"Salk vs. Sabin - non-live and attenuated virus vaccines: The past, present, and future of an old debate"

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INTRODUCTION

In July 2022, an unvaccinated young adult from Rockland Country, New York was diagnosed of poliomyelitis (Chakraborty, 2022). The incident case in Rockland County, New York, a first in the United States in decades, raised alarms and a state of emergency was declared after poliovirus was found in wastewater across five countries (Chakraborty, 2022).

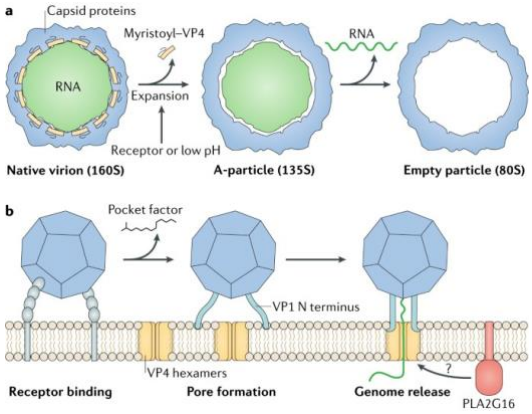
Dr. Leana Wen, a medical analyst at CNN and health policy professor at George Washington University, suggested two possible sources of the virus: either an infected individual or a viral shedding from tourists who received the oral poliomyelitis vaccine (OPV) (Chakraborty, 2022). The re-emergence of the virus raised important questions about the continued use of OPV and the future of oral vaccines.

How Polio Works

Poliovirus is a single RNA strand encased in a 20-sided protein shell made of four viral proteins (VP1, VP2, VP3, VP4), which protect its genetic material (Martín, 2016). Poliovirus transitions through three key forms during infection. In the gut, the virus exists in its infectious, 160S native form, a dynamic structure that transiently exposes its VP terminals through expansions, a motion akin to breathing. When environmental triggers such as receptor binding or low pH occur, the virus stabilizes into the expanded 135S form, forming the altered particle (A-particle). At this stage, the VP1 terminal is irreversibly exposed, allowing the virus to anchor to the cell membrane and release its RNA through hexameric pores formed by myristoyl–VP4. The final stage of the virus is the 80S particle, an empty, non-infectious shell. (Figure 1) (Baggin, 2018)

Figure 1

Poliomyelitis transition states during uncoating and insertion of genetic material

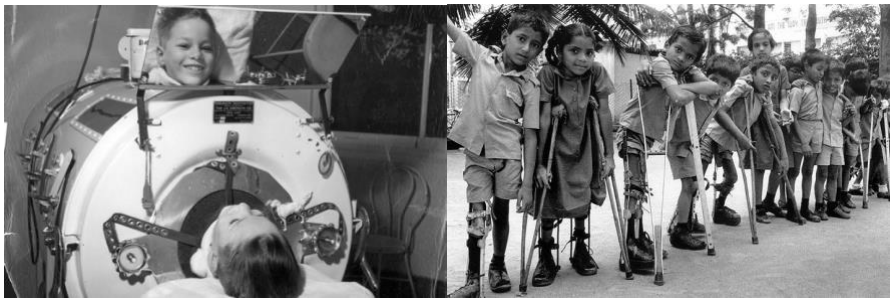


From Baggin, 2018

The virus primarily replicates in the gut before spreading to other areas, including the central nervous system (Martín, 2016). Poliovirus causes poliomyelitis, with mild symptoms ranging from fever and sore throat to severe cases involving neck stiffness and paralysis.(Figure 2)

Figure 2

American children with poliomyelitis



From Science museum, 2018

In 1952 poliomyelitis reached a peak of 57,628 cases in the United States. a) "Iron Lung" Acute poliomyelitis infection caused chest muscle paralysis. Philip Drinker and Louis Agassiz Shaw invented the "iron lung," a negative pressure cabinet with a bellow to support breathing. b) Poliovirus infected children experience muscle weakness and atrophy, severe cases caused lower body paralysis

INVENTION OF IPV AND OPV

In 1954, Jonas Salk, an American virologist at the University of Pittsburgh, developed the first poliomyelitis vaccine, the inactivated poliomyelitis vaccine (IPV) with funding from the March of Dimes, the first Polio social movement campaign (Marks, 2011). IPV used a virus treated with formalin to eliminate infectivity while triggering a protective immune response. (Figure 3a) In the 1960s, IPV was replaced by the OPV, developed by Albert Sabin, which became central to the World Health Organization's global

vaccination efforts (Orsini et al., 2022). (Figure 3b) However, after the eradication of poliomyelitis in the U.S. in 1994, OPV use was discontinued domestically.

