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COMMENTARY

# Biosecurity Implications for the Synthesis of Horsepox, an Orthopoxvirus

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This article examines the biosecurity and biodefense implications resulting from the recent creation of horsepox virus, a noncirculating (extinct) species of orthopoxvirus. Here we examine the technical aspects of the horsepox virus synthesis and conclude that orthopox synthesis experiments currently remain technically challenging—and will continue to be so, even once this work is published in the scientific literature. This limits potential misuse by some types of nefarious actors. We also examine the implications of one stated purpose for the recreation of horsepox virus: the development of a smallpox vaccine. If the development is successful, it could take advantage of US government incentives for the priority FDA review of medical countermeasures (MCMs) against biosecurity threats. However, if this case leads to the determination that this incentive is counterproductive for security, the newly created priority review voucher program should be more clearly defined or limited based on need. Limiting the program could have costs that require further consideration, however, as general incentives for biodefense medical countermeasure development are required for MCMs to be available. Finally, while the recreation of horsepox virus was not technically trivial, nor was it cell-free, this experiment was a de facto demonstration of already-assumed scientific capabilities. The ability to recreate horsepox, or smallpox, will remain no matter what policy controls are put into place. It will be impossible to close off all avenues for nefarious misuse of gene synthesis, or misuse of biological materials more broadly. As a result, we advocate for the implementation of policy, regulations, and guidance that will make illicit recreation harder, more burdensome, more detectable, and, thus, more preventable without having sweeping negative consequences for the research enterprise. As part of our biosecurity efforts, we must also encourage and enable scientists to participate actively and to do all they can to safeguard their technical fields from irresponsible or illicit actions.

The ability to synthesize and alter DNA has enabled progress in public health research and helped researchers understand how pathogens cause and maintain infections. Genome synthesis to construct viruses, in particular, has aided in the development of more efficient vaccines, improving on slow, decades-old technologies.[1] In addition, the speed with which vaccines can be made in response to unpredicted outbreaks also has improved.[2]

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However, as these types of synthetic biology advances have progressed, scientists have acknowledged concerns about the possibility of recreating pathogens through chemical synthesis or, in more colloquial terms, to make a pathogen "from scratch." This procedure has been demonstrated with several viruses, including polio and 1918 influenza, and the possibility exists that this capability can be misused to create a biological weapon.[3,4]

Many viruses that infect humans are found in nature and in a variety of places around the world, including in samples taken from sick patients and clinical and research laboratories.[5] Therefore, the ability to chemically synthesize a virus merely represents an *additional* method of acquiring a pathogen that could be used as a weapon. However, not all pathogens are available in nature. For variola virus, also known as smallpox, acquiring viral samples is significantly more challenging. The disease was declared eradicated from nature in 1980 by the World Health Organization (WHO), and only 2 official repositories are allowed to possess the remaining samples: the Centers for Disease Control and Prevention (CDC) in Atlanta, and the Vector lab in Novosibirsk, Russia. Although scientific research is still performed using remaining variola stocks, the research is tightly regulated internationally. All experiments must be approved by a special committee, the WHO Advisory Committee on Variola Virus Research (ACVVR).

There is the possibility that smallpox samples exist outside of these official sites, either deliberately kept or accidentally forgotten (as occurred when samples were discovered at the US National Institutes of Health in 2014).[6] But the concern that synthetic genomics techniques could be used to manufacture additional stocks of smallpox has been considered since the inception of the synthetic biology field. WHO warned in 2010 that "advances in genome sequencing and gene synthesis would render substantial portions of [variola] accessible to anyone with an internet connection and access to a DNA synthesizer."[7(pp45-46)] At the most recent meeting of the advisory group, ACVVR committee member and University of Alberta pox virologist David Evans presented his research, which, in the eyes of some analysts, brought the future WHO had warned about in 2010 a lot closer. He and his postdoctoral fellow had experimentally recreated horsepox, an extinct cousin of human smallpox virus.[8]

A scientific paper describing the reconstruction of horsepox virus has not yet been published. Therefore, accounts about the composition of the project team, the scientific methods that were undertaken, the vendors used to make the DNA, and other details have come from other sources. These sources include the statements that the researchers themselves made in interviews and presentations, the WHO report from the November 2016 meeting of the ACVVR, and the scientific and popular press.[8-12] From these accounts, several reasons have been offered for why the horsepox work was undertaken, including cancer vaccine development and as a proof-of-principle (ie, to demonstrate that smallpox could be synthesized in the laboratory).

