ITPC

make medicines affordable
END UNFAIR MONOPOLIES

EVERGREENING DURING AN EMERGENCY

Patent and Clinical Landscapes for Mpox Vaccines and Potential Treatments

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ABOUT ITPC

ITPC Global is a global coalition of people living with HIV and community activists, working to achieve universal access to optimal HIV, HCV and TB treatment for those in need. Formed in 2003 by a group of 125 HIV activists from 65 countries at a meeting in Cape Town, ITPC actively advocates for treatment access in eight regions across the globe. ITPC believes that the fight for treatment remains one of the most significant global social justice issues. ITPC actively advocates for treatment access through three strategic focus areas:

- **#MakeMedicinesAffordable**
- **#WatchWhatMatters**
- **#BuildResilientCommunities**

To learn more about ITPC and our work, visit itpcglobal.org.

ABOUT MAKE MEDICINES AFFORDABLE

The Make Medicines Affordable (MMA) consortium works under the Solidarity Project to bring down the prices of HIV, TB, hepatitis C, cervical cancer, COVID-19 vaccines and medicines by removing intellectual property (IP) and other access barriers. The MMA consortium is led by civil society organizations from 24 countries. They include people living with HIV, lawyers, health experts and activists, all choosing to challenge the IP measures that benefit profit but not people.

ACKNOWLEDGEMENTS

This report was written by Tracy Swan, María Lorena Bacigalupo, Gabriela Costa Chaves, María Florencia Pignataro and Carolinne Thays Scopel, with support from ITPC staff Othoman Mellouk, Sergiy Kondratyuk, and Morgane Ahmar

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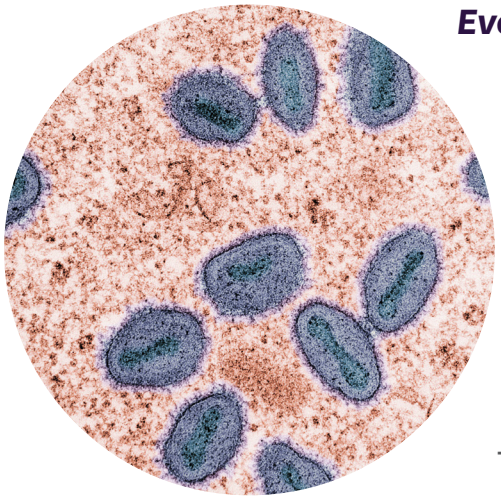
ABBREVIATIONS

API	active pharmaceutical ingredients
ART	antiretroviral therapy
BARDA	Biomedical Advanced Research and Development Authority
BN	Bavarian Nordic
CDC	Center(s) for Disease Control
CEF	Chick embryo fibroblast
CEPI	Coalition for Epidemic Preparedness Innovations
CHO	Chinese hamster ovary
CVA	Chorioallantois Vaccinia Virus Ankara
DRC	Democratic Republic of Congo
ECACC	European Collection of Cell Cultures
EGF	Epidermal Growth Factor
EMA	European Medicines Agency
EPO	European Patent Office
EUL	emergency use listing
EVS	extracellular virions
GSK	GlaxoSmithKline
HERA	Health Emergency Preparedness and Response Authority
HIC	high-income country
IND	investigational new drug
IP	intellectual property
LMIC	low- and middle-income country
LNP	lipid nanoparticle
LPCs	large plaque-forming clones
MVs	mature virions
MVA	Modified Vaccinia Ankara
MVA-BN	Modified Vaccinia Ankara- Bavarian Nordic
NIAID	National Institute on Allergy and Infectious Diseases
NIH	National Institutes of Health
PCT	Patent Cooperation Treaty
PRK	primary rabbit kidney
PHEIC	public health emergency of international concern
PLHIV	people living with HIV
PPE	personal protective equipment
R & D	research and development
RSV	respiratory syncytial virus
SII	Serum Institute of India
SPF	specific pathogen-free
UK	United Kingdom
US	United States
USAID	U.S. Agency for International Development
US FDA	United States Food and Drug Administration
VIGIV	Vaccinia Immune Globulin Intravenous
WHO	World Health Organization

ABOUT THIS REPORT



Evergreening During an Emergency was developed as a resource for people working to expand access to mpox vaccines and treatment. It includes a holistic view of the harmful impact of patents on healthcare systems, a description of mpox clades, transmission, prevention, natural history, care and treatment, clinical characteristics, development history and patent landscapes for mpox vaccines and treatment.

The report includes an overview of clinical evidence for, and access challenges to certain approved and experimental mpox vaccines and therapeutics. Currently, two vaccines, MVA-BN and LC16m8, are included in the WHO Emergency Use Listing, while clinical evidence on mpox treatment candidates is limited.

Previous analysis[1, 2, 3] on access challenges for mpox technologies covered issues related to production, prices, United States (US) patents, availability, regulatory issues and clinical intelligence. This report complements these analyses with additional data on Patent Cooperation Treaty (PCT) applications for vaccines and therapeutics, including background information about the institutions and companies involved in their development and judicial disputes involving their patents and trade secrets.

[1] https://www.citizen.org/wp-content/uploads/Ramping-up-MPX-vaccine-production-Oct-31-final.pdf
[2] https://www.citizen.org/article/mpox-vaccine-access/
[3] https://twn.my/files/20241204_Charting%20Mpox%20Timeline%20%282%29.pdf

EXECUTIVE SUMMARY

The ongoing mpox public health emergency of international concern, initially declared in August 2024, and which continued until September 2025,[4] has again exposed the failure of the global response to health inequity. The defunding and dismantling of USAID underscores the importance and urgency of removing intellectual property (IP) and other barriers, and measures to enable local production of affordable health products in low-and middle-income countries (LMIC).

Mpox continues to spread within and beyond Africa, yet the global public health response has been sluggish – and stingy. In August 2024, the Africa CDC called for 10 million mpox vaccines, yet only 1,137,000 mpox vaccines were allocated to African countries as of March 2025, through the Access and Allocation Mechanism (a collaboration of the Africa Centers for Disease Control and Prevention, the Coalition for Epidemic Preparedness, Gavi, the Vaccine Alliance, UNICEF and the World Health Organization).[5]

Only four companies lead the mpox space: Bavarian Nordic (the MVA-BN mpox vaccine); Siga Therapeutics (tecovirimat and mpox monoclonal antibody candidates); Emergent Biosolutions (the ACAM2000 smallpox vaccine, brincidofovir, vaccinia virus immune globulin), and KM Biologics (the LC16m8 mpox vaccine). Otherwise, save for mRNA mpox vaccine candidates from BioNTech and Moderna and a USD 3.8 million grant from the National Institutes of Health to two universities for developing mpox antivirals,[6] the pipeline is bare.

The monopoly on mpox vaccines has led to supply shortages and high prices. As with COVID-19 vaccines, high-income countries have been hoarding and stockpiling vaccines (rather than sending them where they are needed to prevent illness and death), while single suppliers cannot meet demand for mpox vaccines.

The monopoly on mpox vaccines has led to supply shortages and high prices. As with COVID-19 vaccines, high-income countries have been hoarding and stockpiling vaccines.

Bavarian Nordic's MVA-BN vaccine is recommended by the World Health Organization (WHO) for mpox; it is the safest mpox vaccine, since it does not rely on a replicating virus, but it is not currently recommended for use in children under age 12 – who are vulnerable to severe illness and death from mpox.

Bavarian Nordic was unable to produce enough mpox vaccines to meet current demand. Although vaccines are now available for purchase in African countries, funding cuts have left governments, UNICEF and other donors without the resources to purchase them.

The company has sought to improve its production capacity – while aiming to prolong its monopoly on the vaccine. Recent PCT applications on the MVA-BN vaccine are focused on newer production processes. Aside from justifying patent evergreening by implementing

[4] https://www.who.int/news/item/09-06-2025-fourth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-upsurge-of-mpox-2024-temporary-recommendations

[5] https://www.who.int/news/item/15-03-2025-the-multi-partner-access-and-allocation-mechanism-allocates-238000-doses-of-mpox-vaccine-to-four-countries

[6] https://www.who.int/news/item/15-03-2025-the-multi-partner-access-and-allocation-mechanism-allocates-238000-doses-of-mpox-vaccine-to-four-countriesmu.edu/2025/01/22/grant-to-develop-mpox-treatment/#:~:text=Researchers%20at%20the%20Texas%20A%26M,that%20creates%20a%20noticeable%20rash

Mpox Vaccines and Potential Treatments – All From Single Suppliers

BAVARIAN NORDIC	KM BIOLOGICS	BIONTECH	MODERNA	SIGA THERAPEUTICS	EMERGENT BIOSOLUTIONS
Vaccine	Vaccine	Vaccine (in development)	Vaccine (in development)	Antiviral, Monoclonal Antibody (in development)	Vaccine, VIGIV

improved production processes and entering into a technology transfer and manufacturing agreement with Serum Institute of India (SII),[8] Bavarian Nordic has done little to meet the urgent need for the vaccine. The agreement enables SII to produce MVA-BN for India's market (which is virtually non-existent) – and to supply Bavarian Nordic with low-cost vaccines for resale, likely at a significant profit. Despite its stated commitment to "...establish partnerships to ensure the equitable access to MVA-BN, including with local African manufacturers,"[9] Bavarian Nordic has not engaged in other technology transfer agreements.

The LC16m8 vaccine is recommended by WHO for mpox. It is the only mpox vaccine approved for children ages one year and above, who are particularly vulnerable to severe illness and death from mpox. LC16m8 contains a weakened form of replicating vaccinia virus and cannot be used safely in people who are pregnant, have certain skin conditions or are immunocompromised, including people living with HIV who have a CD4 cell count of <200 cells/mm^3.

Kaketsuken, which has been designated to produce LC16m8 since 2002, has only filed three PCT applications, between 2007 and 2015 - mostly focused on the production process, including methods of purification. With the approval for mpox in Japan and the inclusion of the vaccine in the WHO Emergency Use listing, it is important to monitor whether newer PCT applications will be filed in the future. So far, there have been no sign of technology transfers for LC16m8.

ACAM2000 was developed to counter bioterrorism, and USFDA approved for smallpox prevention in 2007. It includes a replicating vaccinia virus, so safety issues make it a less desirable option.

Only a few PCT applications were filed between 2002 and 2007; the first ones are related to the virus strains, while the latter are related to broad virus-containing pharmaceutical compositions, covering future technologies, such as components of MVA-BN. In 2017, Emergent Biosciences acquired ACAM2000.[10] The US FDA broadened the vaccine's indication to include mpox in 2024, so it will be important to continue monitoring potential PCT filings related to mpox.

mRNA- based mpox vaccine candidates from BioNTech and Moderna are covered in PCT applications (two from BionNTech and one form Moderna). Countries should monitor national filings of these applications, especially those with manufacturing capacity for vaccines, for opportunities to present patent oppositions.

Although mRNA technologies are based on decades of research and development (R&D), there are multiple patents and multiple players in this space, and, as with COVID-19 vaccines, there are multiple PCT filings from BioNTech and Moderna on mRNA technologies, with even more COVID-19-related applications filed after the pandemic. If this trend continues, it is likely that further applications might be filed, especially if clinical evidence evolves towards a potential market approval for mpox.

[7] https://www.cidrap.umn.edu/mpox/mpox-cases-decline-sierra-leone-africa-faces-shortage-vaccine-funding

[8] https://www.bavarian-nordic.com/media/media/news.aspx?news=7026#:~:text=Bavarian%20Nordic%20Enters%20License%20and,equitable%20access%20to%20vulnerable%20populations.

[9] https://www.seruminstitute.com/press_release_sii_161224.php

[10] https://www.seruminstitute.com/press_release_sii_161224.php

BACKGROUND

"But let me be clear: this is not just an African issue. Mpox is a global threat, a menace that knows no boundaries, no race, no creed. It is a virus that exploits our vulnerabilities, preying on our weakest points. And it is in these moments of vulnerability that we must find our greatest strength and demonstrate that we all learned from COVID by applying solidarity.... the fight against Mpox requires a global response. We need your support, your expertise, and your solidarity. The world cannot afford to turn a blind eye to this crisis."

– DR JEAN KASEYA, DIRECTOR GENERAL, AFRICA CENTRES FOR DISEASE CONTROL (CDC)
ADDIS ABABA, 13 AUGUST 2024

Just like a lie, a virus, such as mpox, can travel halfway around the world before a global public health response gets its boots on. Initially, mpox caused small, flickering outbreaks in rural, sparsely populated areas. Decades after the first case was reported in 1970, reports of sexually transmitted mpox emerged from Nigeria in 2017. By 2022, a global mpox outbreak occurred, triggering the declaration of a public health emergency of international concern (PHEIC).[11] Just two years later, the emergence and rapid spread of a new mpox variant led the World Health Organization (WHO) to declare a second PHEIC, which remained in place until September 2025, when WHO announced it would be lifted as cases in the most affected areas of Africa leveled off or began to decline.[12, 13, 14]

The global response to mpox, particularly from high-income countries (HIC), has been tepid and inadequate, and the defunding of USAID has further weakened it. In 2022, HICs deployed cross-protective smallpox vaccines to counter mpox, but mpox continued to go unaddressed in the low-income countries (LIC), where it has been endemic for decades. Mpox smouldered until 2024, when outbreaks of a highly transmissible variant, clade Ib in the Democratic Republic of Congo (DRC) exploded, and spread to adjoining countries. From 1 January until 6 July 2025, WHO reported 46,589 confirmed cases of, and 189 deaths from mpox among 30 African countries (although the number of suspected cases is far greater, due to lack of access to testing; for example, in 2024, only a third of suspected cases in the DRC were tested).[15]

[11] https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern

[12] https://www.who.int/news/item/14-08-2024-who-director-general-declares-mpox-outbreak-a-public-health-emergency-of-international-concern

[13] https://www.who.int/news/item/09-06-2025-fourth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-upsurge-of-mpox-2024-temporary-recommendations

[14] https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-september-2025

[15] https://worldhealthorg.shinyapps.io/mpx_global/#sec-afr

Mpox Vaccines and Potential Treatments – All From Single Suppliers

BAVARIAN NORDIC	KM BIOLOGICS	BIONTECH	MODERNA	SIGA THERAPEUTICS	EMERGENT BIOSOLUTIONS
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As of July 2025, mpox cases have surged in Sierra Leone (where teams of epidemiologists, communication experts and field responders have been sent to address nearly 4,000 cases, which have been reported since the beginning of the year),[16] Uganda and Zambia; together, they account for 88% of Africa's confirmed cases.[17]

The world seems to have forgotten, or is ignoring, painful lessons from COVID-19. Global efforts that relied on voluntary measures to ensure affordability and access to COVID-19 vaccines and treatment were unsuccessful. While pharmaceutical corporations generated billions of dollars in revenue, countries were forced to pay high prices for patented vaccines and treatment, draining their budgets and leaving healthcare systems underfunded – and unprepared – for mpox.

