De novo synthesis of pathogenic viruses: Ethical challenges

By Samuel Zhang

AUTHOR BIO

Samuel Zhang is a sophomore at Harker Upper School in San Jose, California, and a dedicated player on the boys varsity golf team. Outside of academics and athletics, he pursues his passion for biology with a special interest in viruses, dedicating part of his time to independent study and research. Samuel is particularly fascinated by the ethical challenges surrounding the reconstruction of viruses and other pathogens through synthetic biology. He hopes to further his research in this area, exploring both the scientific possibilities and the potential risks involved in artificially engineering diseases. Samuel aspires to contribute to discussions on biosecurity, ethics, and responsible innovation in the life sciences.

ABSTRACT

The rapid advancements in synthetic biology have enabled the de novo synthesis of various viral genomes, raising concerns about the potential risks associated with artificially engineered viruses. Notable examples, such as the laboratory synthesis of poliovirus and horsepox virus, have demonstrated the feasibility of reconstructing infectious agents from genetic sequences. While these developments offer significant benefits in vaccine production and therapeutic research, they also present serious biosecurity and public health risks. The ability to recreate eradicated or highly virulent pathogens, such as smallpox, poses a particular threat, as accidental release or deliberate misuse could have devastating consequences. Additionally, the engineering of viruses like monkeypox raises concerns about unintended mutations and the potential for increased transmissibility or virulence. This paper examines the risks associated with artificial synthesis of viral pathogens, as well as ethical considerations, regulatory challenges, and the need for stringent oversight to prevent the misuse of this powerful technology.

Keywords**:** *de novo synthesis, poliovirus, horsepox, smallpox, monkeypox, synthetic biology, bioterrorism, science policy*

INTRODUCTION

Synthetic biology, a field that combines engineering principles with biology, has the potential to revolutionize many industries including healthcare, agriculture and energy. Central to this field is DNA synthesis, the ability to create custom DNA sequences in a lab. The advantages of synthetic biology and DNA synthesis are numerous. The technology allows scientists to design and create new organisms, or modify existing ones, for specific purposes, such as producing medicine or breaking down environmental pollutants. It also speeds up the process of genetic engineering by eliminating the need to use traditional methods of modifying DNA. However, the rapid pace of progress in this field has also raised ethical concerns. Synthetic biology and DNA synthesis have the potential to create new and powerful technologies that can benefit society, but they also come with significant risks. One major concern is the possibility of creating harmful or uncontrollable pathogenic organisms through the manipulation of DNA. This could lead to accidental releases of synthetic organisms into the environment, causing ecological damage or even potential pandemics.

Additionally, the ability to create synthetic DNA sequences also raises ethical concerns, as it opens the door for potential misuse and abuse by individuals or organizations with malicious intentions. Synthetic biology can be an enabling tool for bioterrorism. Therefore, it is crucial that strict regulations and safety protocols are in place to mitigate these dangers and ensure responsible use of synthetic biology and DNA synthesis. This paper will describe two specific cases of re-creation of a pathogen, namely the 2002 de novo synthesis of poliovirus and the 2017 de novo synthesis of horsepox virus, and discuss the ethical and moral challenges of this research.

THE RE-CREATION OF POLIOVIRUS

One of the most infamous pathogens in history is poliovirus. Poliovirus is a highly infectious virus that primarily affects young children and can cause paralysis. It is a single-stranded RNA virus that belongs to the family of Picornaviridae (Figures 1 and 2). The virus was first identified in 1908 by Austrian scientist Karl Landsteiner, but it was not until the 1950s that the three distinct types of poliovirus were discovered (Wolbert, Rajnik, and Higginbotham, 2024). However, the poliovirus is theorized to have appeared thousands of years ago in ancient egypt. Evidence of this claim is shown in an Egyptian stele portraying a priest with a withered leg.