The synthesis of a poxvirus has longstanding biosecurity and biodefense implications.[8,9,13] Specific objections and concerns were raised by biosecurity experts about the horsepox work. Tom Inglesby of the Johns Hopkins Center for Health Security objected to "creating new risks to show that risks are real."[14] He also wondered how much detail would be provided in the forthcoming publication about the methods used to construct an orthopox virus, whether that information would substantially lower the bar for others to create smallpox, and whether the approval process for this type of work is sufficient.[14] Gregory Koblentz of George Mason University raised additional concerns that this work would open the door to widespread synthesis of other orthopoxviruses for use in biomedical research, public health, and medicine.[9] As "demand grows for chimeric synthetic orthopoxviruses for medical and public health applications, so too will the demand for improved techniques for the assembly, reactivation, and modification of orthopoxviruses. … With this diffusion will come an increased risk that scientists, acting on their own volition or on behalf of a terrorist group, might misuse their know-how to create variola virus, or that governments could use civilian biomedical research with synthetic orthopoxviruses as a cover for offensive applications."[9(p005)] Koblentz argued that, among other actions, the governing body of WHO, the World Health Assembly, should ensure that the handling and synthesis of smallpox virus is forbidden by international law, that the WHO should increase its oversight responsibilities to include the synthesis of other orthopoxviruses besides smallpox, and that a moratorium should be declared on the synthesis of orthopoxviruses until greater oversight can be established.[9] Any government, private company, or individual wishing to synthesize a pox virus would need to request permission from WHO, present safety and security plans for their approval, and accept WHO inspections of their laboratories.[9]

## Purpose of This Analysis

The synthesis of horsepox presents an opportunity to examine the collective risks from misuse of biotechnologies, examine whether the regulatory framework that bounds this work is sufficient to prevent or deter misuse where possible, and ensure that incentive structures are in place that maximize the beneficial applications of these technologies while minimizing risk. To this point, this article outlines the potential regulatory factors in this area and recommends steps that should be taken to minimize the risks of misuse.

**1. Skills and expertise are still required for orthopox synthesis.**

Scientific and technical considerations are critical to understanding the regulatory gaps that could be exploited by a nefarious actor and are the best approaches for responding to experimental achievements. The horsepox synthesis has not been published in a scientific journal, but

it has been reported in the scientific press. Perhaps as a result, there appears to have been an underestimation of the technical skill level and resources required for this undertaking and a misconception of what had been done (see, for example, the alarming headline, "How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA" in *Science* magazine and the researcher's own statements to WHO).[11] In fact, technical hurdles in the recreation of horsepox (and, by analogy, smallpox) still exist, which will be described in this analysis.[15]

First, it should be noted that the lead researcher in this study has decades of experience in working with orthopox viruses.[16] He had access to a sophisticated laboratory infrastructure and the ability to get approval and funds to purchase large pieces of DNA from a gene synthesis company that performs biosecurity screening. The laboratory leveraged an experimental approach it developed in 2003 and new capabilities afforded by gene synthesis providers.[17] Furthermore, review of the incremental scientific steps that had to be taken to reach that point, Dr. Evans's recent publications, and his partnerships and funding sources suggest that the research that ultimately resulted in the horsepox synthesis began well before spring 2016 (ie, prior to the "6 months" cited in Dr. Evans's report to WHO).[15]

In contrast to the implications of the news headlines, cell-free assembly of the horsepox virus was not achieved in the Evans work (this differs from the chemical synthesis and reconstitution of polio or influenza viruses, for example). The *Science* article stated that the 212kb horsepox genome was "stitched together" before being introduced into cells. However, while 30kb fragments of the horsepox genome were obtained from a commercial provider, the Evans laboratory linked the terminal ends that they already had and introduced these fragments (not the full-length genome) into cells with a helper virus to produce infectious virus. Evans had previously published this final step in an experiment with vaccinia virus—specifically, the use of a helper poxvirus to produce infectious recombinant virus. The extra steps to assemble the genetic material of the horsepox virus increase the required experience and skill levels.

