Mitigating biosecurity challenges associated with zoonotic risk prediction

Jonas B. Sandbrink[1,2*], Janvi Ahuja[1,2], Jacob L. Swett[3], Gregory D. Koblentz[4], Claire J. Standley[5,6]

[1] *Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom*

[2] *Future of Humanity Institute, University of Oxford, Oxford, United Kingdom*

[3] *altLabs, Inc., Berkeley, CA, USA*

[4] *Schar School of Policy and Government, George Mason University, Fairfax, VA, USA*

[5] *Center for Global Health Science and Security, Georgetown University, Washington DC, USA*

[6] *Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg, Germany*

*Correspondence to: jonas.sandbrink@trinity.ox.ac.uk

Summary

The COVID-19 pandemic has sparked renewed calls for wildlife pathogen discovery efforts to predict emerging zoonotic diseases. Here we highlight safety and security risks associated with large-scale viral collection and characterization efforts and present risk mitigation strategies. Accidents may be minimized by international standards for sample collection, indirect wildlife sampling, and a culture of continuous learning around laboratory biocontainment. To prevent the proliferation of the ability to create pandemic-capable viruses, the security risks from the characterization of human infectivity need to be recognized and systems for responsible and equitable access to genomic data and machine learning tools created. In light of the contested benefits and unique risks of large-scale wildlife pathogen discovery, a focus on One Health surveillance and behavioral interventions targeted at the human-animal interface may be both superior for preventing naturally emerging epidemics and reducing the risk from accidental and deliberate emergence.

Introduction

The COVID-19 pandemic has demonstrated the need for substantive efforts to create lasting infrastructure for pathogen surveillance integrated with effective interventions. Wildlife pathogen discovery is one among a range of initiatives to understand and prevent the spillover of zoonotic pathogens from animals to humans.[1] Despite questions around its benefits and cost-effectiveness,[2] zoonotic risk researchers from the United States to China have renewed calls for wildlife pathogen discovery for high-risk pathogens and the United States Agency for International Development (USAID) has launched the new DEEP VZN program to fund such work.[3–5]

At the same time, laboratory work on pathogens is associated with a risk of accidents, and advances in reverse genetics protocols and enzymatic DNA synthesis continue to raise the risk from the deliberate misuse of virological research.[6,7] Here we evaluate the possibility that zoonotic risk prediction and in particular wildlife pathogen discovery efforts could inadvertently increase the risk for pandemics through accidents or the generation of "dual-use" insights, defined as insights with potential for malicious misuse. We first summarize the stated objectives of zoonotic risk prediction and relevant technical advances, then analyze the risks of related efforts, before finally proposing

recommendations for risk mitigation both from specific activities and across the wider portfolio of pathogen surveillance approaches.

Zoonotic risk prediction: Strategies, benefits, and advances

Zoonotic risk prediction efforts aim to identify viral threats before they reach humans to steer public health interventions against future pandemics.[8] Large-scale zoonotic risk prediction efforts have focussed on the collection of samples from wild animals to isolate and characterize viruses that might cause human infection. These efforts are often complemented with epidemiological studies of the human-animal interface and public health interventions.[9] Between 2009-2020 the USAID PREDICT I and II programs provided $207m USD for global wildlife pathogen discovery and epidemiological studies to prevent zoonotic spillovers.[10,11] In 2018, a massive expansion of wildlife pathogen discovery in the form of the Global Virome Project (GVP) was proposed.[8] The proposal projects a cost of $1.2bn to identify 71% of the global virome. In 2021, USAID announced the new 5-year, $125m DEEP VZN program to fund wildlife pathogen discovery.[5]

Zoonotic risk prediction that identifies potential viral threats circulating in animal populations may guide clinical assessments and the detection of spillover events as well as local risk communication.[8] For example, PREDICT found Marburg virus in bats in Sierra Leone, which now informs local clinical diagnosis of hemorrhagic fevers. However, this discovery does not appear to have contributed to enhanced preparedness for Marburg in neighboring Guinea, which detected a human case of Marburg virus disease in 2021.[12] As wildlife pathogen discovery uncovers a vast number of zoonotic viruses, it is extremely difficult to assess the true potential for any individual virus to jump species, let alone its human transmissibility or virulence.[10] Given this difficulty, PREDICT only discovered a single conclusive zoonotic virus that spilled over into humans - and this not through wildlife sampling, but from analyzing patient samples.[10,13]