Figure 3

Salk vs. Sabine

From (Vela Ramirez, J. E., et al. 2017)
Times magazine featuring Dr. Jonas Salk and the inactivated polio vaccine (IPV) (Latson, J., 2015). One of the fastest and largest clinical trials in history. IPV was demonstrated as safe except for the Cutter Incident, where a batch of the virus was inappropriately attenuated. (left) (right) Dr. Albert B Sabin and the oral polio vaccine (OPV) (Polio Place., n.d.). Easy to manufacture, distribute and store. Still used in developing countries, although known to occasionally mutate back into the native, pathogenic poliovirus, harboring risks of vaccine induced polio (circulating vaccine-derived poliovirus (cVDPV)) (right)

Why OPV?

The preferences for OPV over IPV are apparent. IPV is generally preferred for its safety but producing it in large quantities with consistent quality is challenging. In contrast, OPV is easier to store, administer, and more cost-effective, making it ideal for widespread use in developing countries. The OPV distribution in China exemplifies this approach.

In addition to being cost-effective, OPV was preferred for its ability to induce a strong immune response. Unlike the IPV, which uses a non-live virus, OPV uses a weakened form of the poliovirus, directly targeting areas like the Peyer's patches, where antigens are transported by M cells across the intestinal lining and presented to immune cells to trigger a response (Vela Ramirez, 2017). Additionally, OPV offers the advantage of viral shedding, allowing the spread of attenuated virus from vaccinated individuals to others, thereby promoting broader community protection (Martín, 2016).

RACE AGAINST THE CLOCK

In 1955, a poliomyelitis outbreak struck Nantong, China, infecting 1,680 children and resulting in 446 deaths within a year (NA, 2020). The virus quickly spread to several major cities, including Qingdao, Shanghai, Nanning,

and Jinan, causing widespread fear as most doctors had never encountered such cases and were unsure how to treat them. The turning point came in 1957 when Chinese virologist Fangzhou Gu returned from the Soviet Union, where he had observed the large-scale testing of Sabin's OPV.

At the time of Gu's return, IPV was known to be effective against poliovirus and could be produced directly where OPV faced many uncertainties and potential side effects. Yet given China's limited vaccine production capacity and medical literacy of voluntary health workers in the 1950s, Gu chose to focus his efforts on researching OPV.

In the 1960s, Gu completed the three-phase clinical trial for OPV and distributed it across major Chinese cities. To address long-term storage issues in remote and temperate regions, he converted OPV into sugar pills. This solution was pivotal in China's fight against poliomyelitis, leading to its eradication by 2000, a milestone marked by Dr. Gu signing the WHO certification (Xinhuanet, 2019). Today, 150 countries still use OPV, with half of these countries procuring bivalent OPV (bOPV) from UNICEF, a modified vaccine that provides immunity against poliovirus serotypes, a classification of viral surface antigen markers, 1 and 3, but not serotype 2.

Danger of Reversion

However, due to these mechanisms, the widespread use of OPV may risk recreating a poliovirus epidemic. OPV's mechanism makes the virus prone to mutation; a single mutation in the attenuated virus can restore its infectivity. Mutations in the attenuated virus have also led to localized outbreaks. Between 2016 and 2023, 273 wild poliovirus 1 (WPV1) and 1,818 cases of vaccine-derived poliovirus (cVDPV) were reported, with most cases in two endemic countries Afghanistan, Pakistan, (Yeh et al., 2023). This raises the question: is there a way to maintain the strong immunogenicity of oral vaccines while ensuring their safety?

Chimeric vaccines

To address this, many countries today administer a combination of bOPV (types 1 and 3) and IPV (types 1, 2, and 3) to mitigate the harmful effects of OPV. Since the development of novel oral poliovirus type 2 OPV (nOPV2), a type 2 vaccine authorized by the WHO in June 2023, two new nOPV vaccines have been re-engineered to target types 1 and 3 (Yeh et al., 2023). These chimeric viruses, which combine genetic material from two or more viruses, retain the robust genetic stability and immunogenicity of nOPV2.

Looking beyond poliomyelitis, utilizing the unique replication mechanisms of poliovirus, researchers are exploring novel oncolytic viral therapies. To treat Glioblastoma multiforme (GBM), a main contributor to primary malignant brain tumor-related death in humans, researchers engineered oncolytic poliovirus to destroy cancer cells and activate host immune system through

the production of viral 2A protease (2Apro), a breakthrough in viral therapies. (Dighe, O. R et.al., 2023)

FUTURE OF AN OLD DEBATE

The call to eliminate the use of OPV is strong, yet the transition to IPV requires the collaborative effort of many. The Global Polio Eradication Initiative (GPEI) launched the Polio Eradication and Endgame Strategic Plan aimed to eradicate Polio by 2018, the goal is to establish national wide campaigns, promote bOPV and IPV delivery and strengthen national survey and certification for vaccinated individuals. However, the plan was revised to eradicate by 2023 then further revised to prolong the campaign to 2026. (GPEI, 2020) In 2024, 190 cases of cVDPV have been reported, including a first case in Gaza in 25 years.