In the first half of the 20th century, polio outbreaks were a major public health concern, leading to the development of the polio vaccine in the 1950s. Up to 5% of cases lead to paralysis, and up to 40% of polio survivors develop a post polio syndrome (Wolbert, Rajnik, and Higginbotham, 2024). Paralysis usually happens in the spinal cord, and causes the nerves on multiple limbs to shut down. There are three types of wild poliovirus: type 1, type 2, and type (Wolbert, Rajnik, and Higginbotham, 2024). Wild poliovirus 1 was the main cause for most of the world's paralytic polio cases until vaccines became widespread. Type 2 wild poliovirus was declared eradicated in September 2015 (U.S. National Authority for Containment of Poliovirus, 2024). The last detection was in India in 1999 (U.S. National Authority for Containment of Poliovirus, 2024). Type wild poliovirus was declared eradicated in October 2019 (U.S. National Authority for Containment of Poliovirus, 2024). Thanks to widespread vaccination efforts, poliovirus has been eliminated from most parts of the world.

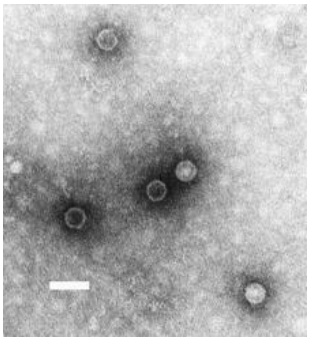

Fig. 1: Electron micrographs of poliovirus (U.S. Environmental Protection Agency)

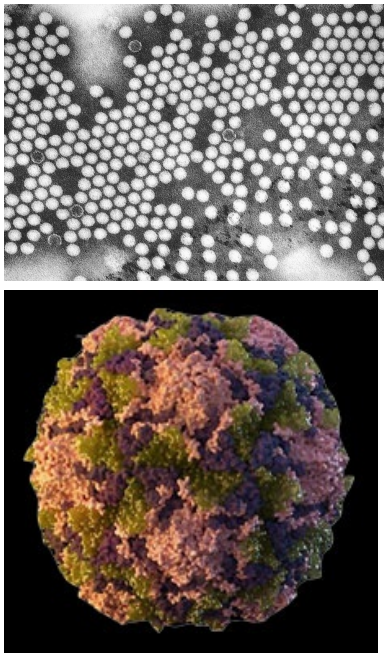

Figure 2: Electron micrograph of polioviruses and three-dimensional visualization of a single poliovirus (U.S. Centers for Disease Control & Prevention).

The development of poliovirus vaccines demonstrates the difficulty and danger involved in combating pathogens. A vaccine is defined as a substance used to stimulate immunity to a particular disease or pathogen, such as against viruses. The oral polio vaccine (OPV) is actually a weakened form of the poliovirus, but it has the ability to immunize individuals, so that their immune systems will be mobilized to stop the spread of poliovirus in the body (U.S. National Authority for Containment of Poliovirus, 2024). In the present day, the most commonly used vaccine against poliovirus is the inactivated polio vaccine (IPV). Due to the risks of OPV developing mutations, it can lose its attenuation and cause vaccine-associated paralytic poliovirus (VAPP), especially in individuals with weaker immune systems such as the elderly and those taking immunosuppressive medications or those with immunodeficiency diseases. As seen in the history of the polio epidemic, a pathogen can do an incredible amount of damage before a safe and effective vaccine is developed, and vaccine development is not always a straightforward process. The complexities of the polio vaccine also show that viruses carry the ability to mutate and become more pathogenic.

In 2002, a team of scientists at the State University of New York successfully synthesized the poliovirus from scratch, marking a major breakthrough in the field of virology. The genome of poliovirus is relatively small at 7741 bases, and the researchers accessed the sequence in a public database (Couzin, 2002). The de novo synthesis involved reconstructing the entire genome of the virus using a computer program and then creating the physical virus in a laboratory (Couzin, 2002).