Additionally, there is hope that zoonotic risk prediction might inform future development of vaccines and therapeutics.[14] Bat coronaviruses collected during work supported through USAID PREDICT funding have helped test the broad-spectrum efficiency of several countermeasures.[15–17] However, it is unclear whether the inclusion of zoonotic viruses in broad-spectrum testing has had an irreplaceable and significant impact on the development of these countermeasures. The importance of zoonotic risk prediction to guide vaccine development may be decreasing as new fast response platform technologies allow vaccine development within days of identifying a new pathogen.[18] Achieving these capabilities is dependent on the study of a small number of prototype pathogens and does not require large-scale pathogen discovery. Since the SARS outbreak in 2003, numerous animal coronaviruses have been gathered and investigated, but this work did little to prevent the COVID-19 pandemic or inform vaccine design.[10] Instead, critical translatable insights came from studies of MERS and SARS after these viruses caused human outbreaks.[19] Nevertheless, PREDICT-funded work has contributed to genomic libraries that allowed rapid classification of SARS-CoV-2, and has resulted in infrastructure for the rapid isolation of the virus.[10]

Recent advances in biotechnology may increase the power of zoonotic risk prediction. New and cheaper sequencing approaches have enabled metagenomics, the characterization of the complete genomic diversity, including all viruses, in a given sample. This approach may be applied to environmental and wildlife samples, allowing the possibility of widespread surveillance for spreading agents.[20] These methods mean that the rate of viral discovery is further outpacing our ability to assess the zoonotic potential of identified pathogens.[21] Informatic approaches such as machine learning

2

models are necessary for interpreting this growing amount of sequencing data and identifying the highest risk viruses for further laboratory characterization.[22,23] The zoonotic risk prediction workflow of the future might look less linear than going from wildlife sample collection to laboratory characterization, and will almost certainly feature the computational characterization of identified genomes (Figure 1).
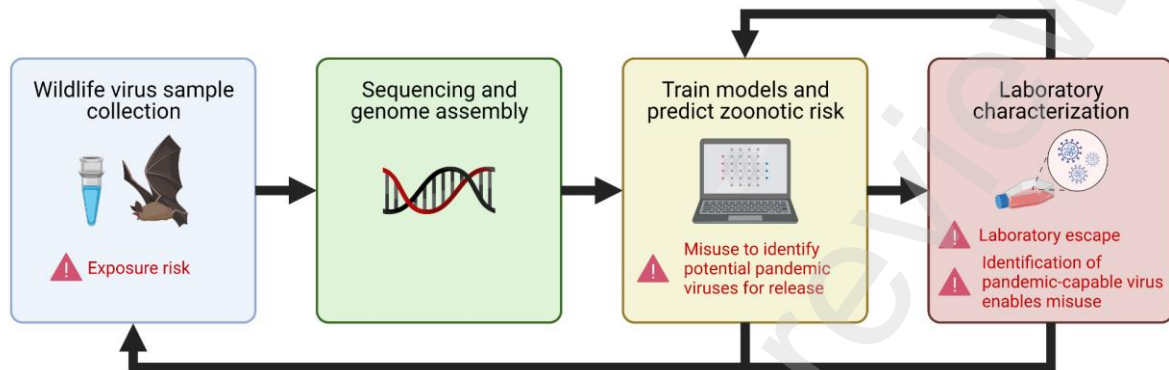

Figure 1: Zoonotic risk prediction workflow and associated risks

The addition of computational methods for predicting viral properties makes the zoonotic risk prediction workflow less linear. The training of machine learning models is informed by both genomic and functional data from laboratory characterization. Both computational models and laboratory characterization studies inform wildlife sample collection. Different safety and security risks arise throughout the zoonotic risk prediction workflow. Inspired by Fig 1 in Carlson et al.[22]

Zoonotic risk prediction approaches uniquely aim to characterize viruses with pandemic potential before the viruses spillover or spread into the human population. Hence, they may increase the risk for an accidental introduction of a zoonotic virus into the human population or the malicious engineering of pathogens for deliberate release. Biosafety and biosecurity risks may emerge throughout the zoonotic risk prediction pipeline (Figure 1). In the following section, we characterize these risks and propose strategies for risk mitigation.

Risks Associated with Zoonotic Risk Prediction

Accidental exposure and laboratory escape risks

Many epidemiological approaches for reducing the risk of viral spillover involve the reduction of high-risk interactions between humans and animal populations.[9] However, viral collection efforts for zoonotic risk prediction itself may constitute such high-risk behavior. A recent article about work conducted as part of PREDICT in Brazil showcases exposure risks: "Monkeys have bitten and sneezed on Gordo [...]. He says his wife complains when he stashes monkey carcasses in their home fridge."[24] Safe field sampling remains a technical challenge as the thin gloves required to maintain dexterity when handling fragile wildlife are easily penetrated by teeth and talons.[8,25,26] Furthermore, recent cases in Asia highlight that exposure can go unnoticed until symptom onset after return to the home environment.[26] Lack of universal standards for and access to personal protective equipment, secure storage facilities, and reliable transport routes can leave pathogen samples unaccounted for and local communities vulnerable to exposure.[27]