The researchers also were able to clear various industry and policy hurdles put into place to make synthesis more challenging for the recreation of poxviruses for nefarious purposes. They ordered poxvirus DNA from GeneArt, a gene synthesis company that has pledged to screen the customer orders they receive, as part of the International Gene Synthesis Consortium (IGSC).[18] IGSC member companies exceed the recommendations of the 2010 guidance of the US Department of Health and Human Services to screen gene synthesis customers as well as the genetic sequences ordered.[19] Customers who request synthetic sequences that match regulated pathogens (eg, from the US select agent list and the Australia Group list) are required by GeneArt to identify themselves and provide necessary import and export documents.[7] We do not know whether the sequences were screened and flagged by the company. They agreed to screen pieces longer than 200bp, and Evans and colleagues ordered 30kb pieces. However, as the principal researcher was a well-known, legitimate pox virologist working at a legitimate institution that provided approval for the experiments, the screening would not have been a barrier.[20]

In addition, although the researchers benefited from the services of a commercial company that specializes in gene synthesis, they still performed the subsequent steps, which included linking those synthetic DNA pieces to terminal ends, introducing those fragments into cells infected with the helper virus, and collecting the resulting infectious virus. Structural features of the poxviruses, called telomere hairpins, are required for viral replication, without which infectious virus cannot be produced.[21] The ability to create an actual infectious virus, which commonly is referred to as "booting," similar to a computer program, varies depending on the virus.[22] These technical methods have been published for other poxviruses, including publications on vaccinia virus by Dr. Evans, but they still require specialized expertise and skill. Similarly, many downstream technical steps, including harvesting and purifying infectious virus, are likely also to require specialized expertise and knowledge.

The technical challenges that faced the horsepox researchers do not eliminate the need for thoughtful consideration of biosecurity risks or ameliorate the concern about malicious efforts of some actors, but they do add to the consideration of *who* might repeat the work of synthesizing an orthopox virus and how accessible the work is. These considerations should be included in an assessment of the biosecurity risks incurred by the horsepox work.

**2. The horsepox virus assembly is yet another example of the dual-use research dilemma in the biological sciences, as the work has beneficial aims.**

David Evans's research focuses on using vaccinia and other orthopox viruses to target cancer cells, another stated beneficial aim of the research.[12] Because the research has caused controversy for biosecurity reasons and yet also has the potential for beneficial applications, the synthesis of horsepox virus is another example of the inherent tension of research that has a legitimate purpose and may be considered risky from a biosecurity standpoint. This tension was captured in the recounting of the WHO advisory group's discussions about the horsepox synthesis, which highlighted concerns raised about the dual-use potential of these studies.[8]

## *Potential Benefits of the Research*

Currently, poxviruses are being developed to seek out and destroy oncogenic (or cancerous) cells, leveraging research on the immune system's ability to be trained to fight cancerous cells. Cancerous cells often look different from

normal or healthy cells, but they are treated by the body's immune system as "self."[23] However, the aim of studies on oncolytic virus therapies is to make the body recognize cancer cells as "non-self" and, in so doing, turn on the immune system to detect and destroy the cancer cells.