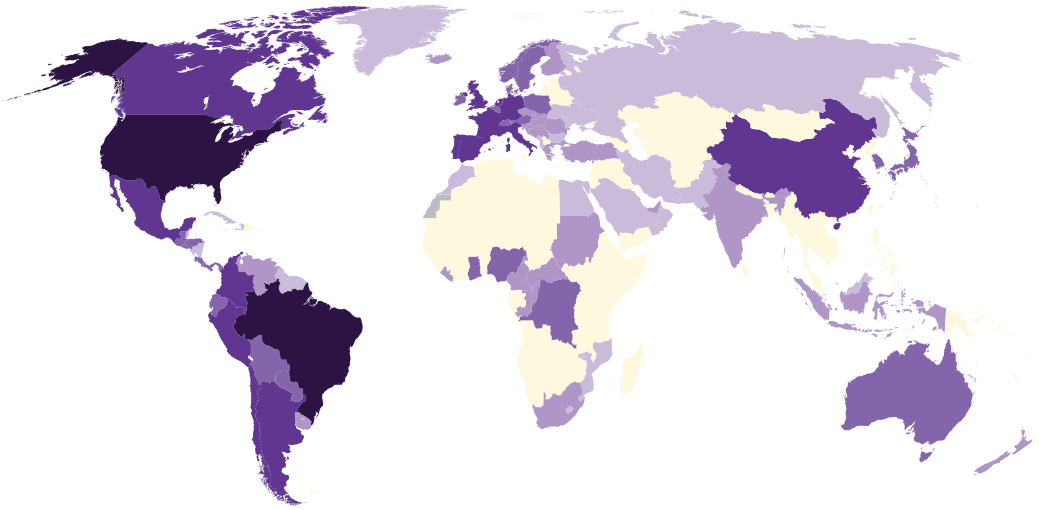
Vaccines and potential treatments for mpox are all from single suppliers – Bavarian Nordic, KM Biologics, BioNTech, Moderna, Siga Therapeutics (which produces the antiviral tecovirimat, and is developing a monoclonal antibody for mpox) and Emergent (which produces the ACAM-2000 vaccine, brincidofovir, and an intravenous vaccinia immune globulin [VIGIV], used to prevent severe reactions from smallpox vaccines and as a potential treatment for severe mpox). There appears to be a distinct, and exasperatingly familiar lack of interest in developing mpox therapeutics among pharmaceutical corporations. Innovative strategies are needed to identify new viral targets, optimized delivery methods, and use of biomarkers.[18]

There appears to be a distinct, and exasperatingly familiar, lack of interest in developing mpox therapeutics among pharmaceutical corporations.

Patents and other intellectual property (IP) barriers to essential health products can undermine local, national, regional and global capacities to respond to outbreaks and pandemics. That is why it is relevant to identify and monitor patent filings at the international and national levels.

Affordability and access are essential to health equity – and for stopping outbreaks, epidemics and pandemics. They can be enabled by multiple suppliers, and local production of health products in LMIC can ensure that the production capacity is able to meet arising needs with timely supplies. Neglecting these priorities has led to a lopsided, inadequate – and deadly – response to mpox.

[16] https://www.afro.who.int/countries/sierra-leone/news/sierra-leone-deploys-avohc-surge-team-halt-mpox-outbreak
[17] https://www.cidrap.umn.edu/mpox/mpox-cases-decline-sierra-leone-africa-faces-shortage-vaccine-funding
[18] https://pmc.ncbi.nlm.nih.gov/articles/PMC10057056/#B3-vaccines-11-00500



MPOX CLADES

There are two clades, or strains, of mpox, and each has subclades (A and B). Clade IIb is endemic in West Africa. Originally, it spread from infected live or dead animals to people, through bites and scratches, during hunting and butchering, and from undercooked meat. Now, clade IIb is also transmitted via respiratory droplets, close physical contact, including between sex partners, among households, during pregnancy and delivery, and from contact with bedding, clothing and towels from a person with mpox.

In 2022, clade IIb spread globally. As of 31 May 2025, it has been reported in 122 countries – 115 of which had never had a case before.[19] Regionally, the majority of clade IIb cases occur outside of Africa, and it continues to circulate at low levels in many countries, including in Australia, Europe and the United States; the most affected population is gay, bisexual and other men who have sex with men, many living with HIV.

In 2024, outbreaks of clade IIa mpox were identified in Côte d'Ivoire, Guinea, and Liberia.[20] Little is known about transmission, although researchers suspect close physical contact is the primary mode.

Clade I mpox was originally called "Congo Basin," and is now known as clade Ia. It can cause more serious illness and has a higher death rate than clade Ib or clade II. Clade Ia originally spread from small mammals, such as rodents and squirrels, to people, through bites, scratches, during hunting and butchering, and from eating undercooked meat. Clade Ia is common among children under age 15, in rural, sparsely populated areas, and is endemic in Cameroon, Central African Republic, Congo, DRC, and Sudan.[21]

As of July 2025, cases of clade Ia have been reported among adults in the Central African Republic, China, the DRC, Ireland, the Republic of Congo and Turkey.[22] Clade Ia is now spreading via community transmission, through sex and close contact between household members.

In 2023, cases of sexually transmitted clade Ib mpox, which has a lower fatality rate than clade Ia,[23] were reported in the eastern DRC, where it began spreading among sex workers and their partners, into households and across national borders to neighboring countries. As of late December 2024, clade Ib has spread from the DRC to adjoining countries (Burundi, Kenya, Malawi, Republic of the Congo, Rwanda, South Sudan, Tanzania, Uganda, Zambia), and travel-related cases have been reported in Belgium, Canada, China, India, Germany, Oman, Pakistan, Sweden, Thailand, United Arab Emirates, the United Kingdom, the United States, Zambia and Zimbabwe.[24]

[19] https://www.cdc.gov/mpox/situation-summary/index.html
[20] https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-44---23-december-2024
[21] https://worldhealthorg.shinyapps.io/mpx_global/
[22] https://www.gov.uk/guidance/clade-i-mpox-affected-countries#clade-i-mpox-outbreak-2024-to-2025
[23] https://www.cdc.gov/mpox/situation-summary/index.html
[24] https://www.gov.uk/guidance/clade-i-mpox-affected-countries#clade-i-mpox-outbreak-2024-to-2025

ABOUT MPOX

Narratives about illness are usually linear; people fall ill and either fully recover or perish, but reality differs. People with mpox may develop a few, or hundreds of itchy and painful lesions that require intensive care and sometimes result in permanent scarring and disfigurement. They may recover completely or develop permanent complications: mpox can affect the brain, the heart, and the lungs, cause inflammation of the genitals and the rectum. It may lead to loss of vision or blindness, especially in children and immunocompromised people, including people living with HIV (PLHIV) who have a low CD4 cell count (<200 cells/mm^3) and are not virally suppressed.[25, 26, 27] The case fatality rate for mpox varies, from 0% to 11%,[28] depending on host and viral factors, as well as access to, resources for, and capacity of healthcare systems.

WHAT HEALTH SYSTEMS NEED TO FIGHT MPOX

Mpox requires robust, well-funded national health systems with capacity to inform and engage communities, perform surveillance and testing, and deliver prevention, care and treatment.

Healthcare workers face shortages of personal protective equipment. Household transmission of mpox may be unavoidable, since there is often no place for a family member to isolate. Government facilities should offer stigma-free, welcoming facilities for children and adults with mpox that can address their health needs, including nutritional support, HIV testing and antiretroviral therapy (ART).

Ring vaccination campaigns should be followed by routinizing mpox vaccination – which would create a large, sustainable market for vaccines – while curbing outbreaks.

Mpox vaccination and testing campaigns should be fully funded and supported to address vulnerabilities to severe illness and death, such as untreated HIV and malnutrition. As examples, in the DRC, an estimated 80,000 of the 520,000 people living with HIV are untreated, while 4.45 million children under age five and more than 3.71 million pregnant and breastfeeding women face malnutrition.[29,30]

The complexity, price, and uneven supply of mpox diagnostics, and limited laboratory access and capacity in remote areas have made mpox testing challenging. As of early

[25] https://pmc.ncbi.nlm.nih.gov/articles/PMC10054449/

[26] https://pmc.ncbi.nlm.nih.gov/articles/PMC11512620/

[27] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00273-8/fulltext

[28] https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals

[29] https://www.unaids.org/en/regionscountries/countries/democraticrepublicofthecongo

[30] https://reliefweb.int/report/democratic-republic-congo/democratic-republic-congo-ipc-acute-malnutrition-snapshot-july-2024-june-2025-published-9-september-2024#:~:text=The%20latest%20data%20shows%20that,the%20first%20half%20of%202025.

December 2024, only 22% of suspected mpox cases in the DRC were confirmed by testing.[31] Additional tests may be needed to rule out other illnesses with overlapping symptoms, such as sexually transmitted infections, measles, shingles, chicken pox, molluscum, disseminated fungal disease (including cryptococcal and histoplasma disease, which are more common in PLHIV), and drug reactions. For example, the DRC's North and South Kivu provinces, already hard hit by mpox, were also experiencing an increase in cases of measles and mpox co-infection in 2024, due to low vaccination rates.[32]

Although there is no recommended treatment for mpox, once therapies have been approved, access and affordability in LMIC will be essential. The current situation is dismal. Cidofovir is not an ideal option, due to severe renal toxicity. Data on tecovirimat has been disappointing. The Palm 007 trial in the DRC, among people with clade Ib and the US-based STOMP trial among people with clade IIb, did not find that tecovirimat made any difference in time to resolution of mpox lesions. Siga Technologies is under investigation for making misleading claims about the efficacy of tecovirimat.[33,34,35]

Notably, the PALM 007 tecovirimat trial highlighted the importance of supportive care for people with severe illness; it reported that nutritional support, hydration and pain management lowered the death rate from 3.6% to 1.7% in both study groups.[36] Brincidofovir, a prodrug of cidofovir, is being studied in a clinical trial.[37]

Supportive care for severe mpox involves further testing and treatment for undiagnosed or untreated HIV, secondary bacterial infections, and ocular complications of mpox, pain management, and an intensive level of skin care (anti-itch products, soap and water, dressings, disinfectant, and fluid management). The value of tecovirimat is unclear, pending publication of data from PALM 007 and STOMP, since it may depend on when mpox treatment is initiated (the earlier, the better for antivirals), and other factors such as viral load, HIV and nutritional status, bacterial and other coinfections, and mpox severity.

Quality supportive care provision involves healthcare staff, as well as supplies. This includes, in addition to nurses and doctors, lab technicians, data managers, counsellors, psychologists, and trained, compensated peer supporters, community health workers and community support networks.

Countries are already trying to stretch dwindling donor resources and their limited healthcare budgets to meet every day needs – let alone outbreaks and pandemics. Their efforts are hobbled by the high prices of patented health products.

[31] https://www.science.org/content/article/can-congo-contain-its-exploding-mpox-epidemic-and-curtail-its-international-spread

[32] https://www.cidrap.umn.edu/mpox/mpox-measles-co-infections-reported-hard-hit-dr-congo-provinces

[33] https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo

[34] https://www.niaid.nih.gov/news-events/nih-study-finds-tecovirimat-was-safe-did-not-improve-mpox-resolution-or-pain

[35] https://www.globenewswire.com/news-release/2024/10/30/2971349/0/en/Bragar-Eagel-Squire-P-C-Is-Investigating-CSX-Stride-and-SIGA-and-Encourages-Investors-to-Contact-the-Firm.html

[36] https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo

[37] https://investors.emergentbiosolutions.com/news-releases/news-release-details/emergent-biosolutions-supports-new-clinical-trial-evaluating

OVERVIEW OF MPOX VACCINES

VACCINE NAME, TYPE AND PRODUCER	STRINGENT REGULATORY AUTHORITY APPROVAL	WHO EMERGENCY USE LISTING	WHO PRE-QUALIFIED	INDICATION	DOSING	METHOD OF ADMINISTRATION
ACAM 2000 Live vaccinia virus Emergent Biosolutions	Yes	In discussion	In discussion	Smallpox and mpox prevention; ages 18 years and above	Single; each vial contains 100 doses	Scarification: given by trained healthcare workers, via 15 jabs with a bifurcated needle that has been dipped into the vaccine
LC16m8 Live, attenuated, minimally replicating vaccinia virus KM Biologics Co., Ltd	Yes	Yes	No	Smallpox and mpox prevention; ages 1 year and above	Single; each vial contains 250 doses	Scarification: given by trained healthcare workers, via 15 jabs with a bifurcated needle that has been dipped into the vaccine
MVA-BN Live, attenuated non-replicating vaccinia virus Bavarian Nordic	Yes	Yes	Yes	Smallpox and mpox prevention; ages 12 years and above, but may used off-label for younger children in certain circumstances. An ongoing trial is assessing safety and efficacy in children ages 2-11 years	Two; a single dose may be given if vaccine supply is limited during outbreaks. Each vial contains a single dose or five fractional doses	Subcutaneous injection or a fractional dose given intradermally by trained healthcare workers with a 0.1 ml syringe and shorter needle[38]
Orthopoxvac Live VACdelta6-based culture[39] State Research Center of Virology and Biotechnology	Only in Russia	No	No	Smallpox and mpox	Not known	Not known

There are four smallpox vaccines, two of which are not ideal candidates for global roll-out, due to safety concerns (ACAM2000, which contains a live, replicating vaccinia virus) and limited published data (Russia's Orthopoxvac).

Two vaccines are Emergency Use Listed and Prequalified by WHO for mpox, LC16m8 and Bavarian Nordic's MVA-BN.[40] LC16m8 is a single-dose, live attenuated virus vaccine which was granted Emergency Use Listing by

[38] https://cdn.who.int/media/docs/default-source/immunization/mpox/who_faq_intradermal_fractional_dosing_mva-bn_vaccine.pdf?sfvrsn=ab124257_3#:~:text=(each%20single%2Ddose%20vial%20provides,4%2D5%20fractional%20doses).&text=A%20summary%20of%20MVA%2DBN,is%20provided-%20in%20Table%201.

[39] https://www.sciencedirect.com/science/article/pii/S2772431X2500005X

[40] https://www.who.int/news/item/19-11-2024-who-adds-lc16m8-mpox-vaccine-to-emergency-use-listing#:~:text=On%2013%20September%202024%2C%20WHO,older%20on%208%20October%202024.

WHO in November 2024, for ages one year and above. LC16m8 is not recommended during pregnancy, and for people who have certain skin conditions or are immunocompromised (including people living with HIV [PLHIV] who have a CD4 cell count of <200 cells/mm^3).[41]

Bavarian Nordic's two-dose mpox vaccine, known as MVA-BN, is based on a weakened version of the vaccinia virus, which cannot replicate, making it safer than other smallpox vaccines. MVA-BN is WHO prequalified for mpox in people ages 18 years and above; it also may be used "off-label" in infants, children and adolescents, during pregnancy and by immunocompromised people in outbreak settings where the benefits outweigh potential risks.[42] The vaccine's safety and efficacy in younger children and during pregnancy are currently being assessed in clinical trials.