The storage and handling of pathogens in a laboratory present another set of risks. SARS-CoV-1 has escaped on four separate occasions from laboratories and hence has more frequently been documented

3

to enter the human population from laboratories than from nature.[28] Laboratory escape risks are increased if viruses are engineered or selected for transmissibility, immune evasion, or virulence. The risks from gain-of-function research on potential pandemic pathogens to inform surveillance and countermeasure development have been extensively debated over the past decade.[29] While not considered gain-of-function research, even assessing for the replication potential of zoonotic viruses in human cell lines can select for viruses with human transmissibility, which may hence feature greater pandemic potential than their ancestors isolated from wildlife. Furthermore, metagenomic sequencing approaches which frequently only yield genome fragments of novel viruses may lead to an increased number of viral recombination experiments.[30,31] Regardless of whether viruses are modified, bringing high-risk zoonotic viruses from remote areas into laboratories in urban centers embedded in the global transportation network could accelerate the local and global spread of disease in the event of an accidental release.[32]

Biosecurity risks of identifying a pandemic-capable virus

Advances in biotechnology continue to lower the barrier to the synthesis and engineering of viruses.[33] As these capabilities improve, the risk increases that the ability to create a pathogen for deliberate release falls into the hands of an individual interested in its misuse. Right now, we are partly protected by our limited knowledge of pathogens that are capable of causing a global pandemic. Though the chance is very low that a given animal virus is transmissible between humans, large-scale viral collection and characterization efforts to identify the majority of the 1.67 million projected unknown viral species may well turn up a rare pandemic-capable pathogen.[8] Currently, collected viruses are sequenced, following which their genomes are uploaded to publicly accessible databases and ranked according to their spillover potential.[14] High-risk viruses are chosen for laboratory characterization of their potential to transmit and cause disease in humans. To identify from all collected viruses with public genomes those which are pandemic-capable allows individuals, groups, companies, or states the ability to start a pandemic - now or down the line, as viral synthesis capabilities become increasingly accessible.[34] This could result in the accidental or deliberate release of the virus, even if the pathogen in question was unlikely to enter the human population via a natural spillover event. Furthermore, a biological event caused by a deliberate release may be worse than one caused by a zoonotic spillover. Even if a synthesised pathogen is not engineered for enhanced transmissibility, virulence, or immune evasion, a malevolent actor could introduce pandemic viruses in multiple highly populated locations at once, making containment nearly impossible.[35]

Dual-use potential of computational tools for zoonotic risk prediction

Advances in genomic sequencing mean that viral discovery is increasingly outpacing the downstream characterization of zoonotic potential. Machine learning approaches are being developed to interpret these data and identify the highest risk viruses for follow-on laboratory characterization.[21,22] Multiple groups have employed sequence interpretation approaches with improving success for identifying human-infecting viruses.[36–38] For instance, Bartoszewicz et al. published a reverse-complement neural network approach to predict whether a virus can infect humans directly from next-generation sequencing reads.[38] These computational capabilities feature dual-use potential, which will only grow as these capabilities become more sophisticated and powerful. For instance, the interpretation of genomes to infer transmissibility and virulence may be misused to identify viruses with these properties from published or experimentally derived datasets for intentional release. In the future, improved versions of these tools might be used to guide experiments attempting to enhance pathogen transmissibility and virus.[39] Present tools do not allow for sensible optimization of viral genomes as

4

they operate on short sequence fragments and do not capture the biologically relevant sequence space in a meaningful way.[38] As these tools advance, this dual-use capability needs to be preemptively addressed. Computational methods for identifying candidate zoonoses that feature less potential for misuse are ones that do not involve sequence interpretation, for instance ones solely using taxonomic data, similarities between host receptors, or genomic signatures of host range including dinucleotide, codon, and amino acid biases.[23,40–42] Reservoir network-based and trait-based studies for predicting viral reservoirs, such as a recent effort to identify undetected betacoronavirus hosts, also feature little potential for misuse and may be beneficial for informing targeted surveillance of the human-animal interface and behavioural interventions.[43]

Mitigating risks from zoonotic risk prediction

Strategies for mitigating biosafety risks

Many of the risks associated with wildlife pathogen discovery and zoonotic risk prediction may be reduced by adopting risk mitigation measures or completely averted using alternative strategies (Table 1). Exposure risk from wildlife sample collection may be reduced through the use of improved PPE and biosafety practices. While universal protocols for the sampling of animals in laboratories exist, there are no international standards for wildlife sample collection. International agencies, for instance through the recently created One Health High Level Expert Panel (OHHLEP),[44] should take the lead on developing universal standards for reducing exposure risks and could draw on existing protocols, such as those employed by PREDICT, to this end.[45] The risk for exposure to wildlife viruses may also be reduced through focussing on alternative strategies for zoonotic risk prediction, such as serological studies of high-risk populations at the human-animal interface or the indirect sampling of wildlife through metagenomic sequencing of waterway samples in dedicated facilities with specialized personnel.[20,46] A focus on these strategies would prevent accidental exposure through bite or scratch injuries, and mitigate risks around sample storage and transfer.