On the journey to eradicate poliomyelitis, we've come a long way since the March of Dimes campaign. Efforts of eradicating poliomyelitis marked the milestone of the collaboration of scientists, international healthcare agencies, foundations and governments worldwide. While there is no cure for poliomyelitis, treatments exist to alleviate the paralytic effects of poliomyelitis. However, with new cases emerging, it is essential to continue seeking new ways to optimize existing vaccines, storage methods and distribution to otherwise remote districts.

Eradication does not mean extinction. The future of poliomyelitis requires the continued collaboration of all.

REFERENCE

Baggen, J., Thibaut, H. J., Strating, J. R. P. M., et al. (2018). The life cycle of non-polio enteroviruses and how to target it. Nature Reviews Microbiology, 16, 368–381. https://doi.org/10.1038/s41579-018-0005-4

Chakraborty, D. (2022, September 16). Polio has reemerged in the US. Who should get a polio vaccine now? CNN。 https://www.cnn.com/2022/09/15/health/polio-paralysis-vaccine-healthwellness/index.html#%3A~%3Atext%3DIn%20rare%20circumstances%2C%20the%20weakened%2Clonger%20used%20in%20the%20US

Dighe, O. R., Korde, P., Bisen, Y. T., Iratwar, S., Kesharwani, A., Vardhan, S., & Singh, A. (2023). Emerging Recombinant Oncolytic Poliovirus Therapies Against Malignant Glioma: A Review. *Cureus*, *15*(1), e34028. https://doi.org/10.7759/cureus.34028

Ehrenfeld, E., Modlin, J., & Chumakov, K. (2009). Future of polio vaccines. Expert review of vaccines, 8(7), 899–905. https://doi.org/10.1586/erv.09.49

GPEI. (2020) "Polio Endgame Strategy." *GPEI*, polioeradication.org/who-we-are/polio-endgame-strategy-2019-2023/.

Latson, J. (2015, February 23). Vaccine history: Everyone wanted the salk polio vaccine. Time. https://time.com/3714090/salk-vaccine-history/

Martín, J. (2016). Poliovirus: Methods and protocols. Humana Press: Springer. Marks, H. M. (2011). The 1954 Salk poliomyelitis vaccine field trial. Clinical Trials, 8(2), 224–234. https://doi.org/10.1177/1740774511399110

Orsini, D., & Martini, M. (2022). Albert Bruce Sabin: The man who made the oral polio vaccine. Emerging Infectious Diseases, 28(3), 743–746. https://doi.org/10.3201/eid2803.204699

Polio Place. (n.d.). Polio place. Albert B. Sabin, MD | Post Polio: Polio Place. https://www.polioplace.org/people/albert-b-sabin-md

Ray, S., Narayanan, A., Vesterbacka, J., et al. (2023). Impact of the gut microbiome on immunological responses to COVID-19 vaccination in healthy controls and people living with HIV. npj Biofilms and Microbiomes, 9(104). https://doi.org/10.1038/s41522-023-00461-w

Science Museum. (2018). Iron lung. Science Museum Group. https://www.sciencemuseum.org.uk/objects-and-stories/medicine/iron-lung

The Doherty Institute. (2024) "World Polio Day 2024: A Challenging Year

for Global Eradication." The Doherty Institute, www.doherty.edu.au/news-events/news/world-polio-day-2024-a-challenging-year-for-global-eradication#:~:text=In%202024%2C%20190%20cases%20associated,a%20threat%20to%20children%20everywhere.

Vela Ramirez, J. E., et al. (2017). Current state and challenges in developing oral vaccines. Advanced Drug Delivery Reviews, 114, 116–131. https://doi.org/10.1016/j.addr.2017.04.008

XinhuaNet. (2019, April 7). "糖丸爷爷"顾方舟：一生做一事 让中国儿童乘上远离脊灰的方舟. http://www.xinhuanet.com/politics/2019-01/07/c_1123958677.htm.

Yeh, M. T., Smith, M., Carlyle, S., et al. (2023). Genetic stabilization of attenuated oral vaccines against poliovirus types 1 and 3. Nature, 619, 135–142. https://doi.org/10.1038/s41586-023-06212-3

Zambon, M., & Martin, J. (2018). Polio eradication: next steps and future challenges. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, *23*(47), 1800625. https://doi.org/10.2807/1560-7917.ES.2018.23.47.1800625

Zimmermann, P. (2023). The immunological interplay between vaccination and the intestinal microbiota. npj Vaccines, 8(24). https://doi.org/10.1038/s41541-023-00627-9

中国科学院遗传与发育生物学研究所. (2020, April 15). 专题_弘扬科学家精神. http://www.genetics.cas.cn/dqyd/ztzl/hykxjjs/202004/t20200421_5557367.html