Poxviruses also are used to develop vaccines for infectious diseases. A great deal of research and development of pathogen-specific vaccines involves engineering viral vectors, such as vaccinia and potentially horsepox, to express specific genes from a specific pathogen or pathogens. These engineered vaccines can be used to prompt the body to make protective immune responses against the pathogens. For example, decades of research on HIV vaccines have involved the use of vaccinia and its attenuated version (modified vaccinia virus Ankara, or MVA) to express key HIV genes with the idea of generating HIV-specific antibodies to prevent infection after exposure.[24]

The experimental processes involved in vaccine or drug development involve the creation and testing of several candidates, whether they are variants of the pathogen, vectors with pathogen sequences, or pathogen components. These candidates undergo a series of tests in cells, animals, and eventually humans, all designed to eliminate candidates that do not work for a variety of reasons, whether they fail to elicit the desired immune responses, are not effective at protecting the animals from infection, or are unsafe in people. If candidate vaccines do not pass any of these steps, researchers must start over as they attempt to identify and develop better vaccines. The process of developing, testing, redeveloping and testing, and approving a candidate product can take more than 15 years and cost $1 billion.[25] For medical countermeasures that are not driven by typical market forces—for example, vaccines and drugs that would be useful after a biological weapons attack with a pathogen that is not typically prevalent, and for which governments are the only customer—creative policy and financial measures have been required to entice biotechnology and pharmaceutical companies to invest.

## *Potential Risks of the Research*

Recreating extinct pathogens from published sequences and resurrecting extinct pathogens from preserved samples have been a part of the dual-use research of concern discussions in the United States since the National Research Council report *Biotechnology in an Age of Terrorism* was published in 2004.[26] These experiments gained much interest in 2005 when researchers created the 1918 influenza virus using reverse genetics.[4] Twelve years later, the biosecurity community is revisiting the broader implications of recreating extinct viruses. Studies conducted with the 1918 influenza virus have revealed new scientific information about how the virus caused infection and disease, which can inform defenses against recent and future influenza outbreaks.[27]

The broader implications of the horsepox synthesis are not as clear. The horsepox virus has the potential to provide another vector that would be useful for vaccines or medicines, or it could be used to shed light on poxvirus biology and evolution, which might have beneficial implications. On the other hand, the methods used to create horsepox have the potential to help malicious actors gain access to this and other poxviruses, including smallpox. Insufficient information exists to anticipate the long-term implications or the risk that the work will actually be misused. Although the horsepox experiments have not yet been published, preventing access to detailed methods for anyone wanting to replicate the work is not possible, primarily because the methods had been optimized and published by Dr. Evans. Whether the technical details of the experiments are translatable to poxviruses other than vaccinia and horsepox will not be clear without doing the work, which already may be happening. In summary, there is a great deal of uncertainty about how much of a biosecurity risk the horsepox synthesis incurs, but we can tell that at this time expertise and tacit knowledge would be needed to apply this work for nefarious purposes in a short time frame.

Importantly, this work does highlight the need to consider the potential biosecurity implications of pathogen research outside of the regulated pathogen lists such as the US Federal Select Agent Program, as horsepox is not a select agent.[28] Scientists, security experts, and others with relevant expertise, in close collaboration, should examine the potential for biosecurity risk within the context of experimental details, proposed benefit, existing science in the field, and security landscape. Only then will we be able to really evaluate experiments objectively and carefully.

**3. Does horsepox synthesis lower barriers to biological weapons development? This is difficult to determine.**

What is not clear is whether the synthesis of horsepox necessarily makes the creation of smallpox easier to achieve. Poxviruses contain host-specific genes that vary between viral species, limiting which humans or animals the viruses can infect and cause disease.[29] Therefore, whether capabilities for assembly and reactivation of smallpox or other orthopox will advance apace with therapeutic use of constructed poxvirus chimeras is not known.

**4. Governance of horsepox synthesis research or vaccinia is substantially different from the governance of smallpox research.**

The synthesis of horsepox virus was conducted by well-respected researchers in Canada, and, to the best of our knowledge, it was conducted in full compliance with Canadian regulations.[11,12] As scientific activities transcend national boundaries, understanding whether and how such experiments would be regulated in one's own country is instructive. Similar experiments could theoretically be conducted in the United States or another country, and,

while there are international policies governing research with smallpox, there are no international standards for research that has dual-use potential. Therefore, we examined the applicability of current US policies to the synthesis of horsepox to identify policy gaps in the United States and potential means to address them. Furthermore, we would suggest that other countries also analyze their governance structure in this area to determine whether and to what degree these experiments would be reviewed, regulated, and/or overseen by knowledgeable authorities.

