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Major Advances in Monkeypox Vaccine Research and Development – An Update

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Abstract

Monkeypox (MPX) is a zoonotic disease that is endemic to the western and central regions of Africa and it is caused by monkeypox virus (MPXV), which is classified as a member of the Poxviridae family, specifically the Chordopoxvirinae subfamily, and the Orthopoxvirus genus. The current multiregional outbreak of MPX, which started in May of 2022, has since swiftly spread across the globe and thus has been declared a global public health emergency by the World Health Organization (WHO). Protective immunity against MPXV can be achieved by administering a smallpox vaccination, as the two viruses share antigenic properties. Although smallpox was declared eradicated in 1980, the vaccine campaign was halted the following year, leaving the population with significantly less immunity than it had before. The potential for human-to-human transmission of MPXV has grown as a result. Due to the lack of a particular treatment for MPX infection, anti-viral medications initially designed for the smallpox virus are being employed. However, the prognosis for MPX may vary depending on factors like immunization history, pre-existing illnesses, and comorbidities, even though the majority of persons who develop MPX have a mild, self-limiting illness. Vaccines and antiviral drugs are being researched as potential responses to the latest 2022 MPX epidemic. The first-generation smallpox vaccinations maintained in national stockpiles of several countries are not recommended due to not meeting the current safety and manufacturing criteria, as stated by the WHO. Newer, safer (second- and third-generation) smallpox vaccines, such as JYNNEOSTM, which has been licensed for the prevention of MPX, are indicated as potentially useful in the interim guideline. Studies on vaccines and antiviral drugs are still being investigated as possible remedies to the recent MPX outbreak. This mini-review article serves as a retrospective look at the evolution of smallpox vaccines from their inception in the 1700s to the current trends up to the end of year 2022, specifically for developing monkeypox vaccines.

Keywords: Monkeypox, Monkeypox Virus, Smallpox, Vaccines, JYNNEOSTM , ACAM2000®

INTRODUCTION

The smallpox virus was the first human disease to be completely eliminated. Eradication was accomplished by vaccination and public health protocols to track and limit the disease, suggesting that it had been completely eliminated from the world.[1-3] When the final case of smallpox in Somalia was reported in 1977, the World Health Organization (WHO) proclaimed the country free of the disease by 1980.[4] Variola major is considered a potential bioterrorism agent despite being extinct in the wild because of its high mortality, ease of transmission, lack of effective therapies for human illness, and the possibility that governments that support terrorism could acquire it. Vaccine research for smallpox and other members of the Orthopoxvirus family began several centuries ago and culminated in the invention of the MPXV vaccine in the early 20th century.[5,6] Orthopoxviruses, of which MPXV is a member, also include vaccinia, cowpox, and variola. Although monkeys were the first to have MPX reported in 1958, it is now thought that rodents are the primary reservoir for this virus, with primates like humans serving only as accidental hosts.[4] The first human cases were discovered in 1970 in the Democratic Republic of the Congo (DRC). There are two genetically distinct strains of MPXV; the one found in western Africa typically results in milder symptoms and a lower mortality rate (1-5 percent vs. 10 percent) than the strain found in central Africa, also known as the Congo Basin.[3,5,6]

Even as the COVID-19 pandemic nears its end or might persist further, new concerns are being raised about monkeypox virus (MPXV) infection. Before the outbreak of COVID-19, experts had not much indication that this particular virus existed, as MPX was considered a neglected and rare disease. The disease known as MPX has been around for quite some time. It was not until 1958 that the sickness was first documented. The DRC, located in central Africa, reported the first case of human MPX in 1970.[7-10] Since then, cases of MPX have been reported outside of the areas where it is naturally found. MPXV, like all poxviruses, is classified in the family Poxviridae and the genus Orthopoxvirus. MPX is a zoonotic disease that gets transmitted from animals to humans mostly

through exotic pet trade and international travel, however current rise of cases is believed to be due to rapid human-to-human transmission.[11-13] Initial signs of MPXV infection include high fever, headache, backache, swollen lymph nodes, and a rash similar to that of chickenpox. The majority of people with MPX experience just mild symptoms and make full recoveries in two to four weeks.[14-16]