Laboratory escapes may be reduced through improved biosafety practices. Any laboratory engaging in high-risk research should adopt the new ISO 35001 standard for laboratory risk management.[47] Additionally, routine diagnostic surveillance of laboratory workers might not only help to contain laboratory-acquired infections but may enable continuous improvement of biocontainment practices. Positive reinforcement for reporting accidents may help to ensure fast response to a release and continuous improvements of equipment and practices. However, laboratory escape risks can never be reduced completely given the important factor of human error in driving these risks.[48] Laboratory escape risk scales with the amount of work taking place - Lipsitch and Inglesby estimate at least a 0.2% escape risk from a BSL-3 laboratory per person-year of work.[49] Strategies that minimize laboratory work on pathogens with the potential for human transmission would help to reduce the risk of escape. This may take the form of adopting safer experimental strategies such as using pseudotyped non-human viruses to study highly pathogenic or transmissible pathogens.[50] The recombination or enhancement of potential pandemic pathogens should only be conducted after extensive and transparent risk-benefit assessment.[51]

Managing biosecurity risks from genomic data and models

Certain information generated by zoonotic disease prediction work may feature potential for misuse and should not be accessible to everyone. A small number of viral characterization experiments that study human fitness indicators in cell culture or animal model experiments can credibly identify pandemic potential. Once a pandemic-capable pathogen has been identified, its genome features high

5

dual-use potential: it may inform biosurveillance while also constituting a blueprint to cause widespread harm. Focusing on wildlife pathogen surveillance without laboratory characterization of human fitness indicators of viruses that might never reach humans would remove the bulk of biosecurity risk from zoonotic risk prediction. This would only involve stopping a small fraction of current efforts and would still allow the use of discovered viruses to help test the broad-spectrum efficiency of countermeasures.

To reduce the risk of genetic information on potential pandemic pathogens enabling the malicious or accidental release of such a virus, open science and biosecurity experts need to collaborate to create solutions for responsible access to such data.[52] Such solutions need to ensure that the genetic information that is needed for certain countermeasure efforts is shared selectively and equitably with relevant stakeholders while barring access to anyone without a legitimate reason. Bedford and colleagues argue that application programming interfaces (APIs) - mechanisms by which users communicate with computers, code, and databases in an automated way - could be used for security authorization for accessing epidemiological data.[53]

Similarly, API access may be used to address dual-use risks from pandemic prediction software tools as their power and range of application increases.[52] OpenAI has deployed an API model to control input parameters and prevent misuse of the language model GPT-3, demonstrating that APIs are a technically feasible and scalable solution to ensure responsible access to general purpose ML models.[54] Indeed, the use of APIs might not only prevent misuse but also ensure equitable access. Modern models are usually difficult to run because of dependencies or requirements for special skills and might require costly compute resources. Free access to cutting-edge zoonotic prediction tools through API models would remove these barriers and ensure that the benefits of these advances can be reaped across different resource settings. The new Berlin-based WHO pandemic and epidemic data hub needs to guide new global solutions for the management of genomic datasets and computational models to ensure responsible and equitable access.

Table 1: Safety and security risks of zoonotic risk prediction and mitigation strategies

Risks	Risk mitigation
Exposure risk on wildlife sample collection	- Develop universal biosafety standards for viral collection - Focus on indirect wildlife sampling, e.g. of waterways or fecal droppings - Focus on human sampling at animal-human interface
Laboratory escape of viruses selected or engineered for human transmission	- Improved biosafety practices - Minimize work with infectious virus, e.g. through using pseudotyped viruses - Minimize enhancement of human transmissibility
Deliberate release of identified pandemic-capable viruses	- Focus on zoonotic surveillance with minimal characterization of pandemic potential - Responsible and equitable sharing of genomes of plausible pandemic-capable viruses
Misuse of computational models for prediction of transmissibility and	Application programming interface (API)-based access to relevant models to prevent misuse and

virulence	ensure equitable access ● Focus on extrapolating from taxonomy and gene markers of host range rather than interpretation of sequences