ACCESS BARRIERS TO MVA-BN

MVA-BN was originally developed in partnership with the US government, for preventing bioterrorism with the smallpox virus. Although the US government contributed nearly USD 2 billion to the development of MVA-BN, the vaccine is priced at USD 229 per dose in the public sector — and it is even more expensive in the private sector. [43,44] UNICEF was only able to secure a price of up to USD 65 per dose for the MVA-BN vaccine[45] although experts have estimated that the vaccine likely costs less than USD 2 per dose to produce.[46]

Bavarian Nordic is currently the sole supplier of MVA-BN. Having a single supplier for an urgently needed health product, particularly during outbreaks and pandemics, can be disastrous, - as happened when the Delta variant of COVID-19 surged in India, leading the country to halt exports of COVID-19 vaccines produced by Serum Institute of India (SII), which COVAX relied upon. The same situation threatens equitable access to mpox vaccines: WHO has noted the importance of "... vaccine technology transfers allowing countries to become producers of their own freeze-dried vaccine and suppliers within their region," as part of smallpox elimination efforts.[47]

In August of 2024, Bavaria Nordic announced that it could produce 10 million doses in addition to current orders by the end of 2025, and up to 2 million doses during 2024 — an amount which is inadequate for a growing epidemic. In a vaguely worded announcement, Bavarian Nordic stated that it was "... working closely with the Africa CDC to further expand the manufacturing capacity to produce the mpox vaccine in Africa through transfer of technology to selected African manufacturers."[48] But the company backtracked in November of 2024, when its President and CEO, Paul Chapin, noted that that the company needs to "...see what the demand forecast will really be in the coming years to justify the costs of expanding our

[41] https://www.who.int/news/item/19-11-2024-who-adds-lc16m8-mpox-vaccine-to-emergency-use-listing

[42] https://www.who.int/news/item/13-09-2024-who-prequalifies-the-first-vaccine-against-mpox

[43] https://www.nytimes.com/2022/08/01/nyregion/monkeypox-vaccine-jynneos-us.html

[44] https://www.cdc.gov/vaccines-for-children/php/awardees/current-cdc-vaccine-price-list.html

[45] https://www.unicef.org/press-releases/unicef-signs-mpox-vaccine-deal-lowest-market-price-77-low-and-lower-middle-income

[46] https://www.theguardian.com/global-development/article/2024/sep/06/democratic-republic-congo-drc-donation-mpox-vaccines-outbreak-speading-africa-cdc

[47] https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-smallpox-vaccination#:~:text=In%201980%2C%20WHO%20declared%20smallpox,and%20disfigurement%20in%20its%20wake.

[48] https://www.bavarian-nordic.com/investor/news/news.aspx?news=6970

manufacturing into Africa," (despite securing more than USD 340 million in revenue for MVA-BN orders in 2025), and that it is discussing "...tech transfer of the fill-finish [which covers only the final steps of vaccine production] of our vaccine into Africa."[49]

In December 2024, Bavarian Nordic announced that it had entered into an agreement with SII. The agreement covers the technology transfer for vaccine manufacturing, and enables SII to distribute and sell the vaccine in India – which had three reported cases of mpox in 2024.[50] SII will also manufacture the vaccine for Bavarian Nordic to resell (likely at a significant profit), which the company says will ensure "...global access even during outbreaks of mpox."[51]

The Africa CDC called for 10 million doses of mpox vaccine by 2025, but familiar problems – unaffordable vaccines, and limited supply – made this impossible. A large part of the blame for inequitable and inadequate access to and unaffordability of vaccines – even during public health emergencies of international concern – comes from guaranteeing exclusivity to sell and produce vaccines and medicines; this forces the world to rely upon a single supplier to obtain urgently needed health products.

[49] https://www.bioprocessintl.com/facilities-capacity/bavarian-nordic-talks-mpox-manufacturing-expansion

[50] https://www.business-standard.com/india-news/kerala-reports-second-mpox-case-third-in-india-strain-being-analysed-124092700513_1.html

[51] https://www.bavarian-nordic.com/media/media/news.aspx?news=7026#:~:text=Bavarian%20Nordic%20Enters%20License%20and,equitable%20access%20to%20vulnerable%20populations.

2024 MPOX VACCINE ACCESS TIMELINE

On August 13, 2024, the Africa CDC issued a continent-wide public health emergency, calling for 10 million doses of mpox vaccine by 2025.[52] There are vast discrepancies between the 10 million doses Africa CDC has called for, versus the number of pledged, purchased and delivered vaccines.

AUGUST 2024

On August 13, 2024, Dr Jean Kaseya, the Director General of Africa CDC, announced that he had signed an agreement with mpox vaccine producer Bavarian Nordic and the EU Health Emergency Preparedness and Response Authority for 210,000 doses.[53]

Bavarian Nordic announced that it will donate 40,000 doses to the Africa CDC.[54]

On August 14, the WHO Director-General declared that mpox outbreak constituted a PHEIC.[55]

In August 2024, the US government delivered 10,000 doses of mpox vaccine to Nigeria.[56]

Bavarian Nordic donates 40,000 doses of its mpox vaccines to the Africa CDC.[57]

At the end of August 2024, UNICEF issued an emergency tender for Mpox vaccines with Africa CDC, Gavi and WHO,[58] while working to secure donations from HIC stockpiles.

[52] https://africacdc.org/news-item/africa-cdc-declares-mpox-a-public-health-emergency-of-continental-security-mobilizing-resources-across-the-continent/

[53] https://africacdc.org/news-item/european-commission-coordinates-procurement-and-donation-of-215-000-vaccine-doses-from-bavarian-nordic-to-support-africa-cdc-in-addressing-the-mpox-outbreak-in-africa/

[54] https://www.bavarian-nordic.com/investor/news/news.aspx?news=6968

[55] https://www.who.int/news/item/14-08-2024-who-director-general-declares-mpox-outbreak-a-public-health-emergency-of-international-concern

[56] https://www.hhs.gov/about/news/2024/09/24/hhs-announces-mpox-vaccine-donations-boosting-domestic-and-international-supply.html

[57] https://fortune.com/europe/article/bavarian-nordic-3-3-billion-danish-only-cure-to-mpox-vaccine-maker/

[58] https://www.unicef.org/press-releases/unicef-issues-emergency-tender-secure-mpox-vaccines-crisis-hit-countries

SEPTEMBER 2024

On September 5, 2024, nearly 100,000 doses of mpox vaccine were delivered to the DRC from the European Commission's Health Emergency Preparedness and Response Authority (HERA).[59]

On September 10, 2024, the US delivered 50,000 doses of mpox vaccine to the DRC.[60]

On September 13, 2024, Gavi, the Vaccine Alliance secured an advance purchase agreement for 500,000 doses of the Bavarian Nordic vaccine (usually given in two doses), to be delivered in 2024.[61]

On September 26, 2024, Bavarian Nordic announced an agreement with UNICEF to provide an additional 500,000 doses of its mpox vaccine (although the press release did not say when the additional doses would be delivered).[62]

OCTOBER 2024

As of October 2024, according to the Think Global Health Mpox Vaccine Tracker, only 281,880 of the 5,391,960 pledged mpox vaccine doses have been delivered to African countries.[63]

NOVEMBER 2024

On November 14, 100,000 doses, donated by Belgium, Germany and Portugal, were delivered to the DRC.[64]

On November 15, 2024, Bavarian Nordic announced its interim financial results for Q1,2 and 3 of 2024 (overall operating profit between DKK 1,450 million – DKK 1,700 million and its secured revenue for mpox vaccines for 2025 (DKK 2,400 million).[65]

On November 19, 2024, WHO granted emergency use listing for Japan's LC16 mpox vaccine, which is the only one approved for use in children ages 1-12 years. The country has pledged 3.05 million doses of its LC16 mpox vaccine (and the bifurcated needles used to deliver it), to the DRC.[66]

[59] https://ec.europa.eu/commission/presscorner/detail/en/ip_24_4523

[60] https://www.hhs.gov/about/news/2024/09/24/hhs-announces-mpox-vaccine-donations-boosting-domestic-and-international-supply.html

[61] https://www.gavi.org/news/media-room/gavi-signs-agreement-bavarian-nordic-rapidly-secure-500000-doses-mpox-vaccines

[62] https://www.bavarian-nordic.com/media/media/news.aspx?news=7006#:~:text=Bavarian%20Nordic%20Signs%20Agreement%20with%20UNICEF%20for%201%20Million%20Mpox%20Vaccines&text=COPENHAGEN%2C%20Denmark%2C%20September%2026%2C,impacted%20by%20the%20mpox%20outbreak.

[63] https://www.thinkglobalhealth.org/article/mpox-vaccine-tracker-millions-pledged-millions-still-be-delivered

[64] https://ec.europa.eu/commission/presscorner/detail/en/ip_24_4523

[65] https://www.bavarian-nordic.com/investor/news/news.aspx?news=7018

[66] https://www.cidrap.umn.edu/mpox/who-grants-emergency-listing-japan-s-lc16-mpox-vaccine#:~:text=Japan%20had%20earlier%20announced%20the,the%20current%20outbreaks%20in%20Africa.

DECEMBER 2024

As of mid-December 2024, 385,000 doses of donated mpox vaccines were delivered to the DRC, but only 53,000 shots have gone into arms there; bureaucracy, infighting over international funding, and a weak healthcare system with low-paid workers have complicated the roll-out.[67]

As of late December 2024, 50,000 of the 3 million donated doses of LC16, which is the only vaccine recommended for children ages 1 to 12 years, are expected to arrive in the DRC.[68]

As of December 27, 2024, only 10% of the necessary vaccines have arrived in Africa, while 99% of available vaccines remain in high-income country stockpiles.[69]

FEBRUARY 2025

As of February 2025, only 61,200 of up to 1 million doses of MVA-BN and USD 340 million of USD 500 million pledged by the Biden administration[70] arrived in Africa; since the US presidential election in November 2024, the announcement of the US commitment to mpox has been removed from the internet,[71] and the Trump administration has not commented on the status of the pledge.[72]

As of February 11, 2025, a donation of 200,000 doses of MVA-BN from Canada, and facilitated by Gavi, arrived in the DRC.[73]

MARCH 2025

As of March 13, 2025, the Mpox Vaccine Tracker is no longer being updated.

MAY 2025

As of May 29, 2025, the Africa CDC called for 6.4 million doses of mpox vaccines to address the outbreak of mpox in Sierra Leone, which is home to 75% of Africa's mpox cases.[74]

[67] https://www.nytimes.com/2024/12/23/health/mpox-spread-congo-kinshasa.html

[68] https://www.cidrap.umn.edu/mpox/africas-mpox-outbreak-nears-70000-cases-officials-lay-out-response-priorities

[69] https://www.oxfam.org.uk/media/press-releases/africa-to-receive-just-10-of-doses-needed-to-control-mpox-outbreak-by-end-of-year/

[70] https://healthpolicy-watch.news/africa-raises-1-billion-to-combat-mpox/

[71] https://www.whitehouse.gov/briefing-room/statements-releases/2024/09/24/fact-sheet-the-united-states-commitment-to-address-the-global-mpox-outbreak/#:~:text=Mpox%20vaccine%20donation.,in%20September%20(50%2C000%20doses).

[72] https://www.thinkglobalhealth.org/article/mpox-vaccine-tracker-millions-pledged-millions-still-be-delivered

[73] https://www.thinkglobalhealth.org/article/mpox-vaccine-tracker-millions-pledged-millions-still-be-delivered

[74] https://healthpolicy-watch.news/africa-cdc-appeals-for-more-mpox-vaccines-as-ethiopia-reports-first-cases/

JUNE 2025

As of June 9, 2025, Public Citizen released its *Mpox Vaccine Shortfall* report, which identified Bavarian Nordic's high prices as a major barrier to vaccine access. The report noted UNICEF's funding gap, which has prevented it from securing an estimated 350,000 remaining doses of MVA-BN from its supply agreement with the company. Among the multiple negative impacts of the Trump administration's defunding and dismantling of USAID are ceasing support for vaccine transfers – and the fate of as many as 695,000 pledged vaccine doses is uncertain. The report noted that Sierra Leone, which has reported over 3,000 new mpox cases, has only received 58,000 doses of the mpox vaccine, although it needs up to 600,000 doses.[75]

JULY 2025

As of July 10, 2025, WHO reports that it has not received any new funding to address mpox, despite the need for USD 145 million. This shortfall endangers deployment of vaccines and other essential supplies, and implementation of its guidance for mpox prevention and clinical care as well as prevention, testing, care and treatment for many other diseases.

While vaccination programs have been launched in Central African Republic, DRC, Liberia, Nigeria, Rwanda Sierra Leone and Uganda, and expected to begin soon in Angola, Cote d'Ivoire, Kenya, and South Africa, only 724,000 of the 2.9 million available mpox vaccine doses have been administered in Africa.[76]

SEPTEMBER 2025

In September 2025, WHO announced the PHEIC would be lifted as cases in the most affected areas of Africa leveled off or began to decline.[77]

[75] https://www.citizen.org/wp-content/uploads/Mpox-vaccine-shortfall-2025.pdf

[76] https://www.who.int/news/item/10-07-2025-fourth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-upsurge-of-mpox-2024

[77] https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-september-2025

MPOX VACCINES AND VACCINE CANDIDATES: CLINICAL SUMMARIES AND PATENT LANDSCAPES

METHODOLOGY

The patent landscape for each technology was based on publicly available landscapes (from Medspal and Public Citizen), complemented by a search of the CAS Scientific Patent Explorer™. The search included international filing through the Patent Cooperation Treaty (PCT) system and the international publication number (WO) (hereafter called PCT applications). The search focused on applicants directly involved in the development of the technology. The results are an initial picture of what these institutions aimed to protect through patenting, but it does not necessarily reflect the landscape in different countries. It is important to confirm whether those PCT applications are filed at the national level, which is outside the scope of this report.

DEVELOPMENT OF SMALLPOX VACCINES

Although smallpox was officially eradicated in 1980, concerns about viral bioterrorism led to development and stockpiling of smallpox vaccines. These vaccines are vaccinia virus-based, and take advantage of cross-protection against all orthopoxviruses (including smallpox and mpox).

The smallpox vaccines produced from various vaccinia virus strains are classified into four generations, which differ by methods and/or the virulence of the seed vaccinia virus.[78] First-generation vaccines were manufactured on the skin of live animals. Second-generation vaccines were developed to improve quality control and reduce the risk of contamination with other microorganisms by using tissue culture systems or embryonated chicken eggs,[79,80,81,82] although they were still associated with adverse effects. Third-generation smallpox vaccines were developed by genetically altering the vaccinia virus to create non-replicating or highly attenuated strains, which are safer and retain immunizing properties against smallpox.[83] These

[78] https://pubmed.ncbi.nlm.nih.gov/34521550/

[79] Fertilized eggs serve as an essential host system for virus propagation in virology. Virus inoculation can be performed by depositing the virus directly onto the chorioallantoic membrane (CAM) or within these sacs, depending on the virus type.

[80] https://pubmed.ncbi.nlm.nih.gov/34521550

[81] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf

[82] https://pubmed.ncbi.nlm.nih.gov/19563829/

[83] https://pubmed.ncbi.nlm.nih.gov/19563829/

alterations were achieved by sequential passage of the virus in culture cells. Fourth-generation vaccines involve highly attenuated strains, obtained through genetic engineering.

Current vaccines approved for smallpox and mpox prevention include a second-generation vaccine, ACAM2000, and two third-generation vaccines, MVA-BN and LC16m8. The attenuated vaccinia candidate VACΔ6 from Vector, Russia's State Research Center of Virology and Biotechnology, is not included in this review, due to lack of published data.