Infections in humans start through contact with an infected animal or person. Thereafter, the virus can spread from person to person by big respiratory droplets or through skin-to-skin contact at an open wound (including through fomites). 3 In most cases, the incubation period lasts between 7 and 21 days, but it might be shorter if the host is exposed to an especially high dose of the virus (eg, bite vs scratch vs light touch). The primary symptoms of a symptomatic case are fever, chills, and malaise, followed by the appearance of a centrifugal rash on the palms and soles of the feet; most cases of this kind are self-limited (i.e. resolved without therapy).6,8 The maculopapular rash transforms into the vesicular rash, pustular rash, and finally, the crusting rash over the course of two to four weeks, while the fever can linger for up to a week. MPX infections, unlike smallpox infections, typically manifest as lymphadenopathy. Interestingly, the current outbreak has shown that MPX can also present atypically, without fever or rash, and with only one or a few skin lesions that can occur asynchronously. These lesions are most commonly found on the genitalia, the oral mucosa, and the rectal mucosa, which correspond to the areas of skin that come into contact during sexual activity.[4,5] Some new clinical symptoms, including urethritis, rectal pain, and urine retention, have been linked to MPX because of its relationship with sexual intercourse, leading to incorrect or delayed diagnosis and treatment. Even though the MPXV can cross the placenta, it is unknown what effects an infection during pregnancy might have. Recent reports of positive PCR assays for MPX in sperm from Germany and Italy, as well as a report of an infectious virus isolated from sperm in August 2022, have stoked fears that the virus may also be spread through sexual contact.[10-14]

Depending on where MPXV originated and the severity of the infection, case fatality rates (CFR) have ranged from 3% to 6% historically. Additionally, there is currently no specific therapeutic strategy for MPXV infection that has been shown to be effective. However, MPXV, variola virus (smallpox virus), and vaccinia virus all share certain characteristics (a component of Orthopoxvirus vaccines). Therefore, it is generally believed that smallpox vaccinations and medicines are also effective against MPX.[8,17] Not only that, but there has been pharmacological repurposing and approval of drugs for COVID-19 treatment. Many nations' healthcare systems have begun providing or stockpiling smallpox vaccines and medications in an effort to contain the spread of MPX.

There have been periodic outbreaks of MPX in areas of Africa where the virus has become endemic, most notably in the DRC and Nigeria in 2017. Outbreaks have also occurred in other parts of central and western Africa over the previous five years.[10] However, there has been an uptick in both the incidence of infections in Africa and the occurrence of outbreaks in non-endemic regions. The discontinuation of smallpox immunization following its eradication in 1980, leaving more people unprotected against Orthopoxvirus cross-protection, and the increased ease and speed with which formerly isolated clusters can swiftly become worldwide epidemics are both possible causes of this uptick.[12,14] For instance, 71 instances of MPX were reported in the United States in 2003 after infected prairie dogs were sold to customers. These animals had come into contact with African rodents that had been illegally imported and were carrying the virus. Finally, it is important to assess how mutations in the virus's DNA have affected its infectiousness.[18]

More than 100 nations have reported instances of MPX, and the disease has rapidly spread through these regions, prompting a global public health emergency declaration.[13,18] Due to antigenic similarity, smallpox vaccines provide protection against MPXV. However, following smallpox eradication, the smallpox vaccination program was discontinued in 1980, resulting in a virtual lowering or loss of immunity. This has increased the risk of human-to-human transmission of MPXV.[19-21] Protecting workers who may be exposed to Orthopoxviruses through vaccination is crucial. Anti-viral medicines originally developed for the smallpox virus are being used to treat MPX infections because no specific treatments

are available at this time. The majority of people who contract MPX have a minor, self-limiting illness; nevertheless, the prognosis for MPX may vary on factors like immunization history, pre-existing illnesses, and comorbidities.[22-26] Vaccines and antiviral medications are being researched as potential responses to the latest MPX epidemic. Novel vaccines are being developed and evaluated to combat current and future outbreaks of MPX.[27-29] Figure depicts the most significant developments in smallpox and then MPX vaccine research and development trending from the year 1700 to the present year 2022 when largest outbreak of MPX occurred. The purpose of this mini-review article was to look back at the history of MPX vaccine development, beginning in 1700 and forward to 2022.

First-generation vaccines focusing smallpox and prospects for MPX

It was through variolation that the first smallpox vaccination programs were initiated in ancient China, India, Persia (modern-day Iran), and Africa. The ancient Chinese used a method very similar to snuff, in which they would sniff smallpox crusts. Variolation was introduced to Europe in the early 1700s by Lady Mary Montagu, the wife of the British ambassador to Turkey. Material from a smallpox pustule was injected under the skin of a healthy volunteer. Given that the inoculum was injected subcutaneously, it is likely that it stimulated the immune system without triggering an infection. Death was one of the unintended outcomes of the procedure.[30] In 1796, a country doctor named Edward Jenner from Gloucestershire used cowpox to successfully vaccinate against smallpox. She performed the first documented smallpox immunization on May 14, 1796, on James Phipps, then 8 years old. Benjamin Jesty, a farmer from Dorset, probably inoculated his family with material from cowpox pustules in 1774, despite the fact that Jenner is commonly credited with inventing vaccination.[31]