The team's success demonstrated the potential for creating viruses without the need for natural samples, which could have significant implications for both scientific research and bioterrorism prevention. Virologists Jeronimo Cello, Aniko Paul, and Eckard Wimmer of the State University of New York, Stony Brook, built an almost perfect replica of the virus by reading the publicly available sequence of nucleotides that make up its chemical code (Couzin, 2002). Mice injected with the synthesized virus became paralyzed after about a week, as did animals infected with normal poliovirus (Couzin, 2002). This result suggested that the synthesized poliovirus generated the same pathology as natural poliovirus. The scientists saw the research as a technical achievement, but some were troubled by its implications. "It is a little sobering to see that folks in the chemistry lab can basically create a virus from scratch," says James LeDuc (Couzin, 2002). Later, the researchers said many of their colleagues encouraged them to publish their discovery, but Jeronimo Cello believed it was alerting the authorities of the potential capabilities of bioterrorists (Couzin, 2002).

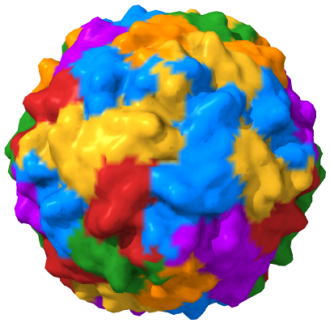

Figure 3: Poliovirus reconstructed from its genetic sequence is indistinguishable from the original, shown here. (U.S. National Institutes of Health)

SMALLPOX AND THE SYNTHESIS OF HORSEPOX

Smallpox is a highly contagious and deadly viral disease caused by the variola virus, which has left a profound mark on human history since the virus emerged thousands of years ago. Characterized by fever, fatigue, and a distinctive rash that evolves into fluid-filled blisters, smallpox spreads rapidly through respiratory droplets and direct contact with infected individuals. Once prevalent across the globe, smallpox claimed the lives of millions, instilling fear and devastation in societies (U.S. Centers for Disease Control and Prevention, 2024). Its most notorious episodes include frequent outbreaks in Europe during the 18th century, where it was responsible for an estimated 400,000 deaths annually, particularly affecting children. The disease's significance extends beyond its immediate health impacts; it played a crucial role in shaping public health policies and sparked pioneering vaccination efforts. In 1796, Edward Jenner's groundbreaking discovery of the smallpox vaccine marked the beginning of an extensive global campaign that eventually led to the disease's eradication in 1980, making smallpox the first human disease to be completely wiped out through vaccination (U.S. Centers for Disease Control and Prevention, 2024).

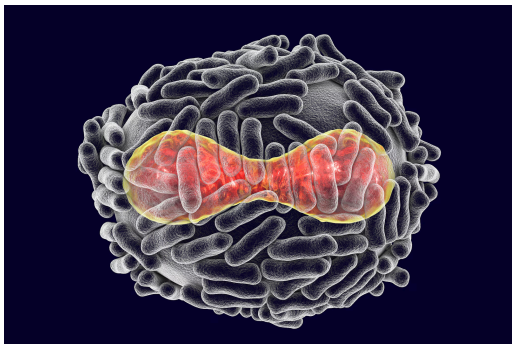

Figure 4: Variola, the virus that causes smallpox (U.S. Centers for Disease Control and Prevention)

Similarly, horsepox is a viral disease caused by the horsepox virus, a member of the Orthopoxvirus family, which is closely related to its famous cousin, smallpox. This disease primarily affects horses but can also pose a risk to other equine species. Characterized by fever, lesions, and pustules on the skin, horsepox has historically been a concern for horse populations worldwide. Although the horsepox virus isn't known to be harmful to humans, in 2016, a group led by virologist David Evans of the University of Alberta in Edmonton, Canada, says it has synthesized the horsepox virus from genetic pieces ordered in the mail. Like smallpox, horsepox is believed to no longer exist in nature; nor is it seen as a major agricultural threat (Kupferschmidt, 2017).