Discussion

Is wildlife pathogen discovery more trouble than it's worth?
In this article, we identify significant safety and security risks associated with large-scale wildlife pathogen discovery. Wildlife pathogen discovery may be associated with a unique risk of bringing zoonotic pathogens from the remotest areas into human proximity - both physically and in the form of dual-use genomic information. While wildlife pathogen discovery undoubtedly increases our general ecological knowledge, the benefits and cost-effectiveness of these activities for pandemic preparedness are controversial.[1,2,30] Zoonotic risk assessment based on wildlife sampling results may produce data that is inherently biased and rapidly changing, limiting its usefulness.[30] Some leading epidemiologists argue that the importance of viral discovery for pandemic prevention has been overstated, and these efforts divert funding and attention from effective early detection systems.[2]

A closer focus on the human-animal interface and detecting pathogens that are most likely to infect humans may generate more meaningful data for predicting and preventing zoonotic epidemics.[55] Evidence suggests that zoonotic viruses can often infect humans many times without causing long chains of transmission before acquiring mutations that allow for enhanced human-to-human transmissibility.[1] Hence, accurately identifying infection with novel pathogens in individuals in high-risk occupations and locations may be a promising approach to predict which zoonotic pathogens might at some point cause a pandemic.[30] This may be achieved through accurately identifying the source of a suspicious infection using genomic sequencing methodologies and conducting immunological screening for signs of previous exposure to novel pathogens.[56,57] A close focus on the human-animal interface would enable a One Health approach for zoonotic risk prediction that integrates human, animal, and ecological health. Once spillover of a novel zoonotic pathogen is detected, this can inform efforts to isolate and characterize the pathogen in question to guide further surveillance activities and public health interventions.[1] Adopting such a highly focused approach for zoonotic risk prediction may not only avoid safety and security risks associated with the large-scale collection of wildlife viruses, but also generate more actionable insights - and likely at a lower price tag.

An important part of PREDICT were social and behavioral interventions that could concretely reduce zoonotic spillover risks, such as informing local populations of risks from animal handling.[9] Additionally, better management of wildlife trade and reduction in deforestation may reduce high-risk behaviors and spillover risk.[58] In contrast to the investigation of the molecular nature of spillover events that is both of questionable benefit and creates dual-use insights, these interventions can reduce the risk of zoonotic outbreaks without generating additional risks. Similarly, programs that aim to strengthen global public health infrastructure are critical for pandemic preparedness and should receive dedicated investments rather than being relegated to a side effect of wildlife pathogen discovery efforts.[10]

7

Beyond zoonotic risk prediction

Pathogen surveillance to detect novel pathogens in human populations not only contributes to zoonotic risk prediction when employed in high-risk settings but is critical for containing outbreaks of any origin and guiding fast response countermeasures. However, it is important to note that human pathogen surveillance efforts may also generate predictive models with potential for misuse (see Figure 2), and the public sharing of human genetic data may be associated with privacy risks.

Approach	Benefits				Risks			
	Prevention	Clinical Detection	Non-Clinical Detection	Response	Exposure & Release	ID Pandemic-Capable Virus	DU ML tools	Privacy
Tiered surveillance	medium	high	low	medium	low	low	low	low
Sequencing surveillance	medium	high	high	medium	low	low	medium	high
Immunological surveillance	medium	medium	low	high	low	low	medium	medium
Metagenomic seq. (wastewater)	low	n/a	high	medium	low	low	medium	n/a
Metagenomic seq. (waterways)	medium	n/a	medium	low	low	high	high	n/a
Wildlife pathogen discovery	medium	n/a	low	low	high	high	high	n/a

Figure 2: Benefits and risks associated with different pathogen surveillance approaches.
Benefits are stratified into prevention (identification of zoonotic pathogens before human-to-human transmissibility is acquired), clinical detection (detection of early spread of novel pathogens in individuals presenting clinically), non-clinical detection (detection of early spread of novel pathogens in non-clinical setting, for instance in high-risk populations, wastewater, or waterways), and response (supporting response efforts through providing actionable information otherwise not available). Risks are stratified as discussed into safety (accidental exposure or release), identification of pandemic-capable viruses, creation of dual-use computational tools, or privacy risks. ID = identification of; DU = dual-use, ML = machine learning.

The lowest risk may feature approaches that do not generate large genomic datasets suitable for virological prediction, such as tiered surveillance methods which only employ sequencing if other diagnostics have failed to identify the source of infection. For instance, the Sentinel project conducted by Africa CDC combines the use of paper strip tests for common pathogens, multiplexed Cas13 diagnostics that test for a broad range of known pathogens, and sequencing for all otherwise unidentified cases.[59] In-depth evaluation of analysis of the benefit and risk profiles of different approaches needs to inform the strategic allocation of pandemic preparedness funding. A mixed methods portfolio consisting of a focus on tiered surveillance of clinical patients, coupled with immunological surveillance of at-risk populations for zoonotic risk prediction, and eventually environmental metagenomics might be a solution that maximizes the ability to predict, detect, and respond to biological events from any source while minimising biosecurity and privacy risks.