MVA-BN

CLINICAL SUMMARY

MVA-BN, a third-generation smallpox vaccine, is WHO-prequalified for mpox. It is given in two doses, one month apart, either subcutaneously or intradermally (which extends the number of doses per vial from one to five).

Unlike ACAM2000 and LC16m8, there is human data on MVA-BN's efficacy against mpox. In high-income country studies, the overall efficacy for prevention of mpox was 76% after a single dose, increasing to 82% after two doses; using the vaccine as post-exposure prophylaxis was 20% effective.[84] A study of MVA-BN in Germany among 3,027 men who have sex with men and in transgender people reported overall efficacy of 57.8% at 14 days after a single dose, which was lower among people living with HIV (34.9% vs. 84.1%); no data on the efficacy of two doses were provided.[85] A cohort of 19,777 PLHIV enrolled in primary care in the US reported vaccine efficacy of 71% after at least one dose of MVA-BN, increasing to 86% among those with a CD4 cell count of ≥350 cells/mm^3 or viral load suppression.[86]

Because the vaccinia virus used in MVA-BN cannot replicate in human cells, it is safer than smallpox vaccines which include replicating vaccinia virus. For this reason, it is considered the best option for LMIC, since it can be used during pregnancy and in people who are immunocompromised or living with certain skin disorders. MVA-BN can be given off-label to people ages 12 and above and is being studied in younger children.

The duration of immunity is unknown; generally, live, attenuated vaccines provide longer protection than inactivated vaccines. Booster recommendations for MVA-BN vary; some studies have found that antibody responses wane within months of vaccination, while a study of 1,600 healthcare workers in the DRC found that boosters may not be needed for five to seven years.

The most common (>10%) adverse events were pain (84.9%), redness (60.8%), swelling (51.6%), induration (45.4%), and itching (43.1%) at the injection site; muscle pain (42.8%), headache (34.8%), fatigue (30.4%), nausea (17.3%) and chills (10.4%).[87] Although rare, the vaccine may cause severe allergic reactions.

DEVELOPMENT OVERVIEW

MVA-BN is a replication-incompetent, attenuated virus vaccine, derived from the Modified Vaccinia Ankara (MVA) strain. The story of MVA-BN vaccine began in Germany in the 1950s, when the Bavarian State Vaccination Institute was manufacturing a smallpox vaccine using a poxvirus called vaccinia.[88] Dr Anton Mayr and his team started

[84] https://www.sciencedirect.com/science/article/pii/S0264410X24006947#:~:text=VE%20of%201%20dose%20of,calculated%20from%20random%20effects%20estimates.

[85] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(25)00018-0/fulltext

[86] https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciae464/7811450?redirectedFrom=fulltext&login=false

[87] https://www.fda.gov/media/131078/download

[88] https://www.citizen.org/article/zain-rizvi-how-a-danish-company-grabbed-control-of-the-monkeypox-vaccine/

to work with the chorioallantois Vaccinia Virus Ankara (CVA) vaccine strain, which was maintained by the Vaccination Institute in Ankara, Turkey. Between 1960 and 1974, Dr Mayr and his colleagues attenuated the CVA strain by 570 continuous passages in primary chicken embryo fibroblast cells. By passage 516, the attenuated CVA strain became unable to replicate in most mammalian cells; it was renamed MVA.[89,90,91] The MVA genome harbors six deletions vs. the parent CVA strain, resulting in a reduction of the entire genome's size from 208 Kb to 177 Kb.[92]

MVA initially belonged to the public. In the 1970s, the Bavarian government filed a patent and began producing MVA, which by then had undergone 571 passages, as part of a smallpox eradication campaign.[93] Around 1996, the pharmaceutical corporation Bavarian Nordic (BN), which was founded in 1994, entered into a confidential agreement with Dr Anton Mayr, which granted "...exclusive and sole access to the MVA vaccine stock and MVA viral stock in his possession" to the company, while Dr Mayr retained the right to distribute MVA for research purposes.[94] Bavarian Nordic further passaged the strain and plaque-purified a single clone, which they called MVA-Bavarian Nordic (MVA-BN).[95] The company claims the "new" strain is "derived from Anton Mayr's seed virus" but has "superior characteristics compared to other MVA strains." [96]

Following the events of September 11, 2001, the United States (US) government began to support development of MVA-BN as a smallpox vaccine. Since 2003, the US government, primarily through the National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA), has awarded over USD 2.3 billion to support the development, licensure and purchase of the MVA-BN vaccine.[97]

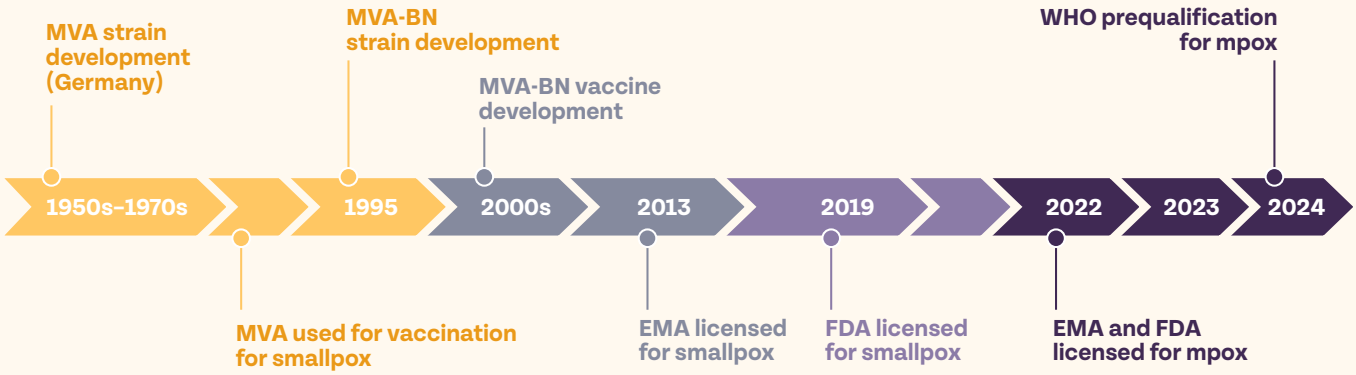
MVA-BN was first licensed by the European Medicines Agency (EMA) in 2013 under the brand name Imvamune,[98] and by the US Food and Drug Administration (US FDA) in 2019 under the brand name Jynneos; both agencies extended the indication to include mpox in 2022.[99] In September 2024, MVA-BN became the first WHO-prequalified mpox vaccine. In October, WHO prequalification extended the indication to include use in adolescents ages 12-17 years.

PRODUCTION OF MVA-BN

The major steps for MVA-BN vaccine production were described in Public Citizen's report, *Ramping Up MPXV Vaccine Production: A Global Survey*, which is based on public information, as follows: Step 1) Chick embryo fibroblast (CEF) cell preparation; Step 2) Virus inoculation, harvest and purification; Step 3) Fill and finish.[100] According to the report, in the first step, CEF cells are freshly prepared from specific pathogen-free (SPF) embryonated eggs (the most critical biosimilar raw material). After disinfecting the egg, the embryos are harvested, and

[89] https://pubmed.ncbi.nlm.nih.gov/36146594/
[90] https://pubmed.ncbi.nlm.nih.gov/33077299/
[91] https://pubmed.ncbi.nlm.nih.gov/39188013/
[92] https://pubmed.ncbi.nlm.nih.gov/2033387/ Meyer, Sutter, and Mayr, 'Mapping of Deletions in the Genome of
[93] https://www.citizen.org/article/zain-rizvi-how-a-danish-company-grabbed-control-of-the-monkeypox-vaccine/
[94] https://www.citizen.org/article/zain-rizvi-how-a-danish-company-grabbed-control-of-the-monkeypox-vaccine/
[95] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf
[96] https://www.citizen.org/article/zain-rizvi-how-a-danish-company-grabbed-control-of-the-monkeypox-vaccine
[97] https://dukeghic.org/wp-content/uploads/sites/20/2024/11/QuickStart-Mpox-report-Issue-3-Nov-22-2024.pdf
[98] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf
[99] https://pubmed.ncbi.nlm.nih.gov/39188013/.
[100] https://www.citizen.org/wp-content/uploads/Ramping-up-MPX-vaccine-production-Oct-31-final.pdf

FIGURE 1: Chronology of MVA-BN development and the institutions and companies involved



the head is removed. Then, the embryos are macerated, and trypsin is added. Primary CEF cells are isolated by centrifugation and seeded in a bioreactor in serum-free medium comprising Epidermal Growth Factor (EGF) and antibiotics. In 2006, a disposable Wave Bioreactor, developed by Wave Biotech LLC, was used in MVA-BN production.[101]

The use of primary CEF cell culture represents a significant challenge to large-scale production, due to factors such as the time, cost, and labour involved in preparing these cells, variability of the cell substrate in each batch, and because the preparation procedure is prone to contamination. Therefore, there has been increasing interest in using continuous cell lines for production.

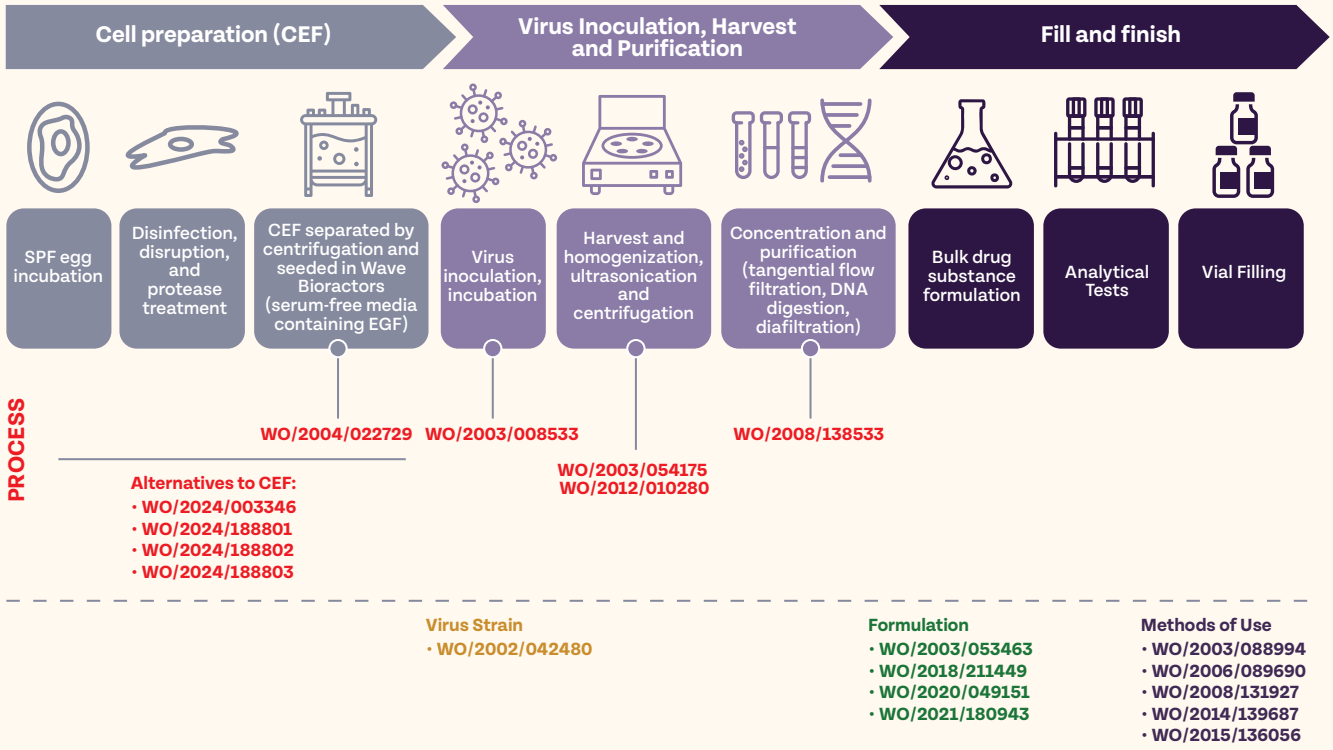
PATENT LANDSCAPE

Although development of the MVA-BN vaccine was supported by decades of public funding, BN engaged in intense patenting activity between 2001 and 2024, with 19 PCT applications, as described in Figure 2. Nine are related to the production process, four to compositions and five with methods of use. Figure 3 summarizes the stages of production of MVA-BN and which stage each PCT application is related to, according to the steps previously described. Further detail about each PCT application is described in Annex 1.

[101] https://www.biospace.com/wave-biotech-llc-release-wave-bioreactor-r-used-in-new-vaccine-production-facility

FIGURE 2: Patent landscape related to MVA-BN vaccine

FIGURE 3: MVA-BN production process and related PCT patent applications



In April 2023, Charles Chaplin, CEO of BN, said "...the rapid spread of mpox last year was a wake-up call for the company," which is now looking at ways to dramatically scale-up its production capacity (which is constrained by the primary CEF cells), adding that the company "...has developed a permanent avian cell line that will simplify production and make it easier to bring in other manufacturers in an emergency," and that Bavarian Nordic "plans to introduce the new cell line in the next 18 months." [102] This statement reflects the four patent PCT applications, filed within a single year, focusing entirely on substrate alternatives to CEF cells for virus production.

In June 2023, a PCT application related to a mammalian cell line for the production of MVA was filed (WO/2024/003346). Specifically, a Chinese hamster ovary (CHO) cell line, expressing a combination of poxvirus host range genes not expressed by MVA, and the process to produce the cell line are covered by the claims. According to the applicant, the possibility of using CHO cells as an alternative to primary CEF cells for reproducing MVA provides a significant advance in MVA-based vaccine production.

On March 7th, 2024, Bavarian Nordic filed three PCT applications (hereafter '801, '802, '803) related to the production of MVA in quail cell lines. All of them cover processes to produce poxviruses or a composition comprising poxviruses in quail cell lines, in particular MVA-BN and MVA-BN-RSV poxviruses in the continuous cell line CCX.E10. '801 covers "a method to produce poxviruses in quail cell lines," disclosing five examples related to the suspension quail cell lines for producing poxviruses; the virus yields from suspension of quail cells cultured in various media and media mixtures.

'802 covers "A method of producing a pharmaceutical composition from an avian

[102] https://www.cnbc.com/2023/04/25/mpox-shows-smallpox-risk-vaccine-maker-bavarian-nordic-says.html

cell culture infected with MVA or recombinant MVA," with five examples regarding the purification process of the viruses in quail cell culture and a comparison with the CEF cell process. '803 also covers "A method of producing a pharmaceutical composition from an avian cell culture infected with MVA or recombinant MVA," presenting 10 examples that are merely a combination of the exact examples disclosed in 801 and 802.

The filing of these three PCT applications for what is effectively the same "invention" exhibits the company's evergreening strategy. Regarding the proposed cell substrate as an alternative to CEF, the cell line CCX.E10 is a quail suspension cell line developed by **Nuvonis Technologies GmbH** (Austria). There is no available information about a partnership or commercial agreement between the companies.

OTHER COMPETITIVE STRATEGIES FROM BAVARIAN NORDIC

In a prospectus prepared by the company in 2020,[103] BN declared that IP assets primarily include patents and patent applications, trademarks and trade secrets (page 85). Moreover, page 87 describes that the "... current manufacturing process used for Bavarian Nordic's MVA-BN-based vaccines, including the smallpox vaccine manufacturing, is primarily protected as a trade secret and is therefore not disclosed to competitors."