In the United States, possession of 85% of the gene sequence of variola virus is unlawful.[30] However, poxviruses, including vaccinia virus, may have greater than 90% sequence identity to the smallpox genome, raising questions about whether research involving poxviruses in the same family as smallpox, but not actually smallpox, is a criminal offense. (This specific section of the US Code was added in 2004.) This tension was highlighted in the recommendations of the National Science Advisory Board for Biosecurity (NSABB) in their report on the synthesis of select agents, which called for clarification on the definition of "smallpox" in 18 USC 175c, given that vaccinia, along with a variety of other orthopox viruses, is widely used in basic and clinical research settings.[31]

Synthetic chimeras based on orthopox viruses are being explored to develop therapeutic applications, particularly for the delivery of cancer therapies, and vaccines for infectious diseases, including HIV.[32] A Department of Justice legal determination of 18 USC 175c in 2008 did not include naturally occurring orthopoxviruses in the interpretation of the law, but it did include viruses "engineered, synthesized, or otherwise produced by human manipulation from the variola major virus or its components."[33] The horsepox genome has been shown to have 98% identity with vaccinia, and it shares identical genes with smallpox, raising new questions about whether this experiment would fall under the scope of the law if conducted in the United States.[34] The dialogue for orthopox exclusions under 18 USC 175c and discussions of sequence homologies between orthopoxviruses should be revisited, as they form the basis for sequence screening and have legal ramifications. If an academic research group in the United States attempted to synthesize horsepox virus, the research would not necessarily be restricted by regulation or policy. The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* would hold US universities responsible for reviewing the proposed research for biosafety.[35] At this stage of review, the institutional biosafety committee and/or biosafety official may prevent the research from continuing, request that the research be conducted using alternative approaches, or require certain conditions to be put in place to prevent exposure or release of the agent. This guidance is required for institutions receiving federally funded research, but it is voluntary for research institutions that do not receive US government funding. The research institution also would aim to comply with the *Biosafety in Microbiological and Biomedical Laboratories* guidance for biosafety.[36]

The Animal Welfare Act and Animal Welfare Regulations require institutions to review and oversee research involving animals. According to Dr. Evans's collaborator, Tonix Pharmaceuticals, the synthetized horsepox virus was studied in mice.[37] Advanced testing of the synthesized virus likely would be reviewed by the Institutional Animal Care and Use Committee, and questions about the source of the virus may have been raised by the responsible veterinarian and/or committee members.

In 2010, the US government released its Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA, which is voluntary for industry and resembles industry guidance for sequence and customer screening of gene synthesis orders.[19] If a researcher orders the synthetic horsepox DNA from a company that follows this guidance, the company may inquire further, decline to fulfill the order, or contact the Federal Bureau of Investigation (FBI), given the high degree of similarity among the horsepox, vaccinia, and cowpox virus genomes. The company's scrutiny of the order may have delayed the research further or prevented it from continuing. However, as described earlier, Dr. Evans is a well-known pox virologist whose order might have been fulfilled, even if delayed.

The horsepox virus is not listed as a biological select agent and toxin and, consequently, does not fall under the oversight of the Federal Select Agent Program (42 USC 73 and 9 USC 121).[28] Similarly, horsepox virus does not fall under the purview of the US Government Policy for Oversight of Life Sciences Dual Use Research of Concern because the virus is not included in the list of agents specified in the policies.[38] If the research resulted in a virus that was used to harm humans or animals deliberately, the perpetrator could be prosecuted under the Biological Weapons Anti-terrorism Act of 1989, which is the United States' implementing legislation for the Biological and Toxins Weapons Convention.[39]