Conclusion

Our evaluation of risks associated with zoonotic risk prediction efforts highlights how considering both risks and risk mitigation is important when making pandemic preparedness investments. Prevention of viral zoonotic pandemics may be very cost-effective[58] - but only if chosen interventions do not inadvertently increase risks from accidental or deliberate pandemics. National agencies and international organizations, for instance through OHHLP, need to engage in high-level strategic evaluation of how to build preparedness infrastructure for maximal benefit: How do we trade off prevention, detection, and response and which approaches contribute to all of these? What is the cost-effectiveness and risk-benefit ratio of different approaches? What approaches might complement each other versus which ones create unnecessary redundancies? Risks around the creation of large-scale

dual-use data need to be further characterized and the broader question of how to ensure data management that is "as open as possible but as closed as necessary".[60] Given we are approaching a future with increasingly accessible and powerful biotechnology with potential for misuse, we need to consider how to achieve preparedness infrastructure that addresses pandemics of any origin.

Bibliography
1 Gray GC, Robie ER, Studstill CJ, Nunn CL. Mitigating Future Respiratory Virus Pandemics: New Threats and Approaches to Consider. *Viruses* 2021; **13**: 637.
2 Holmes EC, Rambaut A, Andersen KG. Pandemics: spend on surveillance, not prediction. *Nature* 2018; **558**: 180–2.
3 Daszak P, Olival KJ, Li H. A strategy to prevent future epidemics similar to the 2019-nCoV outbreak. *Biosafety and Health* 2020; **2**: 6–8.
4 Qin T, Ruan X, Duan Z, *et al.* Wildlife-borne microorganisms and strategies to prevent and control emerging infectious diseases. *Journal of Biosafety and Biosecurity* 2021; **3**: 67–71.
5 USAID Announces New $125 Million Project To Detect Unknown Viruses With Pandemic Potential | Press Release | U.S. Agency for International Development. 2021; published online Oct 5. https://www.usaid.gov/news-information/press-releases/oct-5-2021-usaid-announces-new-125-million-project-detect-unknown-viruses (accessed Nov 9, 2021).
6 Manheim D, Lewis G. High-risk human-caused pathogen exposure events from 1975-2016. 2021; published online Aug 4. DOI:10.12688/f1000research.55114.1.
7 Sandbrink JB, Koblentz GD. Biosecurity risks associated with vaccine platform technologies. *Vaccine* 2021; published online Feb 25. DOI:10.1016/j.vaccine.2021.02.023.
8 Carroll D, Daszak P, Wolfe ND, *et al.* The Global Virome Project. *Science* 2018; **359**: 872–4.
9 Saylors K, Wolking DJ, Hagan E, *et al.* Socializing One Health: an innovative strategy to investigate social and behavioral risks of emerging viral threats. *One Health Outlook* 2021; **3**: 11.
10 Carlson CJ. From PREDICT to prevention, one pandemic later. *The Lancet Microbe* 2020; **1**: e6–7.
11 USAID PREDICT. Reducing pandemic risk, promoting global health. https://ohi.sf.ucdavis.edu/sites/g/files/dgvnsk5251/files/files/page/predict-final-report-lo.pdf (accessed Nov 9, 2021).
12 Marburg virus found in Sierra Leone bats. *ScienceDaily* https://www.sciencedaily.com/releases/2020/01/200124073910.htm (accessed Nov 10, 2021).

9

13 Steffen I, Liss NM, Schneider BS, Fair JN, Chiu CY, Simmons G. Characterization of the Bas-Congo Virus Glycoprotein and Its Function in Pseudotyped Viruses. *J Virol* 2013; **87**: 9558–68.

14 Grange ZL, Goldstein T, Johnson CK, *et al.* Ranking the risk of animal-to-human spillover for newly discovered viruses. *PNAS* 2021; **118**. DOI:10.1073/pnas.2002324118.

15 Sheahan TP, Sims AC, Zhou S, *et al.* An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Science Translational Medicine* 2020; **12**: eabb5883.

16 Sheahan TP, Sims AC, Graham RL, *et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science Translational Medicine* 2017; **9**: eaal3653.

17 Rappazzo CG, Tse LV, Kaku CI, *et al.* Broad and potent activity against SARS-like viruses by an engineered human monoclonal antibody. *Science* 2021; **371**: 823–9.