Besides intense **patent filing activity**, Bavarian Nordic has strategically positioned itself as a dominant player in the smallpox and mpox vaccine market, by leveraging several competitive tactics: efforts to dismiss competitors' strategic partnerships with the US government, and control of trade secrets, mainly for the production process.

Recently, Bavarian Nordic entered a license and manufacturing agreement for the MVA-BN mpox vaccine with the Serum Institute of India (SII). Under the agreement, BN will transfer technology of the current manufacturing process to SII, enabling it to supply the Indian market only, thus, Bavarian Nordic keeps its exclusive control of MVA-BN in the rest of the world.[104, 105]

An intense legal battle between BN and Acambis took place over MVA technology patents. Acambis was developing a smallpox vaccine based on the MVA strain, MVA3000, in partnership with Baxter Healthcare SA.[106] The vaccine reached phase II, but it was discontinued in 2007, probably due to strategic and market factors.[107] In 2005, BN sued Acambis in the Commrcial Court in Vienna, Austria, and in the US, wherein Acambis was accused of stealing trade secrets at the US Federal District Court in Delaware, and of patent infringement at the US International Trade commission in Washington, DC.[108]

Acambis filed two oppositions to European Patent No. 1 335 987 (WO/2002/042480 patent family), which was granted to Bavarian Nordic A/S (Bavarian Nordic) by the European Patent Office (EPO),[109] who decided to maintain the patent in the amended form.[110]

In 2007, Acambis and Bavarian Nordic reached a global settlement, bringing an end to their

[103] https://www.bavarian-nordic.com/media/292506/bavarian_nordic_rights_issue_2020_prospectus.pdf
[104] https://wtww.bavarian-nordic.com/media/media/news.aspx?news=7026
[105] https://www.citizen.org/news/bavarian-nordic-mpox-vaccine-deal-still-sidelines-equity/
[106] https://www.biospace.com/acambis-plc-announces-significant-progress-on-its-mva-smallpox-vaccine-programme-with-publication-of-phase-i-trial-results
[107] https://pmc.ncbi.nlm.nih.gov/articles/PMC9709927/#:~:text=ACAM2000™%2C%20a%20second%2Dgeneration,such%20as%20a%20bioterrorist%20attack
[108] https://sciencebusiness.net/news/73868/Intellectual-Property%3A-Patent-war-over-smallpox-vaccine.
[109] https://www.biospace.com/acambis-plc-opposition-to-mva-patent.
[110] https://register.epo.org/application?documentId=EYY9GTF63317DSU&number=EP01991753&lng=en&npl=f alse

legal dispute.[111] Acambis concomitantly withdrew its oppositions to Bavarian Nordic's patents.[112] According to a 2016 document from Bavarian Nordic:

> *"The settlement involved patent disputes at the U.S. International Trade Commission and the Commercial Court in Vienna, Austria, as well as the conversion, unfair trade acts and unfair competition action at the U.S. Federal District Court of the District of Delaware. Under the agreement, we granted a license to some of our MVA patents in return for Acambis making an undisclosed upfront payment. Acambis will also make royalty and milestones payments should it develop or commercialize certain MVA products in the future. Acambis was later acquired by Sanofi Pasteur."*[113]

As with mRNA technologies,[114] several other oppositions on patents related to components of MVA-BN were filed by Baxter, Sanofi Pasteur, Emergent Product development Germany, Innogenetics NV, VIRBAC and Oxford Biomedica Limited. For example, the first opposition, filed by Baxter, requested revocation of the respective patent, based on lack of novelty and inventive step of the subject-matter:

> *"The opposition is primarily based on the fact that the allegedly new strain claimed (MVA-BN) is in fact the same as the prior art MVA F6 strain. Alternatively, is the patentee is able to prove that MVA-BN is not identical to MVA F6, we nevertheless submit that the relevant properties of the "two" viruses are the same such that no technical problem has been solved by the claimed subject-matter.*
>
> *Furthermore, the deposited strain is the same as the prior art MVA strain that was called MVA M4. More specifically, we demonstrate below that is has the same sequence as MVA M4.*
>
> *The whole basis of the patent is therefore an illusion. The patent does not contain any new ideas concerning the uses of MVA viruses and so there is nothing in the sub-claims that patentably distinguishes them from the prior art."*
>
> – Extract of filed opposition, page 11.[115]

The competitive space for a vaccine platform based on intense litigation and patent oppositions, and disputes by multiple players adds legal uncertainty to LMIC manufacturers aiming to develop alternative versions of a vaccine.[116]

[111] https://pharmatimes.com/news/acambis_and_bavarian_nordic_make_peace_over_mva_vaccines_990492/.
[112] https://register.epo.org/application?documentId=EL9RCI1W2317J10&number=EP01991753&lng=en&npl=false
[113] https://register.epo.org/application?documentId=EL9RCI1W2317J10&number=EP01991753&lng=en&npl=false
[114] https://ipwatchdog.com/2021/04/30/mrna-patent-competitive-landscape-pioneers-litigation-outlook-big-pharmas-next-moves-part-iii/id=132936/
[115] https://register.epo.org/application?documentId=EKG2TXZJ2406FI4&number=EP01991753&lng=en&npl=false
[116] https://www.nature.com/articles/s41587-021-00912-9

LC16m8

CLINICAL SUMMARY

LC16m8, a single-dose smallpox vaccine that contains an attenuated, minimally replicating vaccinia virus, was developed to be safer than ACAM2000. It received WHO Emergency Use Listing (EUL) for mpox in November 2024. LC16m8 is important, because it is the only vaccine that can be used in children ages 1 year and up, who are vulnerable to severe illness and death from mpox.

A small study of its efficacy against mpox found that LC16m8 induced neutralizing antibody responses against clades I and II.[117] Currently, the vaccine's duration of protection against mpox is unknown.

LC16m8 is given by multiple punctures with a bifurcated needle; healthcare workers require training to safely administer it. The vaccine is freeze-dried in 250-dose vials, which must be used within hours of opening. [118]

LC16m8 should not be used during pregnancy, for people with certain skin disorders, or in people who are immunocompromised, including PLHIV with a CD4 cell count of <200 cells/µl.[119] Since CD4 cell count is no longer performed routinely, it may be challenging to identify PLHIV who can safely receive this vaccine.

Adverse events from LC16m8 may include fatigue, headache, fever, chills, rash, muscle aches, swollen lymph nodes, swelling and reddened skin at injection site. Although rare, it may cause a severe allergic reaction. LC16m8's minimally replicating vaccinia virus reduces – but does not eliminate – the risk of vaccinia spreading from the vaccination site to other parts of the body.

DEVELOPMENT OVERVIEW

LC16m8 is a replication competent, attenuated virus obtained after serial passages of the Lister strain in primary rabbit kidney cells (PRK) at 30° C.[120] The Lister virus was initially passaged 36 times in PRK cells, after which individual clones were assessed for their growth on Vero cells, to evaluate replication capability in primate tissues. The LC16 clone was selected and subjected to six additional passages, resulting in the isolation of the LC16m0 clone. Subsequently, LC16m0 was passaged three more times in PRK cells, ultimately leading to the isolation of the LC16m8 clone.[121] LC16m8 has a temperature-sensitive phenotype in PRK cells and forms a smaller pock in the chorioallantoic membrane of embryonated chicken eggs than LC16mO, LC16, and Lister strain.[122]

The attenuated phenotype of LC16m8 was attributed to a frameshift mutation due to a single base deletion in the B5R gene, which introduces a stop codon within the open reading frame.[123] The B5R protein is an essential component of the viral envelope that plays a critical role in the formation and function of the extracellular enveloped virus form. The LC16m8 strain spontaneously reverts to large plaque-forming clones (LPCs), and the proportion of

[117] https://evidence.nejm.org/doi/full/10.1056/EVIDoa2300290
[118] https://www.tandfonline.com/doi/pdf/10.1080/14760584.2024.2397006
[119] https://www.who.int/news/item/19-11-2024-who-adds-lc16m8-mpox-vaccine-to-emergency-use-listing
[120] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf
[121] https://pubmed.ncbi.nlm.nih.gov/17052815/
[122] https://pubmed.ncbi.nlm.nih.gov/34521550/
[123] https://pmc.ncbi.nlm.nih.gov/articles/PMC1212643/

these LPC revertants increases rapidly with successive passages in cell culture.[124]

LC16m8 was originally manufactured by the Chiba Serum Institute. In 2002, following the dissolution of the Institute, the Japanese government designated the Chemo-Sero-Therapeutic Research Institute (commonly known as KAKETSUKEN) in Kumamoto, Japan, to take over the production of LC16m8.[125] In 2018, Kaketsuken joined the Meiji Group, and was renamed as KM Biologics.[126] (Figure 4).

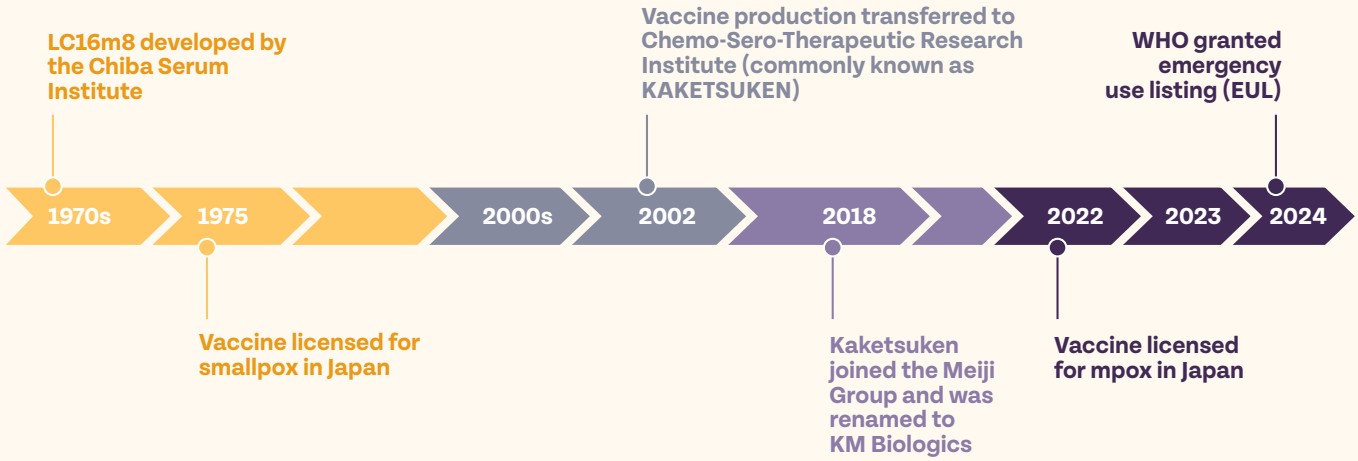
LC16m8 has been licensed in Japan since 1975 for smallpox prevention. In August of 2022, Japan extended the indication of the vaccine to include protection against mpox. The WHO granted EUL for LC16m8 for mpox on November 19th, 2024.[127]

In January 2025, the DRC received the first of a Japanese donation of 3.05 million doses of LC16m8 vaccines.[128]

PATENT LANDSCAPE

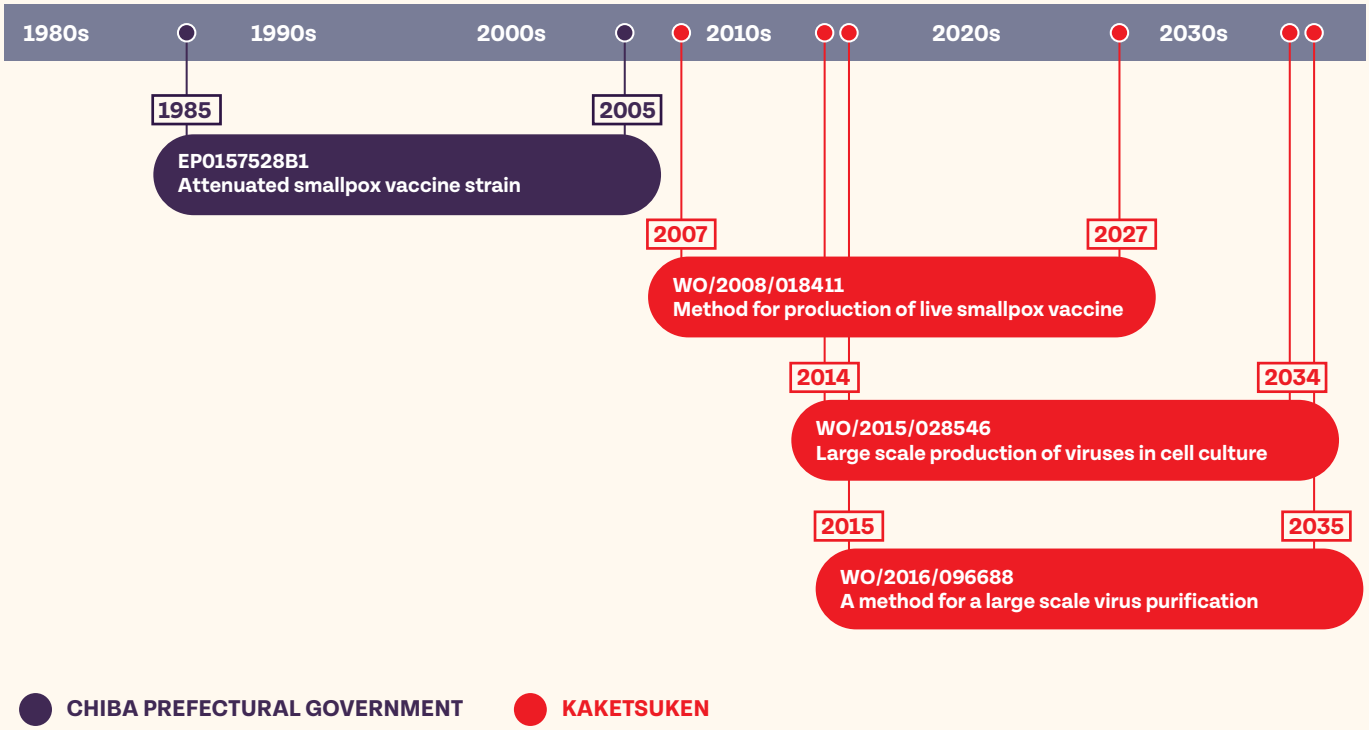
As shown in Figure 5, the first patent covering the attenuated Lister strain was filed in 1985 by CHIBA PREFECTURAL GOVERNMENT in Canada, Austria, Europe, Japan, and the US, with no correspondent PCT application. In 2007, Kaketsuken filed a PCT application aiming to protect a cell-cultured live smallpox vaccine as well as a process for manufacturing the vaccine. The process aimed to reduce revertants in the production of the LC16m8 live smallpox vaccine, taking advantage of the distinct plaque formation characteristics of the strains in RK-13 and Vero E6 cells. Later, in 2014 and 2015, two PCT applications were co-filed by Kaketsuken and GlaxoSmithKline (GSK), targeting the large-scale production or purification of viruses. Both of the PCT applications are broad in scope, potentially encompassing processes applicable to any virus, without specifically mentioning orthopoxviruses.