There was a dramatic drop in the prevalence of smallpox in the nineteenth century, following the discovery of the vaccine for the disease in 1796 (which eventually led to the development of the MPX vaccine). By late 1960, the danger of contracting smallpox in North America and Europe had been reduced to zero thanks to the mass immunization program that had begun in 1940.[32] Before the introduction of the freeze-dried live-virus vaccine Dryvax®, calf lymph was used as a smallpox vaccination from the early eighteenth century to the nineteenth century. The smallpox vaccine was originally only available in liquid form, but since the 1920s, factories in France and the Netherlands East Indies (now Indonesia) have produced air-dried and freeze-dried vaccines. It was necessary to chill liquid vaccinations so that

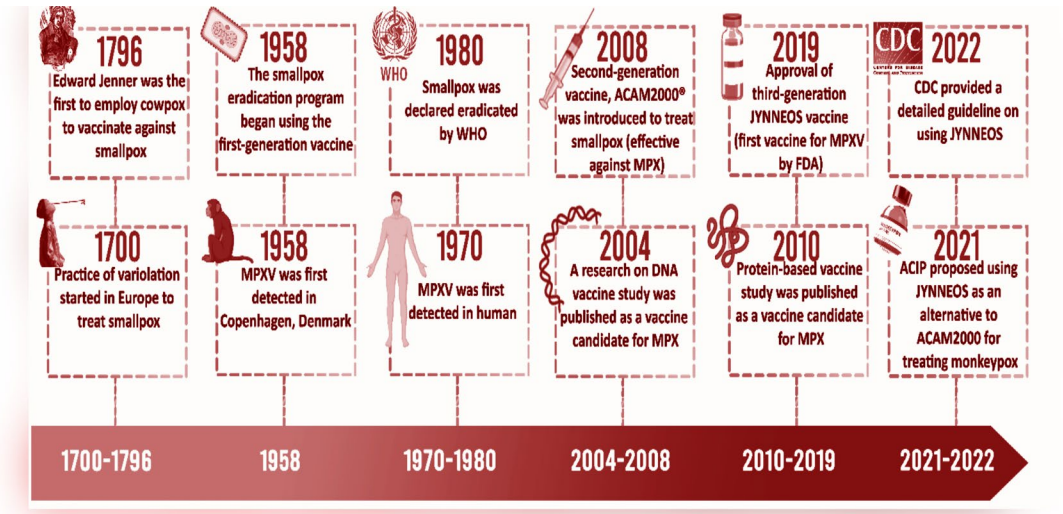

Figure. Major advances in MPX vaccine research and development including smallpox between the years 1700 and 2022

they would maintain their potency for longer than a few days.[3,33,34]

The freeze-dried vaccine, on the other hand, maintained its full efficacy even after being stored at room temperature for more than a month, even in tropical climates. Freeze-dried vaccines were employed to prevent smallpox in tropical countries beginning in 1959, yet it was not until 1967–1968 that they were administered on a significant scale. In the years following 1971, this vaccination was the only one used worldwide to successfully eradicate smallpox.[5,21]

In 1958, during the 11th World Health Assembly, Professor Zhdanov pushed for the global eradication of smallpox. Vaccination campaigns for large groups of people made use of freeze-dried vaccinations.[31] The development of freeze-dried vaccine in United Kingdom was a game-changer in the effort to wipe out smallpox throughout the industrialized world. In addition to the freeze-dried vaccine, vaccinia can also be injected into the skin using a special bifurcated needle. This has the benefit of only using a single ampoule for a vaccination, which reduces vaccine wastage significantly. It was estimated that the first-generation live vaccinia virus vaccination (VACV) used to wipe out smallpox was 85% effective against MPX infection. Pregnant women, people with impaired immune systems, and those with a history of eczema were particularly vulnerable to the severe side effects associated with the initial generation of vaccinia vaccination.[1,5] There were 68 deaths in the United States attributed to adverse reactions to the smallpox vaccine in the nine years from 1959 to 1966 and 1968. Of these deaths, 19 were attributable to vaccinia necrosum, 36 to postvaccinal encephalitis, 12 to eczema vacciniforme, and 1 to Stevens-Johnson syndrome.[33,35]

Second-generation MPX vaccines

Pre-exposure immunization has been advised by the Advisory Committee on Immunization Practices (ACIP) since 1980 for some laboratory and healthcare professionals who may be exposed to Orthopoxviruses owing to their occupation. A second-generation vaccine, ACAM2000®, was released in March 2008 to take the place of Dryvax®. It is made from a plaque-purified clone of the same New York City Board of Health strain used to produce Dryvax®.[36-38] The United States government contracted a pharmaceutical company to manufacture the ACAM2000® vaccine as a precautionary measure against potential pandemics on behalf of the Centers for Disease Control and Prevention (CDC). On August 31, 2007, the Food and Drug Administration (FDA) approved the ACAM2000® vaccine for use in persons at high risk of getting smallpox. Animal studies consistently found that the ACAM2000® vaccination was highly effective against MPX.[39,40]