18 Monrad JT, Sandbrink JB, Cherian NG. Promoting versatile vaccine development for emerging pandemics. *npj Vaccines* 2021; **6**: 1–7.

19 Corbett KS, Edwards DK, Leist SR, *et al.* SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature* 2020; **586**: 567-571(2020).

20 The Nucleic Acid Observatory Consortium. A Global Nucleic Acid Observatory for Biodefense and Planetary Health. *arXiv:210802678 [q-bio]* 2021; published online Aug 5. http://arxiv.org/abs/2108.02678 (accessed Aug 12, 2021).

21 Ladner JT. Genomic signatures for predicting the zoonotic potential of novel viruses. *PLOS Biology* 2021; **19**: e3001403.

22 Carlson CJ, Farrell MJ, Grange Z, *et al.* The future of zoonotic risk prediction. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2021; **376**: 20200358.

23 Mollentze N, Babayan SA, Streicker DG. Identifying and prioritizing potential human-infecting viruses from their genome sequences. *PLOS Biology* 2021; **19**: e3001390.

24 Grossman D. Scientists scour the Amazon for pathogens that could spark the next pandemic. 2021; published online April. https://www.science.org/content/article/scientists-scour-amazon-pathogens-could-spark-next-pandemic (accessed Nov 9, 2021).

25 Patlovich SJ, Emery RJ, Whitehead LW, Brown EL, Flores R. Assessing the Biological Safety Profession's Evaluation and Control of Risks   Associated with the Field Collection of Potentially Infectious Specimens. *Applied Biosafety* 2015; **20**: 27–40.

26 Callahan M. A Virus-Hunter's Advice on Dealing with China's Resistance on Covid. *POLITICO* 2021; published online Sept 15. https://www.politico.com/news/magazine/2021/09/15/covid-origin-investigation-china-cooperation-511898 (accessed Jan 3, 2022).

27 Monrad JT, Katz R. Biosecurity, Biosafety, and the Management of Dangerous Pathogens for Public Health Research. In: Katz R, Halabi SF, eds. Viral Sovereignty and Technology Transfer: The Changing Global System for Sharing Pathogens for Public Health Research. Cambridge: Cambridge University Press, 2020: 100–19.

28 Demaneuf G. The Good, the Bad and the Ugly: a review of SARS Lab Escapes. 2020; published online Nov 27. DOI:10.5281/zenodo.4293257.

29 Imperiale MJ, Casadevall A. Rethinking Gain-of-Function Experiments in the Context of the COVID-19 Pandemic. *mBio*; **11**: e01868-20.

30 Wille M, Geoghegan JL, Holmes EC. How accurately can we assess zoonotic risk? *PLOS Biology* 2021; **19**: e3001135.

31 Smits SL, Bodewes R, Ruiz-Gonzalez A, *et al.* Assembly of viral genomes from metagenomes. *Frontiers in Microbiology* 2014; **5**: 714.

32 Smith TP, Flaxman S, Gallinat AS, *et al.* Temperature and population density influence SARS-CoV-2 transmission in the absence of nonpharmaceutical interventions. *PNAS* 2021; **118**. DOI:10.1073/pnas.2019284118.

33 Atlas RM, Dando M. The dual-use dilemma for the life sciences: perspectives, conundrums, and global solutions. *Biosecur Bioterror* 2006; **4**: 276–86.

34 Pannu J, Sandbrink JB, Watson M, Palmer MJ, Relman DA. Protocols and risks: when less is more. *Nat Protoc* 2021; : 1–2.

35 Esvelt KM. Opinion | Manipulating viruses and risking pandemics is too dangerous. It's time to stop. Washington Post. https://www.washingtonpost.com/opinions/2021/10/07/manipulating-viruses-risking-pandemics-is-too-dangerous-its-time-stop/ (accessed Nov 5, 2021).

36 Zhang Z, Cai Z, Tan Z, *et al.* Rapid identification of human-infecting viruses. *Transboundary and Emerging Diseases* 2019; **66**: 2517–22.

37 Kou Z, Huang Y-F, Shen A, Kosari S, Liu X-R, Qiang X-L. Prediction of pandemic risk for animal-origin coronavirus using a deep learning method. *Infectious Diseases of Poverty* 2021; **10**: 128.

38 Bartoszewicz JM, Seidel A, Renard BY. Interpretable detection of novel human viruses from genome sequencing data. *NAR Genomics and Bioinformatics* 2021; **3**. DOI:10.1093/nargab/lqab004.

39 O'Brien JT, Nelson C. Assessing the Risks Posed by the Convergence of Artificial Intelligence and Biotechnology. *Health Security* 2020; **18**: 219–27.