FIGURE 4: Chronology of institutions/companies involved in LC16m8 development



[124] https://www.pnas.org/doi/10.1073/pnas.0406671102
[125] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf
[126] https://www.theworldfolio.com/companies
[127] https://www.who.int/news/item/19-11-2024-who-adds-lc16m8-mpox-vaccine-to-emergency-use-listing
[128] https://www.oxfam.org.uk/media/press-releases/africa-to-receive-just-10-of-doses-needed-to-control-mpox-outbreak-by-end-of-year/

FIGURE 5: Patent applications related to LC16m8



ACAM2000®

CLINICAL SUMMARY

ACAM2000, a single-dose, second-generation smallpox vaccine, was US FDA approved to prevent smallpox in 2007. It has also been approved in Australia, Canada, and Singapore. In August 2024, Emergent Biosolutions, which produces ACAM-2000, filed an Expression of Interest with WHO for EUL of ACAM2000 for mpox prevention,[129] and the US FDA expanded the vaccine's indication to include mpox prevention (based on existing safety data in people, and efficacy data from animal studies).[130] Although the duration of immunity conferred by this vaccine is unknown, the US recommends boosters every 3 years, or at least every 10 years for healthcare and laboratory workers with occupational exposure to orthopoxviruses.

ACAM2000 is indicated for use in adults ages 18 -64 years, who are at high risk for mpox. Healthcare workers need specialized training to administer the vaccine by scarification, a process involving multiple jabs from a two-sided needle, which leaves a sore, called a pock, that is infectious with vaccinia virus for several weeks. The pock requires special care to avoid spreading vaccinia virus to other parts of the body, and to other people (particularly babies under one year of age, people who are immunocompromised or pregnant, [because vaccinia can lead to fetal death], and people who have heart or eye disease, or a history of chronic inflammatory skin disorders).

ACAM2000 cannot be used in people with severe immunodeficiency, because it contains a live, replicating vaccina virus, unless benefits outweigh potential risks (including inflammation of the heart, brain and spinal cord, lesions that spread beyond the vaccination site, serious skin infections, including extensive rash, as well as systemic illness, eye infections that can lead to blindness, permanent neurological damage, and death).

ACAM2000 is not recommended for people who are immunocompromised, pregnant, living with heart disease, eczema, psoriasis, and other skin conditions, as well as infants and children (who are at higher risk of death and complications). It also causes milder adverse events, most commonly, pain, itching and swelling at the injection site, swollen lymph nodes, fever, tiredness and weakness, muscle aches and headache.[131] These safety concerns, as well as the age restrictions and the complications of administering it, make ACAM2000 a less than ideal candidate for mpox prevention.

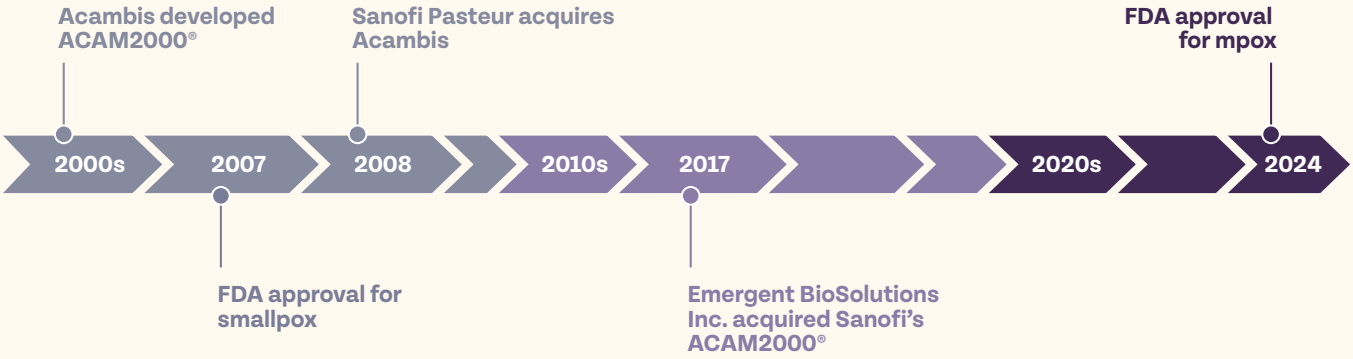
DEVELOPMENT OVERVIEW

ACAM2000 is a second-generation, replication-competent, live attenuated vaccine, produced from a single plaque-purified vaccinia virus strain, which originated from the Dryvax® first-generation smallpox vaccine (based on the New York City Board of Health strain).[132] One clonal virus (Clone 2, renamed ACAM1000) was selected for further development and produced in MRC-5 human diploid cells.[133]

After the events of September 11, 2001, concerns about bioterrorism prompted significant investment in smallpox vaccine research and production capacity. Acambis was required to rapidly produce 209 million doses of its smallpox vaccine for the US national stockpile. To meet this requirement,

[129] https://investors.emergentbiosolutions.com/news-releases/news-release-details/emergent-biosolutions-responds-mpox-public-health-emergency
[130] https://investors.emergentbiosolutions.com/news-releases/news-release-details/emergent-biosolutions-acam2000r-smallpox-and-mpox-vaccinia
[131] https://www.fda.gov/media/75792/download
[132] https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Nov2013/8_session_smallpox/Nov2013_session8_smallpox_vaccine.pdf
[133] https://pubmed.ncbi.nlm.nih.gov/12925845/

FIGURE 6: Chronology of the institution/companies responsible for the development of ACAM2000®



Acambis teamed with Baxter BioScience, which had large-scale production capability, using a different cell line (African green monkey kidney [Vero] cells). The ACAM1000 master virus seed was used to prepare a vaccine, designated ACAM2000, at large scale in Vero cells under serum-free conditions (Figure 6).[134]

ACAM2000 was developed by Acambis, which was acquired by Sanofi Pasteur in 2008. In 2017, Emergent BioSolutions Inc. acquired Sanofi's ACAM2000 business.[135] (Figure 6).

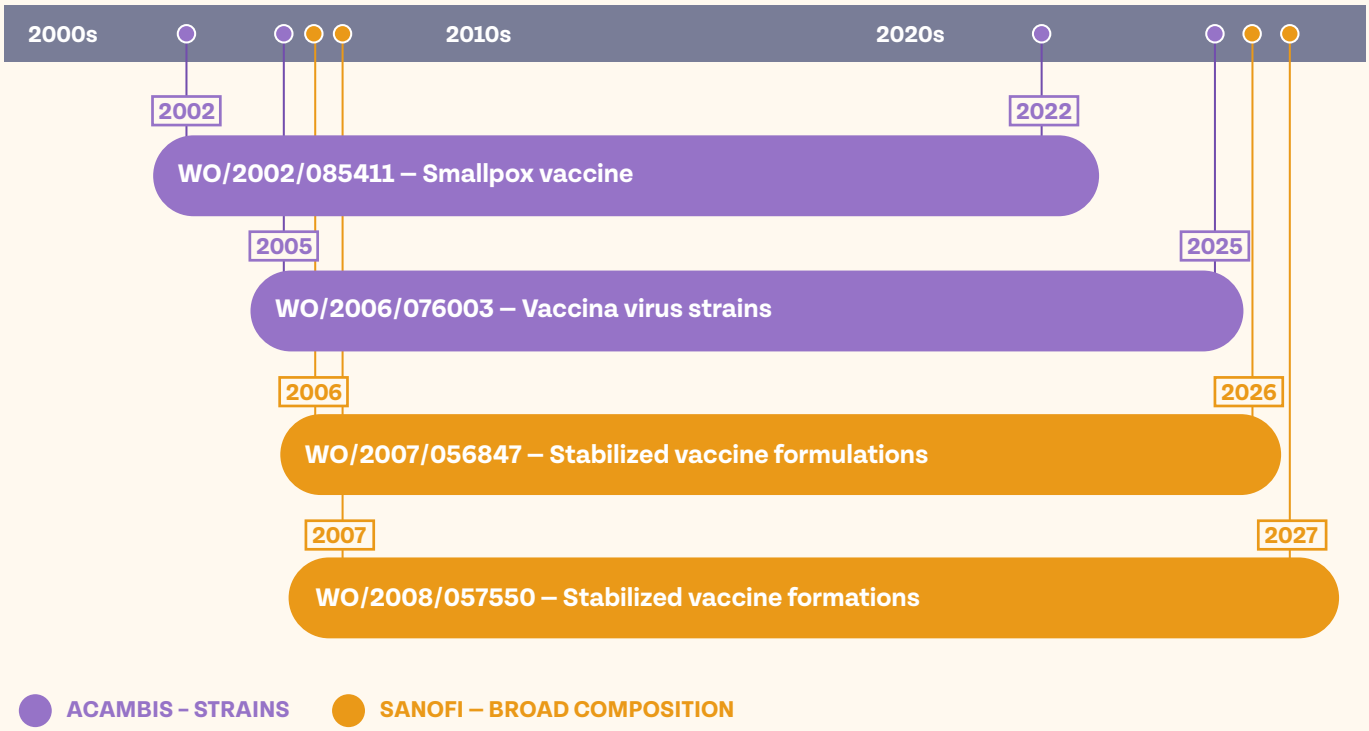
ACAM2000 was first approved by the US FDA in 2007 to prevent smallpox. In 2024, the indication was expanded to include prevention of mpox in individuals determined to be at high risk for mpox infection (Figure 6). Emergent BioSolutions is reported to have received orders of ACAM2000 estimated at USD 210 million for 2024 and 2025.[136]

PATENT LANDSCAPE

Patent search (Figure 7) results show that two PCT applications filed by Acambis in 2002 and 2005,respectively, pursued the protection of the clonal strains related to the ACAM2000 vaccine, as well as pharmaceutical compositions comprising the clonal strain and methods of use as a vaccine for variola infection. There were two PCT applications covering stabilized vaccine formulations comprising "a virus" or a "virus-based pharmaceutical product" wherein a poxvirus or smallpox virus are one possible embodiment claimed. Therefore, the latter PCT applications filed by Sanofi are focused on the components of a vaccine formulation with enhanced stability, which encompass ACAM2000 and other vaccine developments. A patent search in November 2024 did not find PCT applications related to mpox (as a new medical indication) filed by Emergent Biosolutions.

[134] https://pubmed.ncbi.nlm.nih.gov/15491873/
[135] https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/mpox
[136] https://www.fiercepharma.com/manufacturing/emergent-biosolutions-racks-400m-mpox-preparedness-orders-outbreak-continues-its

FIGURE 7: PCT applications related to ACAM2000®



mRNA VACCINES

CLINICAL SUMMARY

mRNA-based vaccines have certain advantages – they can be mass-produced more quickly, inexpensively, flexibly and safely than live, attenuated virus vaccines, and elicit cellular and humoral immune responses.

BNT166 is a two-dose, quadrivalent mRNA-based mpox vaccine being developed by BioNTech, with support from CEPI. A study in macaques reported no deaths (vs. 5 of 6) in vaccinated animals, who also had milder symptoms than those who were not vaccinated.[137] It is currently in a 96-person, dose-escalation phase I/II trial to assess safety, tolerability, reactogenicity and immunogenicity, in the UK and the US. Results are expected in late 2025.[138]

mRNA-1769 is a two-dose, quadrivalent mRNA-based mpox vaccine being developed by Moderna. In a non-human primate study, mRNA-1769 led to a stronger reduction of viremia and mpox lesions than MVA-BN.[139] It is currently in a 351-person, placebo controlled dose-ranging phase I/II trial in the United Kingdom to assess safety, tolerability and immunogenicity; results are expected in mid-2025.[140]

[137] https://www.cell.com/cell/fulltext/S0092-8674(24)00054-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867424000540%3Fshowall%3Dtrue

[138] https://www.clinicaltrials.gov/study/NCT05988203

[139] https://www.nature.com/articles/s41392-024-02058-x

[140] https://clinicaltrials.gov/study/NCT05995275?cond=MPOX&term=vaccine&rank=6

DEVELOPMENT OVERVIEW

The success of mRNA-based COVID-19 vaccines has led to expectations that the leaders in the field, BioNTech and Moderna, would develop an mpox vaccine candidate using the mRNA platform.

Both companies published preclinical results in the same journal, just months apart, and filed the corresponding PCT applications just days apart, demonstrating their prioritization of IP protection.

Orthopoxviruses have two distinct infectious forms, mature virions (MVs) and extracellular virions (EVs), each with distinct surface antigens. Immune responses targeting a single antigen can provide partial protection, but animal studies with subunit vaccines and monoclonal antibody prophylaxis have underscored the enhanced efficacy combining antibodies against both EV and MV antigens.[141,142,143]

Both mRNA-based vaccine candidates target proteins from EVs and MVs. In terms of target proteins, the difference is one target protein of MVs (H3 or A29. BioNTech's vaccine candidate, **BNT166**, targets MPXV proteins A35 and B6 (EVs) and M1 and H3 (MVs).[144] Moderna's vaccine candidate, **mRNA-1769**, targets A35, B6 (EVs) and M1 and A29 (MVs).[145]

In 2024, each company published preclinical data on their mpox vaccine candidates in *Cell*,[146,147] and started their phase I/II clinical trials in August and September of 2023 (Biontech NCT0598823;[148] Moderna NCT05995275[149]), respectively.

PATENT LANDSCAPE

While BioNTech and Moderna gathered preclinical data on their mRNA mpox vaccine candidates – before clinical trials started - both companies quickly filed the PCT application (May 2023) (Table 1), highlighting their strategy of IP protection by ensuring competitive positioning in vaccines for emerging infectious diseases. In both cases, PCT applications cover compositions comprising mRNA encoding mpox antigens in a lipid nanoparticle (LNP), and related methods of vaccination. BioNtech filed a second PCT application in 2024 covering methods of treating or preventing an orthopoxvirus infection (Table 1).

[141] https://pubmed.ncbi.nlm.nih.gov/12620810/
[142] https://pubmed.ncbi.nlm.nih.gov/27768891/
[143] https://pubmed.ncbi.nlm.nih.gov/16227266/
[144] https://pubmed.ncbi.nlm.nih.gov/38366591
[145] https://pubmed.ncbi.nlm.nih.gov/39236707/
[146] https://pubmed.ncbi.nlm.nih.gov/38366591/
[147] https://pubmed.ncbi.nlm.nih.gov/38366591/
[148] https://clinicaltrials.gov/study/NCT05988203
[149] https://clinicaltrials.gov/study/NCT05995275

TABLE 1: mRNA vaccine candidates

	BNT166 (BIONTECH)	MRNA-1769 (MODERNA)
Antigens	A35, B6, M1, H3 (BNT166a) A35, B6, M1 (BNT166c)	A35, B6, M1, A29
Preclinical data	Published online February 15, 2024[150]	Published online September 4, 2024[151]
Clinical trial	NCT05988203 **START:** 2023-09-21[152]	NCT05995275[153] **START:** 2023-08-15
International patent application	WO/2023/230295 **FILING DATE:** 25.05.2023 (priority 25.05.2022) **CLAIM 1.** A composition comprising a polyribonucleotide encoding one or more monkeypox antigens or fragments thereof and a pharmaceutically acceptable carrier. WO/2025/054556 **FILING DATE:** 06.09.2024 (priority 07.09.2023) **CLAIM 1.** A method of preventing or treating an orthopoxvirus infection in a subject comprising administering a composition or combination to the subject, wherein the composition or combination comprises: a therapeutically effective amount of one or more polyribonucleotides encoding one or more mpox virus antigens or antigenic fragments thereof; and a pharmaceutically acceptable carrier.	WO/2023/230481 **FILING DATE:** 23.05.2023 (priority 24.05.2022) **CLAIM 1.** A composition, comprising: a first messenger ribonucleic acid (mRNA) polynucleotide comprising an open reading frame (ORF) encoding a first orthopoxvirus protein and a lipid nanoparticle.