**5. Technically, the ability to recreate poxvirus is available regardless of whether the use of engineered poxviruses in therapeutics is restricted or not. Given the clear beneficial work that requires these technologies, we strongly object to a moratorium on poxvirus synthesis and to an expansion of the WHO mandate to include the review of additional orthopox synthesis work.**

The synthesis of horsepox virus presents a unique opportunity to convene scientific, industry, policy, and security experts (including pox virologists) to explore the potential dual-use implications of the experiments, assess the potential risks that may be presented, identify risk mitigation options that complement existing review and oversight activities, and examine policy gaps and solutions presented by this experiment. However, we do *not* believe that poxvirus studies should be paused or stopped, because we are concerned that halting them could damage research

and development efforts geared toward preventing infection and/or disease against many pathogens (including HIV and biothreat agents) and destroying tumors.

As seen with the gain-of-function process for influenza research, a moratorium could disincentivize widespread objective and transparent dialogue about the risks of the experiments and may have long-lasting harmful effects on research.[40-45] In the process undertaken by the US government to assess the risks and benefits of the gain-of-function research, those most engaged in the process were affected researchers, their institutions, and vocal objectors to the research. Broader dialogue may not have changed the final analysis, but it may have included different perspectives, raised additional questions, and highlighted other considerations for assessing risk and benefits. (Although policy on gain-of-function pathogens has been issued, the moratorium, begun in 2014, still remains in effect for the affected research in the United States.[46]) We must develop a way of examining the broader implications of particularly concerning research (including identifying approaches for reducing risk) without disrupting the less risky, legitimate, and potentially beneficial efforts of all other research in the field or associated fields. Without such a measured effort, the United States may find itself lagging behind other countries that may not share the same concerns, thus limiting US engagement and thought leadership on these issues internationally.[13,47]

**6. Do we need another smallpox vaccine? If not, incentives for biodefense medical countermeasures should be considered, to make sure that they are aligned with biodefense priorities.**

Five months after WHO learned of the horsepox synthesis experiments, a US-based company, Tonix Pharmaceuticals, issued a press release describing its recent efforts to develop innovative vaccine platforms in collaboration with the principal researcher who synthesized horsepox.[48] This press release states that the company and its academic partners have created a vaccine candidate for smallpox (a material threat in the United States), making the product eligible for the priority review voucher program for medical countermeasures (established in 2016 by the 21st Century Cures Act). Through this program, the Food and Drug Administration (FDA) may provide priority review vouchers for medical countermeasure (MCM) products meeting certain criteria after approval of a material threat application. This program incentivizes companies to develop MCMs against material threats (for which a commercial market does not exist) by providing opportunities to buy down the financial risks of product development for both MCM and other FDA-regulated pharmaceuticals. After a company receives an initial voucher for MCMs, subsequent vouchers can be transferred to other entities. As of this writing, no priority vouchers have been approved.[49]

The work done by Tonix and their academic partners (ie, Dr. Evans) may receive qualification for the priority review voucher, demonstrating the open-ended incentive provided by Cures (and providing direct legitimate justification for the synthesis of horsepox virus).[49] Furthermore, unlike another priority review voucher program for tropical diseases, no guidance has been issued by FDA to clarify specific products that may qualify for the MCM priority review voucher program.[50]

We believe that the creation of horsepox demonstrates the need for dialogue in the biodefense arena about the need for another smallpox vaccine.[51] Should priority be given to products for which products already exist? What level of scientific data is needed to qualify for this program? At what stage in product development would a product qualify? Will biosecurity risk and benefit assessment be required as part of product review? Providing clear responses to these and other questions may reduce the likelihood of incentivizing research that elicits biosecurity concern. We suggest that the FDA provide additional guidance on MCM priorities for the priority voucher program. This guidance could ensure that research with a moderate or high dual-use potential, but little or no promise of benefit, would not continue. Similarly, the guidance could allow for research that holds great promise of benefit to be conducted with appropriate biosafety and biosecurity measures in place. This guidance would need to be crafted carefully, however, to preserve the biosecurity protections that are gained as a result of encouraging biotechnology and pharmaceutical companies to produce vaccines and drugs that are likely to be used only in the event of a biological weapons attack.