But the technique Evans applied could be used to recreate smallpox, a horrific disease that was declared eradicated in 1980. "No question. If it's possible with horsepox, it's possible with smallpox," says virologist Gerd Sutter of Ludwig Maximilians University in Munich, Germany (Kupferschmidt, 2017). Evans hopes the research—most of which was done by research associate Ryan Noyce—will help unravel the origins of a centuries-old smallpox vaccine and lead to new, better vaccines or even cancer therapeutics. Evans' research can be considered as a dual-use research technique [6], where his findings and resources could lead to both positive and negative effects.

Like previous poliovirus reconstitutions, the work done by Evans is raising troubling questions about how terrorists or rogue states could use modern biotechnology to wreak destruction. Given that backdrop, the study marks "an important milestone, a proof of concept of what can be done with viral synthesis," says bioethicist Nicholas Evans (not related to David Evans) of the University of Massachusetts in Lowell (Kupferschmidt, 2017). In this light, Evans' technology not only classify as dual-use research, but also as dual-use research of concern, defined by the National Institutes of Health as scientific research that can 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." Furthermore, the practice of such research is supervised by the Dual Use Research of Concern Institutional Review Entity (DURC-IRE), which monitors DURC (Dual Use Research of Concern) including PPP (Pathogen of Pandemic Potential) research (U.S. National Institutes of Health, 2023). The responsibilities of this organization include the oversight of experiments and synthesis of viruses (U.S. National Institutes of Health, 2023). While the engineering synthesis of a virus like horsepox can be utilized for bioweapons, it also gives the possibility of developing new and improved vaccines to help the human immune system destroy cancer cells.

THE RE-EMERGENCE OF THE MONKEYPOX VIRUS

Monkeypox is a viral zoonotic disease caused by the monkeypox (Mpox) virus, also a member of the Orthopoxvirus genus. Monkeypox was first identified in 1958 among monkeys shipped from Singapore to Denmark (Mitija et al., 2023). During the following decade, several outbreaks were reported in captive monkeys in the USA, the Netherlands, and France (Mitija et al., 2023). The first case of monkeypox infection in humans was reported in 1970 in the Democratic Republic of the Congo in a 9-month old boy who was the only member of his family without a smallpox vaccination. Human infections were initially rare, often resulting from direct contact with infected animals or through contaminated objects. After the first human case, more outbreaks were reported in countries in west and central Africa, mainly among children in rural, rainforest areas (Mitija et al., 2023). Children in such areas are likely to have limited access to healthcare, as well as substandard sanitation conditions. In addition, sporadic clusters and cases of human monkeypox have also occurred outside of Africa. Monkeypox generated some international attention in 2003, when 71 human cases were reported in the USA (Mitija et al., 2023).

In 2003, Gambian giant rats imported from Ghana infected cohabitant prairie dogs sold as household pets in the Midwestern United States (Mitija et al., 2023). This resulted in fifty-three human cases of Mpox. Between 1981 and 2017, the virus spread rapidly in the Democratic Republic of the Congo, with extremely high fatality rates (1-12%) (Mitija et al., 2023). Additionally, a global outbreak of a new monkeypox virus variant, clade 2b, affected countries worldwide such as in Europe and Asia. This led to the declaration of a Public Health Emergency of International Concern and by November 2022, more than 78,000 cases in over 100 countries had been reported (Mitija et al., 2023). Early symptoms may include fever, headache, muscle aches, backache, swollen lymph nodes, chills, and fatigue. Next, the most well-known feature of monkeypox is the appearance of a rash, which begins one to three days after fever onset. The rash usually progresses through several stages, starting as macules (flat, discolored spots), evolving into papules (raised bumps), then vesicles (small fluid-filled blisters), and ultimately forming pustules (pus-filled lesions) before crusting and healing (Mitija et al., 2023).