[150] linkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867424000540%3Fshowall%3Dtrue https://www.cell.com/cell/fulltext/S0092-8674(24)00054-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867424000540%3Fshowall%3Dtrue

[151] https://www.cell.com/cell/fulltext/S0092-8674(24)00972-3

[152] https://clinicaltrials.gov/study/NCT05988203

[153] https://clinicaltrials.gov/study/NCT05995275

OTHER BARRIERS

Multiple approaches ensure exclusivity of vaccines and their production. Trade secrets in manufacturing processes are a key barrier to global production and distribution of vaccines and other health products.

From a historical perspective, the manufacturing of penicillin highlights the complexity of IP in public health innovation.[154] During World War II, the US issued compulsory licenses, which forced private companies to license penicillin-related patents to the government. After the war, and international agreement divided these patent rights among participating firms, while still granting non-exclusive, royalty-free licenses to the US and UK governments. In 1948, WHO was created as a specialized United Nations Agency. WHO began work on penicillin production and equitable access, but this initiative faced several drawbacks. Pharmaceutical companies pursued patent protection of the manufacturing process, entering into litigation with those attempting to produce the antibiotic in India, while the US government tried to hinder the technology transfer by denying visas, blocking equipment export licenses and pressuring India to refuse the WHO proposal and accept a contract with Merck instead.

During COVID-19, some countries sought to address these barriers by seeking a waiver from the World Trade Organization on several sections of the Trade-Related Aspects of Intellectual Property (TRIPS) agreement, which would have enabled them to address prevention, treatment and containment of COVID-19 by not granting or enforcing patents or other IP obligations on copyright, industrial design, and protection of undisclosed information for COVID-19 diagnostics, therapeutics, and personal protective equipment for a three-year period.[155] Ultimately, the waiver only applied to COVID-19 vaccines; it did not cover protections on trade secrets, copyrights, and industrial designs and included additional, significant limitations.[156]

[154] https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0003940

[155] https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:/IP/C/W669R1.pdf&Open=True

[156] https://www.msf.org/lack-real-ip-waiver-covid-19-tools-disappointing-failure-people

POTENTIAL MPOX THERAPEUTICS: CLINICAL SUMMARIES AND PATENT LANDSCAPES

In September 2024, the Africa CDC, the Coalition for Epidemic Preparedness Innovations (CEPI), the NIH and WHO launched their ***Coordinated Research Roadmap***,[157] focused on aligning mpox research with outbreak response goals. The Roadmap established 10 steps for R& D, including to "...promote the development of new therapeutics and the evaluation of safety and efficacy of prioritized candidate therapeutics for mpox, in coordinated, collaborative multicenter trials," and to "define regulatory pathway for 'next generation' medical countermeasures."

Current options for mpox treatment are limited, as is information on their safety and efficacy from randomized controlled trials – and the pipeline is sparse, seemingly limited to a USD 3.8 million grant from NIH awarded to researchers at Texas A&M College of Veterinary Medicine and Biomedical Sciences and the University of Minnesota to develop mpox antivirals.[158]

TECOVIRAMAT

CLINICAL SUMMARY

Tecoviramat, an antiviral developed to treat smallpox, has been studied and used for mpox. It has been approved as a treatment for mpox by the European Medicines Agency, the Norwegian Medicines Agency, the Medicines and Healthcare products Regulatory Agency and Japan's Pharmaceuticals and Medical Devices Agency, but it is not recommended by WHO.

Two randomized clinical trials have assessed tecoviramat for mpox: PALM 007[160] (a placebo-controlled, double-blind trial of tecoviramat vs. placebo in the DRC among people with clade I mpox) and STOMP[160] (a double-blind trial of tecoviramat vs. placebo in people with non-severe clade IIb mpox in Argentina, Brazil, Japan, Mexico, Peru, Thailand and the United States, which included an open-label arm for children, people who are immunocompromised, pregnant/breastfeeding, or living with severe inflammatory skin conditions).

Both trials did not find that tecoviramat improved pain or time to resolution of mpox lesions. Nonetheless, Siga, the patent applicant, stated

[157] https://www.who.int/publications/m/item/a-coordinated-research-roadmap-on-monkeypox-virus--immediate-research-next-steps-to-contribute-to-control-the-outbreak

[158] https://vetmed.tamu.edu/news/press-releases/new-mpox-antivirals/

[159] https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo

[160] https://www.cdc.gov/mpox/hcp/clinical-care/tecovirimat.html

that, "A meaningful improvement was observed in patients [in PALM 007] receiving tecovirimat whose symptoms began seven days or fewer before randomization and in those with severe or greater disease, defined by the World Health Organization (WHO) as having 100 or more skin lesions,"[161] adding that "The STOMP results are not unexpected as the study design was similar to the PALM007 study except it was in patients with mild to moderate clade II mpox compared to patients with clade I mpox. It is important to note that approximately 75% of mpox patients in the randomized arms of the STOMP trial received tecovirimat more than five days after symptom onset, and higher risk patients were included in an open-label arm."[162] Subsequently, multiple legal investigations have been launched into Siga, for making misleading statements to their investors about the efficacy of tecovirimat.[163,164,165]

DEVELOPMENT OVERVIEW

Tecovirimat, a small molecule, is commercialized under the brand name TPOXX by SIGA Therapeutics. Its development trajectory started in 2002, when the molecule was identified as a potential antiviral candidate and assessed in pre-clinical studies in 2003. In 2006, a phase I trial started, and the compound was granted orphan drug status for the treatment and prevention of smallpox in the US. Phase II and phase III trials started, respectively, in 2009 and 2015, covering safety, tolerability and pharmacokinetics for orthopoxviral disease and smallpox.[166]

Tecorivimat was US FDA-approved for smallpox in 2018 (as an oral formulation). An intravenous formulation was approved in 2022. The drug has been used for mpox under an Expanded Access Investigational New Drug (IND) protocol. In Canada it was approved for mpox in 2021 (oral formulation). In 2022, the EMA approved oral tecovirimat for a broader scope of orthopoxviruses: smallpox, mpox and cowpox.[167] Tecovirimat's application in mpox is part of a repurposing strategy.[168]

Despite the declaration of the mpox PHEIC in August of 2024, WHO did not include tecovirimat in the December 2024 EUL, although it recognised its use in clinical trials and expanded access protocols, and the knowledge produced in these contexts.[169]

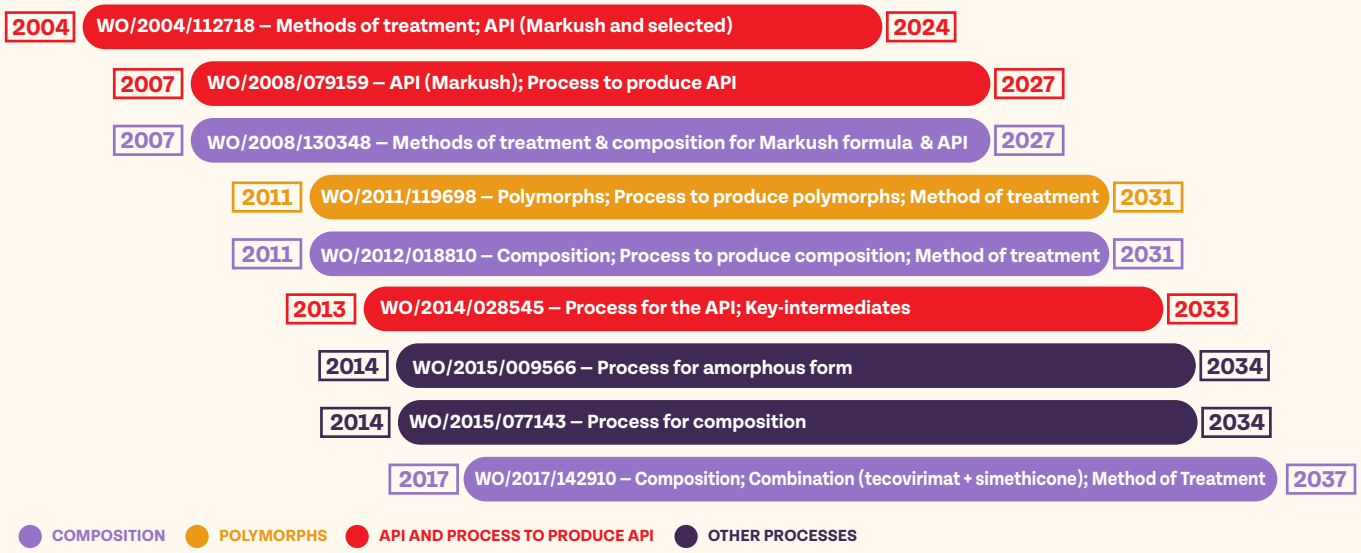
PATENT LANDSCAPE

As shown in Figure 8, nine PCT applications were filed between 2003 and 2017, focusing on multiple compounds (Markush formula), including the active pharmaceutical ingredient (API), its synthesis process and key intermediates; polymorphs and its processes; compositions; combinations, and methods of treatment. All PCT applications were available in existing landscapes, complemented by further filings in the US, and a few which were filed by other applicants.

The current landscape (Figure 8) presents an initial picture of the trends for protection, if filed and granted at the national level. While the main patent application would hypothetically expire in 2024, further applications would extend this for an additional 12 years.

[161] https://investor.siga.com/investors/news/news-details/2024/Topline-Results-from-PALM-007-Study-of-SIGAs-Tecovirimat-in-Treatment-of-Mpox-Released/
[162] https://investor.siga.com/investors/news/news-details/2024/Interim-Results-from-STOMP-Study-of-SIGAs-Tecovirimat-in-Treatment-of-Mpox-Announced/default.aspx
[163] https://www.hbsslaw.com/cases/siga-technologies-inc-siga-investigation
[164] https://www.accessnewswire.com/newsroom/en/business-and-professional-services/siga-technologies-inc-being-investigated-on-behalf-of-siga-techno-924315
[165] https://www.hbsslaw.com/cases/siga-technologies-inc-siga-investigation
[166] https://pubmed.ncbi.nlm.nih.gov/36146675/.
[167] https://pubmed.ncbi.nlm.nih.gov/36146675/
[168] https://www.science.org/doi/10.1126/science.abb9332Guy et al., 'Rapid Repurposing of Drugs for COVID-19'.
[169] https://www.who.int/news-room/fact-sheets/detail/mpox

FIGURE 8: PCT patent filings by SIGA Therapeutics covering tecovirimat



An initial analysis in countries where Make Medicines Affordable campaign members are working suggests that those applications are not filed at the national level in most countries, except in Argentina, Brazil and India, where some PCT applications were filed: WO/2011/119698, (BR112012023743 and IN3206/KOLNP/2012), and WO/2012/018810 (AR082566, BR112013002646, IN305/KOLNP/2013).

The experience on repurposed COVID-19 therapeutics calls for close monitoring of potential new patent filings for tecovirimat, as clinical trials in mpox may have promising results. There were multiple patent filings for a broad scope of medical indications for some of the repurposed COVID-19 medicines before the pandemic - and additional PCT applications were filed after the pandemic, usually focusing on the most recent indication for the drug.[170]

[170] https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2023.1287542/full

CIDOFOVIR AND BRINCIDOFOVIR

CLINICAL SUMMARY

Topical and intravenous cidofovir and /or oral brincidofovir have been used, either alone or sequentially (since overlapping toxicities prevent concomitant use) to treat severe, TPOXX-resistant mpox, but data are scarce.[171,172]

Cidofovir was US FDA- approved in 1996 to treat CMV retinitis in people living with AIDS; it is given intravenously or topically. Cidofovir is toxic to the kidneys and can cause renal failure after only one or two doses; it must be given with a renal-protective drug called probenecid. Data on its use in people with mpox are very limited. There are no ongoing clinical trials.

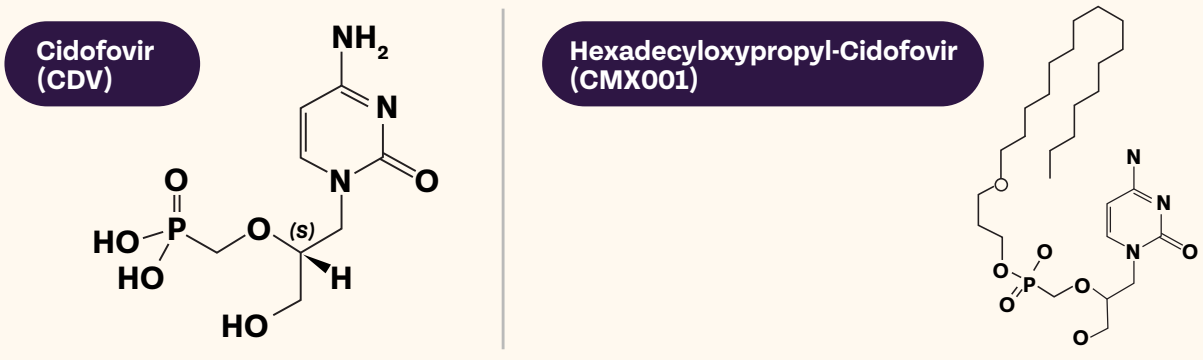
Brincidofovir is a less toxic formulation of cidofovir; it was US FDA approved in June 2021 to treat smallpox in people of all ages (although it cannot be used during pregnancy and breastfeeding). There are a few case reports of its use in mpox, and it is being assessed in the randomized, placebo-controlled, double-blind MOSA (MpOx Study in Africa) trial, overseen by the Africa Centers for Disease Control.[173]

DEVELOPMENT OVERVIEW

Cidofovir and brincidofovir are nucleoside analogues that block DNA replication , as shown in Figure 9. The active compound is cidofovir diphosphate (CDV-pp); therefore, cidofovir is a prodrug that needs to be phosphorylated in the human body.