40 Babayan SA, Orton RJ, Streicker DG. Predicting reservoir hosts and arthropod vectors from evolutionary signatures in RNA virus genomes. *Science* 2018; **362**: 577–80.

41 Fischhoff IR, Castellanos AA, Rodrigues JPGLM, Varsani A, Han BA. Predicting the zoonotic capacity of mammals to transmit SARS-CoV-2. 2021; : 2021.02.18.431844.

42 Karabulut OC, Karpuzcu BA, Türk E, Ibrahim AH, Süzek BE. ML-AdVInfect: A Machine-Learning Based Adenoviral Infection Predictor. *Front Mol Biosci* 2021; **8**: 647424.

43 Becker DJ, Albery GF, Sjodin AR, *et al.* Optimising predictive models to prioritise viral discovery in zoonotic reservoirs. *The Lancet Microbe* 2022; **0**. DOI:10.1016/S2666-5247(21)00245-7.

44 26 International experts to kickstart the One Health High Level Expert Panel (OHHLEP). https://www.who.int/news/item/11-06-2021-26-international-experts-to-kickstart-the-joint-fao-oie-unep-who-one-health-high-level-expert-panel-(ohhlep) (accessed Dec 10, 2021).

45 PREDICT One Health Consortium. PREDICT Operating Procedures: Biosafety and Personal Protective Equipment (PPE) Use. 2016.

46 Mina MJ, Metcalf CJE, McDermott AB, Douek DC, Farrar J, Grenfell BT. A Global Immunological Observatory to meet a time of pandemics. *eLife*; **9**: e58989.

47 Rodgers J, Lentzos F, Koblentz GD, Minh L. How to make sure the labs researching the most dangerous pathogens are safe and secure. Bulletin of the Atomic Scientists. 2021; published online July 2. https://thebulletin.org/2021/07/how-to-make-sure-the-labs-researching-the-most-dangerous-pathogens-are-safe-and-secure/ (accessed Dec 15, 2021).

48 Klotz LC. Human error in high-biocontainment labs: a likely pandemic threat. *Bulletin of the Atomic Scientists* 2019; published online Feb 25. https://thebulletin.org/2019/02/human-error-in-high-biocontainment-labs-a-likely-pandemic-threat/ (accessed June 14, 2021).

49 Lipsitch M, Inglesby TV. Reply to "Studies on Influenza Virus Transmission between Ferrets: the Public Health Risks Revisited". *mBio* 2015; **6**: e00041-15.

50 Millet JK, Tang T, Nathan L, *et al.* Production of Pseudotyped Particles to Study Highly Pathogenic Coronaviruses in a Biosafety Level 2 Setting. *JoVE (Journal of Visualized Experiments)* 2019; : e59010.

51 Inglesby TV, Lipsitch M. Proposed Changes to U.S. Policy on Potential Pandemic Pathogen Oversight and Implementation. *mSphere* 2020; **5**. DOI:10.1128/mSphere.00990-19.

52 Smith JA, Sandbrink J. Open science practices and risks arising from misuse of biological research. 2021; published online Dec 10. DOI:10.31222/osf.io/8afwn.

53 Black A, MacCannell DR, Sibley TR, Bedford T. Ten recommendations for supporting open pathogen genomic analysis in public health. *Nat Med* 2020; **26**: 832–41.

54 OpenAI API. OpenAI. 2020; published online June 11. https://openai.com/blog/openai-api/ (accessed Nov 13, 2021).

55 Geoghegan JL, Holmes EC. Predicting virus emergence amid evolutionary noise. *Open Biol* 2017; **7**: 170189.

56 Gardy JL, Loman NJ. Towards a genomics-informed, real-time, global pathogen surveillance system. *Nat Rev Genet* 2018; **19**: 9–20.

57 Xu GJ, Kula T, Xu Q, *et al.* Viral immunology. Comprehensive serological profiling of human populations using a synthetic human virome. *Science* 2015; **348**: aaa0698.

58 Bernstein AS, Ando AW, Loch-Temzelides T, *et al.* The costs and benefits of primary prevention of zoonotic pandemics. *Science Advances*; **8**: eabl4183.

59 African researchers lead scientific coalition developing surveillance system for detecting emerging pandemics in real-time. Africa CDC. https://africacdc.org/news-item/african-researchers-lead-scientific-coalition-developing-surveillance-system-for-detecting-emerging-pandemics-in-real-time/ (accessed Nov 10, 2021).

60 Landi A, Thompson M, Giannuzzi V, *et al.* The "A" of FAIR – As Open as Possible, as Closed as Necessary. *Data Intelligence* 2020; **2**: 47–55.