The US government also could consider requiring that they be made aware of experiments for developing products that may qualify for the program before the experiments are conducted, which could serve as an important biosecurity mitigation step. Furthermore, the US government could consider establishing a product review process that involves the relevant offices in the Department of Health and Human Services and the Department of Defense to work with researchers and industry early in product development to ensure that all relevant questions are considered and risks mitigated from the outset.

**7. Steps need to be taken regarding gene synthesis screening as a biosecurity control.**

Commercial gene synthesis providers largely are affiliated with the International Gene Synthesis Consortium. Over 80% of the market is encompassed by this worldwide industry group.[20,52] Members of this group, which include GeneArt, the company that synthesized the horsepox DNA, have agreed voluntarily to screen double-stranded DNA (dsDNA) synthesis orders over 200bp to check for matches to regulated pathogens and to screen customers. The ability to use this screening as a biosecurity tool is under threat for a variety of reasons, including technical and corporate challenges.[20,53] Regarding the technical challenges, sequence similarities between horsepox virus and vaccinia

virus may not be sufficiently distinguishable to raise any questions about the orders. In addition, screening orders for embedded sequences (eg, identical sequences to smallpox virus within a context of horsepox sequence) may be challenging based on published information about the sequence similarities of orthopoxviruses. These challenges apply to orders on most other viruses. Regarding the corporate challenges, the costs of screening are high and, as the cost of DNA synthesis goes down, will become a significant portion of the operating cost for DNA synthesis providers.

Screening is not a perfect solution to DNA synthesis challenges, simply because multiple methods can be used to genetically modify an existing pathogen, which can increase its biosecurity risk, or to use a personal DNA synthesizer to make the desired genetic material. Nonetheless, tangible actions could be taken to preserve the effectiveness of DNA order screening as a security tool and to develop additional mechanisms to increase the safety and security of DNA synthesis challenges.[20] The United States could pursue developing a more refined database for screening, contributing to the costs that companies incur for screening, or expanding the range of companies that perform screening, among other policy options.[20]

## Conclusions

The possibility of synthesis of an orthopoxvirus has been assumed since the polio virus synthesis in 2002. Indeed, after the synthesis and "booting up" of the much larger bacterium by the researchers at the J. Craig Venter Institute in 2010, the probability that it could be achieved was not in doubt.[54-57] The recent horsepox virus synthesis experiment provides a "proof of concept" for that assumption, generating timely and important biosecurity concerns. Expertise still is required for successfully conducting the experiment, which was not fully emphasized in the WHO advisory committee report and in the press coverage. Further, scientific discussions about the sequence homologies of orthopoxviruses and the legitimate uses of such viruses in research need to be taken into account in biosecurity policy discussions to ensure that real and perceived benefit and risk are appropriately weighed. Existing US and international policies governing smallpox should be evaluated in light of the horsepox synthesis experiments. But these evaluations should not lead to the addition of biological agents onto existing control lists or restricting technologies that have wider uses than pathogen research. Instead, they should focus on the direct and long-term consequences (both beneficial and risk-based) of the research and feasible approaches for reducing risks and harnessing the benefits.

These policy suggestions do not suggest that the horsepox experiment is necessarily a biosecurity risk. Rather, the experiments highlight policy gaps and challenges that were previously thought to have been addressed. One challenge we allude to in this article is the need for responsibility in communication about scientific results to ensure that inaccurate or inflammatory statements do not cloud the analysis of the dual-use potential of research. The biosecurity dialogue could focus more on the policy challenges, feasible risks, and feasibility of benefit rather than propagating alarmist statements. Furthermore, biodefense incentives, such as the priority review voucher program for MCMs established by the 21st Century Cures Act, may need to be refined to ensure that biosecurity risks are addressed while helping to make biodefense vaccines and drugs available. Finally, as part of our biosecurity efforts, we must also encourage and enable scientists to participate actively in safeguarding their fields from irresponsible to illicit actions.

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