Brincidofovir is a prodrug of cidofovir, with an added alkoxyalkyl moiety. This change aimed to improve oral bioavailability and reduce the nephrotoxicity associated with cidofovir, Brincidofovir is hydrolysed in the body to become cidofovir, which is then phosphorylated into the active ingredient, CDV-pp.[174]

FIGURE 9: Molecular structure of cidofovir and brincidofovir (CMX001)[175]



[171] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00044-0/fulltext
[172] https://www.mdpi.com/2075-1729/13/10/1969
[173] https://investors.emergentbiosolutions.com/news-releases/news-release-details/enrollment-starts-africa-cdc-led-mpox-therapeutic-study-mosa
[174] https://pubmed.ncbi.nlm.nih.gov/35904001/
[175] https://www.researchgate.net/figure/Chemical-structures-of-cidofovir-and-CMX001-The-chemical-structures-for-cidofovir-CDV_fig1_46170021

Cidofovir has a broad range of activity against DNA viruses, but it has only been US FDA-approved for treatment of cytomegalovirus retinitis for people with AIDS (in 1996), due to its potential to cause severe renal toxicity. It is commercialized by Gilead, under the brand name Vistide.[176] There is an investigational new drug (IND) protocol for cidofovir for smallpox.[177]

In 2021, brincidofovir was US FDA approved to treat smallpox. It was commercialized under the brand name Tembexa by Chimerix.[178] Currently, the safety and efficacy of brincidofovir treatment for mpox are being assessed in the Africa CDC-led MOSA phase III clinical trial.[179]

Brincidofovir was originally designed by the University of California, to address the kidney toxicity and bioavailability issues associated with cidofovir. The research was funded by the National Institute on Allergy and Infectious Diseases (NIAID), in the context of biodefense initiatives. Despite the university's attempt to license the patent on brincidofovir to several companies, the leading researcher of the project set up Chimerix, to continue research on bincidofovir and other antivirals. Brincidovofir was assessed in clinical trials for cytomegalovirus – and even Ebola virus – but these trials were terminated or withdrawn, respectively.[180]

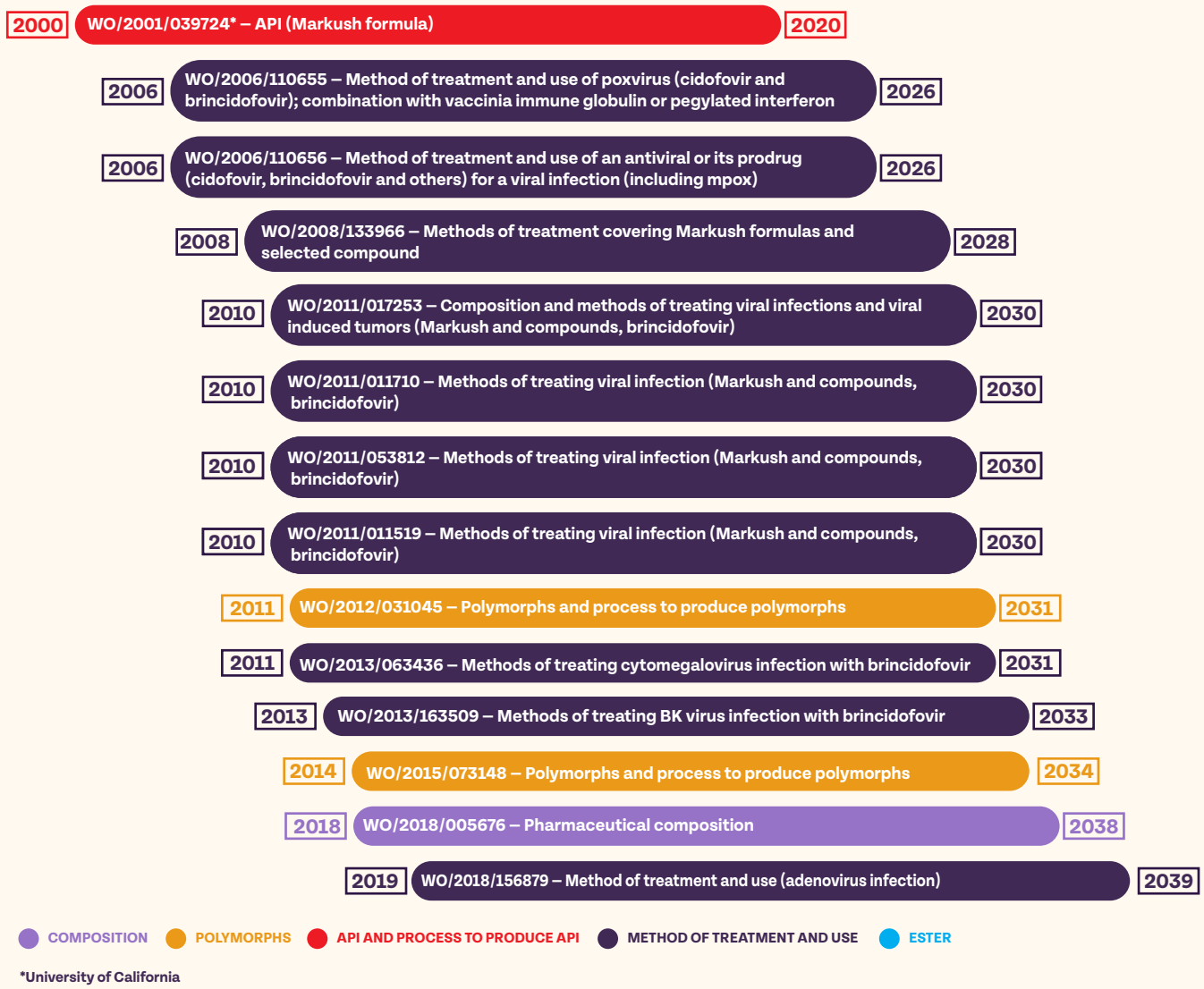
Chimerix was given BARDA funding for early R & D in animal models and, later, clinical trials for brincidofovir as a smallpox countermeasure.[181] In 2022, the company was awarded a 10-year contract from BARDA to supply brincidofovir, with initial procurement of 319,000 treatment courses for approximately USD 115 million.[182] In 2022, Chimerix sold the rights to brincidofovir to Emergent BioSolutions for USD 225 million, plus USD 100 million, dependent on the procurement agreement established with BARDA.[183]

PATENT LANDSCAPE

Chimerix has filed at least fourteen PCT applications related to brincidofovir (Figure 10). The initial PCT application, covering the API, was filed by the University of California in 2000. These PCT applications focus on methods of treatment and use, covering either several compounds (Markush formulas) and combination with other orthopoxvirus therapies; polymorphs and its process; and composition.

[176] https://pubmed.ncbi.nlm.nih.gov/35904001/
[177] https://pubmed.ncbi.nlm.nih.gov/37519276/.
[178] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf
[179] https://investors.emergentbiosolutions.com/news-releases/news-release-details/enrollment-starts-africa-cdc-led-mpox-therapeutic-study-mosa
[180] https://www.forbes.com/sites/davidkroll/2015/01/31/chimerix-ends-brincidofovir-ebola-trials-to-focus-on-adenovirus-and-cmv/
[181] https://www.pappas-capital.com/chimerix-and-barda-announce-continued-partnership-in-the-development-of-brincidofovir-for-smallpox/
[182] https://ir.chimerix.com/news-releases/news-release-details/chimerix-awarded-barda-contract-tembexa-medical-countermeasure
[183] https://medcitynews.com/2022/05/to-focus-on-cancer-chimerix-sells-rights-to-antiviral-drug-that-defined-the-biotech/

FIGURE 10: PCT patent filings by Chimerix covering brincidofovir



*University of California

CONCLUSION

A bench-to-bench mpox response is long overdue.

Although global health actors have taken some action to address mpox, their efforts are inadequate and unsustainable, because they are working within a system that prevents full global health equity. The combined impacts on mpox of racism, health neocolonialism, greed, and the IP system, including patents, are tragic – and infuriating, and have been exacerbated by drastic funding cuts to global health by the US and other donors. Mpox continues to strike vulnerable people, including children, pregnant women, and people living with HIV in African countries – even though vaccines can prevent it. These low-income countries have forced to rely on stingy, delayed donations of vaccines, instead of having the autonomy and the agency to source and locally produce desperately needed, affordable health products. For these products to have impact, sustainable strategies are urgently needed for health products, healthcare systems and the people who work in them.

A bench-to-bedside mpox response, which encompasses a robust development pipeline with LMIC access, affordability and opportunities for local production – and that will uphold global health equity and the human right to health – is long overdue.

RECOMMENDATIONS

Amidst the recent withdrawal of international support, adequate funding must be provided to strengthen surveillance, laboratory capacity, community protection, safe clinical care and vaccination efforts, as described in the WHO *Global Mpox Global Strategic Preparedness and Response Plan*.[184]

Creating access to affordable, locally produced vaccines and therapeutics for mpox and other illnesses involves both immediate and longer-term interventions:

High-income countries must share mpox (and other) vaccine stockpiles with affected countries during global health emergencies.

Technology transfer to LMIC manufacturers is essential for enabling local production of mpox (and other) vaccines; it should be mandated during public health emergencies of international concern – and for emerging threats.

IP barriers to mpox diagnostics, vaccines and therapeutics need to be removed or overcome.

- → Publicly-funded R&D can deliver patent-free mpox diagnostics, vaccines and therapeutics as a global public good, following the example of the COVID-19 vaccine Corbevax.[185]
- → Newer PCT filings for mpox diagnostics, vaccines and therapeutics need to be monitored for intervention as their development progresses.
- → For the MVA-BN vaccine, assess national IP barriers to inform access strategies (patent oppositions, compulsory licensing).
- → For mpox antivirals, after safety and efficacy are established, assess national IP barriers to inform access strategies.
- → Work to strengthen national patent laws to enable access to new health products for mpox and other conditions

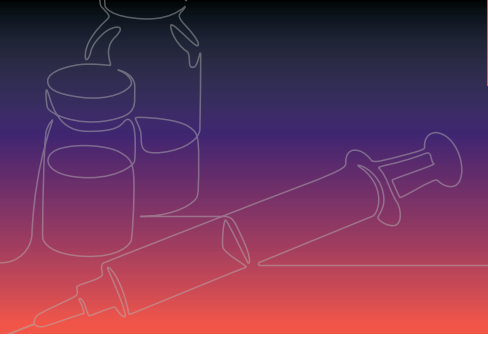
[184] https://www.who.int/publications/m/item/mpox-global-strategic-preparedness-and-response-plan-april-2025

[185] https://www.npr.org/sections/goatsandsoda/2022/08/31/1119947342/whatever-happened-to-the-new-no-patent-covid-vaccine-touted-as-a-global-game-cha

ANNEX

ANNEX

Detailed analysis of PCT applications related to MVA-BN vaccine



INTERNATIONAL PUBLICATION NUMBER (PCT)	CONTENT OF THE CLAIMS
V00083008 (UK)	Covers the MVA-BN strain (deposited at the European Collection of Cell Cultures [ECACC], in Salisbury, United Kingdom under number V00083008), and related compositions, use and methods of treatment.
WO/2003/008533	Describes culturing CEF cells at temperatures below 37 ºC, which leads to a higher yield of virus particles (in particular MVA-BN) per infected cell.
WO/2003/054175	Describes a method for the recovery and purification of poxviruses (in particular MVA-BN) from infected cells, comprising the step of high-pressure homogenization (instead of ultrasound) which is "reproducible, easy to control and allows an easy scaling up from laboratory to industrial scale."
WO/2003/053463	Aims to protect a poxvirus formulation comprising a disaccharide, a pharmaceutically acceptable polymer, and, optionally, a buffer suitable for freeze-drying the said poxvirus.
WO/2003/088994	Related to the use of a virus (in particular, MVA-BN) for the vaccination of a neonatal or prenatal animal (also including human beings).
WO/2004/022729	Refers to a method for cell culture, in which the virus is propagated, as well as a method for virus production in those cells. Particularly, the claims cover a method for the cultivation of primary avian cells (in particular, CEF) in a serum-free medium, comprising a factor selected from the group consisting of growth factors and attachment factors (examples provided in the application refer to EGF and fibronectin). According to the PCT application, the method disclosed avoids the use of animal sera in the cell culture process, which may contain adventitious pathogenic agents.
WO/2006/089690	Related to methods of inducing immunity using the poxvirus (or the poxvirus-containing composition), focusing on the timing in which the immunity is induced: "rapid" (defined as the generation of a protective immune response within seven days or less). Also covers the use and methods related to MVA-BN for the rapid induction of immunity against poxvirus or other infectious agents (optionally expressing heterologous antigens and/or antigenic epitopes).
WO/2008/131927	Related to methods of inducing immunity using the poxvirus (or the poxvirus-containing composition), focusing on the timing in which the immunity is induced: "immediate". Also refers to the use and methods related to poxvirus composition (MVA-BN) for inducing an immune response against an infectious agent in which the composition is administered between 36 hours prior to,72 hours after infection with the infectious agent. The latter also claims the composition or vaccine and related "kit".
WO/2008/138533	Related to virus harvesting and purification methods for industrial-scale production. Discloses a chromatography-based method for the purification of vaccinia virus involving the following steps: a) loading a solid-phase matrix, to which a ligand is attached, with a vaccinia virus contained in a liquid-phase culture; b) washing the matrix, and c) eluting the virus.
WO/2012/010280	Related to virus harvesting and purification methods for industrial-scale production. Describes a method for recovering the poxvirus (preferably MVA) expressed by appropriate host cells: a) culturing said host cell under conditions that allow expression of the virus; (b) collecting said host cell in/on a filter unit; (c) disrupting said host cell in/on the filter unit; and (d) separating the poxvirus from said disrupted host cell, wherein the said method can further comprise a chromatography-based purification step. The focus is the use of a filter unit to separate expression products from host cells.

INTERNATIONAL PUBLICATION NUMBER (PCT)	CONTENT OF THE CLAIMS
WO/2014/139687	The claims cover the use and methods of inducing an immune response in a human neonate or infant under six months of age, comprising the single high-dose administration of MVA.
WO/2015/136056	In the context of "the need for compositions able to achieve strong T-cell and/or antibody responses using a single dose and/or a smaller dose," this PCT application relates to methods of treatment and the use of a composition comprising MVA virus in an oil and water emulsion to induce vaccinia-neutralizing antibodies (wherein the composition induces at least a 2-fold higher level of vaccinia-neutralizing antibodies at 26 days after immunization when compared to the same composition in the absence of the emulsion).
WO/2018/211419	Co-filed by Bavarian Nordic and Janssen, in the context of their partnership to create a vaccine regimen against Ebola virus, comprising a dose of Ad26.ZEBOV (Janssen adenovirus vector-based vaccine) followed by a boost dose of MVA-BN-Filo (MVA-BN expressing Filovirus proteins). However, claims are broad enough to cover an aqueous composition comprising any poxvirus (in particular, MVA), a buffer, a sulphate salt, and optionally a sugar, sugar alcohol and/or polyol, suitable for long-term storage.
WO/2020/049151	Covers an aqueous formulation comprising a poxvirus having improved stability, and the actual focus of the applications are compositions for an MVA-BN respiratory syncytial virus (RSV) vaccine. Refers to a poxvirus composition (in particular, MVA), comprising at least one disaccharide, sorbitol, gelatin, albumin, a buffer, and at least one monovalent salt, having improved stability in liquid and liquid frozen states.
WO/2021/180943	Covers an aqueous formulation comprising a poxvirus having improved stability, and the actual focus of the applications are compositions for an MVA-BN respiratory syncytial virus (RSV) vaccine. Covers a poxvirus (preferably MVA) composition comprising arginine, albumin, gelatin and further comprising a buffer, a salt, a disaccharide, and sorbitol.
WO/2024/00334	Mammalian cell line for the production of modified vaccinia virus ankara (MVA). Specifically, a Chinese hamster ovary (CHO) cell line expressing a combination of poxvirus host range genes not expressed by MVA and the process to produce the cell line are covered by the claims.
WO/2024/188801	Use of quail cell lines for poxvirus production
WO/2024/188802	Methods of isolating poxviruses from avian cell cultures
WO/2024/188803	Production of poxviruses from quail cell cultures

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