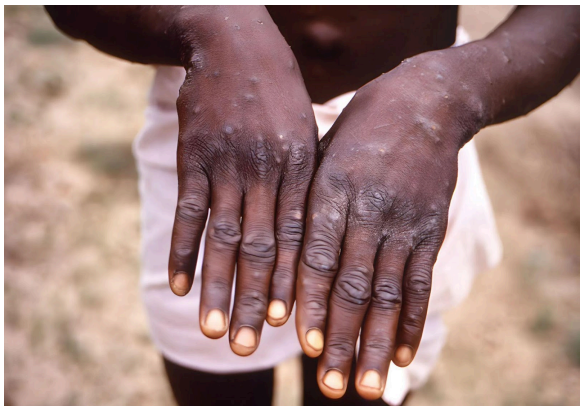

Figure 5: A patient with Mpox in 1997 in the Democratic Republic of Congo (U.S. Centers for Disease Control and Prevention)

Two main clades of the monkeypox virus have so far been identified in different regions of Africa. Clade 1 (which has fatality rates of 1-12%) is usually responsible for disease in central Africa and the Congo Basin, whereas clade 2 (which is less deadly, with case fatality rates less than 1%) is mostly found in West Africa (Mitija et al., 2023). A new B.1 lineage of monkeypox, classified as clade 2b for its close relationship to clade 2, has been identified in the 2022 global outbreak (Mitija et al., 2023). This new lineage is also associated with strains circulating Nigeria during the 2017 outbreak, and its mutation rates are 6-12 times higher than previously expected, much greater than both clade 1 and clade 2 (Mitija et al., 2023). There is evidence of a new clade emerging in the present outbreak (Moore, Rathish, and Zahra, 2023). The reemergence of monkeypox, with the development of new clades, raises the riskiness of synthesizing related viruses such as horsepox.

CONCLUSION

The synthesis of known pathogenic viruses, such as poliovirus and horsepox virus, raises ethical concerns about the potential misuse of this technology. By creating a virus from scratch, scientists have essentially provided a blueprint for bioterrorism and the potential for deliberate release of a highly infectious and deadly disease. For example, the new re-creation of the poliovirus has received mixed opinions regarding public safety and scientific value at the same time. Moreover, the re-creation of the horsepox virus raises the threat of new outbreaks of related viruses including smallpox and monkeypox. The trust between government entities and science facilities serves as a cornerstone for progress. As science advances at an unprecedented pace, governments and scientific entities, including universities and research institutes, must work together to address ethical concerns and the social implications of new technologies. This crucial bond between government and science enables governments to allocate funding and provide oversight, ensuring that research aligns with societal needs and addresses pressing challenges. Conversely, science facilities rely on government support to maintain cutting-edge infrastructure, attract top talent, and facilitate groundbreaking discoveries.

REFERENCES

J. G.Wolbert, K. Higginbotham (2020). *Poliomyelitis (Polio)*. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK558944/

U.S. Centers for Disease Control and Prevention. (2024, October 15). *Polio Disease and Poliovirus Containment*. U.S. National Authority for Containment of Poliovirus. https://www.cdc.gov/poliovirus-containment/diseaseandvirus/index.html

J. Couzin "Active poliovirus baked from scratch." (2002): 174-175 K. Kupferschmidt. “How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA.” July, 2017

U.S. Centers for Disease Control and Prevention. (2024, October 22). *What is Smallpox?* Centers for Disease Control and Prevention. https://www.cdc.gov/smallpox/about/index.htm

“Dual-Use Research, NIH Office of Intramural Research.” *Oir.nih.gov*, Oct 11 2023,

oir.nih.gov/sourcebook/ethical-conduct/special-research-considerations/dual-use-research.

M. J. Moore, B. Rathish, F. Zahra, “Mpox (Monkeypox).” *Nih.gov*, StatPearls Publishing, 3 May 2023, www.ncbi.nlm.nih.gov/sites/books/NBK574519/

O. Mitija, D. Ogoina, B. K. Titanji, et al. “Monkeypox.” *The Lancet* vol. 401, U.S. National Library of Medicine, 7 Jan. 2023, pmc.ncbi.nlm.nih.gov/articles/PMC9671644/