Sterling Bay

McKinney is the principal and director of Life Sciences for Sterling Bay. She is also a member of the Bulletin's Science and Security Board. She previously served as CEO and executive director of the Illinois Medical District. In 2020, Dr. McKinney was appointed by IL Governor JB Pritzker as Operations Lead for the State of Illinois' Alternate Care Facilities, a network of alternate medical locations designed to decompress the hospital system during the COVID-19 pandemic. Dr. McKinney holds her Doctorate degree from the University of Illinois at Chicago School of Public Health, her BA from Brandeis University, and her MPH and certificates in Managed Care and Health Care Administration from Benedictine University in Lisle, IL.

Megan Palmer
Adjunct Professor, Department of Bioengineering Affiliate, Center for International Security and Cooperation

Palmer is an Adjunct Professor of Bioengineering at Stanford University and an affiliate of Stanford's Center for International Security and Cooperation where she previously served at a Senior Research Scholar. She also previously held roles as Executive Director of Bio Policy & Leadership Initiatives at Stanford, leading integrated research, teaching and engagement programs to explore how biological science and engineering is shaping our societies, and to guide innovation to serve public interests.

Gustavo Palacios
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Palacios is a distinguished virologist with over 20 years of experience in the study of emerging infectious diseases. His research focuses on understanding the genetic makeup of viruses and their emergence and transmission. He is a professor in the Department of Microbiology at the Icahn School of Medicine at Mount Sinai and a member of the Global Health and Emerging Pathogens Institute. Dr. Palacios previously worked at the Center for Infection and Immunity at Columbia University. He is an accomplished educator and mentor and has published extensively in top-tier scientific journals. Dr. Palacios earned his Master's degree in Biochemistry and his Ph.D. in Virology from the University of Buenos Aires.

Nahoko Shindo
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Shindo's background is in medicine, infectious diseases, emergency & intensive care, and public health. She trained at Dana-Farber Cancer Institute in Boston, St. Thomas' Hospital in London, Radcliff Infirmary in Oxford and Jikei University Hospital in Tokyo, where she also earned her PhD in Medical Science. She went on to train in epidemiology/surveillance at the Infectious Disease Surveillance Centre of the National Institute of Infectious Diseases in Tokyo, which is a WHO Collaborating Centre. She joined WHO in 2002. She was involved in WHO's global responses to the outbreaks of SARS, avian influenza, viral hemorrhagic fever in Africa, the 2009 influenza pandemic, MERS in the Middle East, avian influenza H7N9. She served as the Chair of WHO COVID-19 Publication Review Committee (2020-21).

Volker Thiel
Head of Virology, Institute of Virology and Immunology, and Chair Virology, Vetsuisse Faculty, University of Bern

Thiel has worked since the 1990s on basic aspects of coronavirus replication, immune responses, and virus-host interactions. Many of his studies included highly pathogenic coronaviruses such as SARS-CoV, MERS-CoV and SARS-CoV-2. Since 2014 he has led the virology division at the Institute of Virology and Immunology (IVI) in Bern and Mittelhäusern and served as chair of virology at the Vetsuisse Faculty, University of Bern. He is co-chair of the Multidisciplinary Center for Infectious Diseases (MCID), a strategic center of the University of Bern for pandemic preparedness. Thiel is a member of the National Swiss Biosafety Expert Committee and has served during the pandemic as a member of the Swiss National Science Task Force and the WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution.

Weiwen Zhang
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Zhang is a Baiyang Chair Professor of Tianjin University; Founding Director of Tianjin University Center for Biosafety Research and Strategy (TJU-CBRS); Deputy director of Frontier Science Center of Synthetic Biology of Ministry of Education of China. Dr. Zhang graduated from the Chinese Academy of Sciences in 1996 with a doctoral degree in microbiology. Prior to joining Tianjin University, Dr. Zhang was a faculty with Arizona State University, and a Senior Principal Investigator with the Pacific Northwest National Laboratory of the U.S. Department of Energy. Dr. Zhang is currently Chief Scientist for the National Key R&D Research Program of China - Synthetic Biology program, and Chief Investigator for the Key Strategic Project of the Chinese Association for Science and Technology on dual-use biotechnology governance.

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Ameneiros is a research associate at King´s College London, Centre for Science and Security Studies at the Department of War Studies. She is an Emerging Leader in Biosecurity Initiative Fellow through Johns Hopkins Center for Health Security and an Arms Control Negotiation Academy Fellow through Harvard University's Davis Center for Russian and Eurasian Studies. Ameneiros is deputy coordinator for the Next Generation Global Health Security Network. She is a certified professional in Biorisk Management and Biosecurity from the International Federation of Biosafety Associations and holds a BSc in Biochemistry, a MSc in transfusion medicine and immunohematology, and a postgraduate degree in international security. She is a member of the WHO's Technical Advisory Group on Health Security Interface.

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Earnhardt is a Presidential Scholar and PhD student in the Biodefense program at the Schar School for Policy and Government at George Mason University. Prior to joining the Biodefense PhD program, Earnhardt was a Faculty Specialist in the Unconventional Weapons and Technology Division at the National Consortium for the Study of Terrorism and Responses to Terrorism, and a Research Associate with the Nuclear Security Program at the Stimson Center. Her current research focuses on biorisk management, health security, and CBRN terrorism. Earnhardt holds a B.A. in Political Science and a B.A. in Homeland Security/Emergency Preparedness from Virginia Commonwealth University, and a M.S. in Biodefense from George Mason University.

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Posner is the assistant director of programs for the *Bulletin of the Atomic Scientists*. She was part of the 2021 cohort of the Nuclear Scholars Initiative at the Center for Strategic Studies' Project on Nuclear Issues and recently was a fellow with N Square Collaborative. Posner holds a BA in history from Bates College, where she was also the editor-in-chief of the student-run newspaper, The Bates Student. Academically, she focused on nonproliferation, deterrence, and asymmetric warfare theory. In addition to her Bulletin work, Posner is pursuing a Master of Public Administration at Columbia University's School of International and Public Affairs.

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