ACAM2000® is delivered as a lyophilized preparation of purified live viruses and administered in a single dose by the percutaneous route (scarification). After receiving the ACAM2000® vaccine, a person is deemed fully immunized after 4 weeks.[4,6] Regular immunization with ACAM2000 has been recommended by ACIP for laboratory workers who handle or cultivate vaccinia virus since 2015. It has been shown that ACAM2000, which is produced in African green monkey kidney (Vero) cells, contains no detectable levels of any known adventitious agents.[41,42]

In 2015, ACIP endorsed ACAM2000®, which is administered via a bifurcated needle. From 2015 to 2019, the FDA only authorized the use of the ACAM2000® vaccination to prevent Orthopoxvirus infection. The United States Department of Defense (DoD) uses ACAM2000 vaccine to safeguard selected service members. Due to its replication competence, ACAM2000 can cause serious adverse effects like progressive vaccinia and eczema vaccinatum. Some people developed myopericarditis due to ACAM2000® (estimated rate of 5.7 per 1,000 primary vaccinees based on clinical trial data).[43-45] Studies on ACAM2000® show it has a safety profile similar to that of Dryvax. Serious adverse effects, such as progressive vaccinia, postvaccinal encephalitis, eczema vaccinatum, and myopericarditis, are possible with ACAM2000®. People with impaired immune systems, those with skin problems including atopic dermatitis/eczema, and pregnant women are discouraged from using ACAM2000®.[42] A study conducted by Faix et al (2020) described a small, statistically insignificant increase in the risk of myopericarditis, mostly subclinical, after receiving ACAM2000 in military personnels. Recently a report of a MPX case having vaccinated

with ACAM2000® eight years ago has been published.[14] This infection can be attributed to human-to-human transmission which has became main mode of transmission for current MPX outbreak.[14,26]

Third-generation MPX vaccines

An attenuated, replication-competent, third-generation vaccinia vaccine, LC16m8 has been approved for use in Japan and has a high safety profile and high immunogenicity after just one dose. While Japan did issue a license for LC16m8 in the 1970s, it was never used in the country's successful effort to eradicate smallpox. After LC16m8 production resumed in Japan in 2002, its safety and effectiveness had to be re-evaluated. Over 50,000 children in Japan were vaccinated with LC16m8 in the 1970s, and around 3,500 healthy adults were vaccinated with LC16m8 in the 2000s. Multiple studies in animal models have shown that LC16m8 protects the host from viral challenges, demonstrating the drug's safety and efficacy.[44-48]

Smallpox immunization with an injectable vaccine called modified vaccinia Ankara (MVA) is approved for use in the European Union (marketed as IMVANEX) and Canada (marketed as IMVAMUNE). The FDA has authorized the use of modified live attenuated vaccine (MVA; brand name: JYNNEOSTM) in 2019 for the prevention of both smallpox and MPX in populations at high risk of infection.[22,23] The FDA has granted approval to JYNNEOSTM, making it the first vaccine of its kind to target MPX. In contrast to the replication-deficient JYNNEOSTM, the replication-competent ACAM2000® is a vaccinia Ankara strain.[18,25,26] Developed by Bavarian Nordic A/S, this vaccine is safe and effective against smallpox and MPX for anyone aged 18 years and above. Due to the recent MPX outbreak, JYNNEOSTM has become the major vaccination utilized (Chandran et al. 2022; Soheili et al. 2022). It is also considered as efficient and safe for patients of HIV and atopic dermatitis hence important for endemic areas of MPX.[48,49]

In November 2021, ACIP advocated using JYNNEOSTM instead of ACAM2000® and unanimously accepted JYNNEOSTM as an acceptable alternative to ACAM2000® for both the primary vaccine and the booster doses against MPXV.[6,22,23] Those who are concerned about contracting Orthopoxvirus now have access to two vaccinations (ACAM2000® and JYNNEOSTM) that have shown to be effective in preventing the disease.[49,50] Because JYNNEOSTM protects against a virus that lacks the ability to replicate, serious adverse reactions to the vaccination are not anticipated. Myopericarditis following ACAM2000® administration is thought to be an immune-mediated disease; however, it is unknown whether the antigen or antigens that produce autoantibodies are also present in JYNNEOSTM.[22-34]

Over the course of more than 570 passages in primary chicken embryo fibroblast cells, the MVA strain became replication-restricted to only avian and a few mammalian cell types. JYNNEOSTM is exclusively available as a subcutaneous injectable suspension. Individual 0.5 mL doses are packaged in single-use vials. Two injections, spaced out by four weeks, are required. Around two weeks after receiving their second dose of JYNNEOSTM, a person is regarded to be fully immunized.[22-24] Injection site reactions include itching, discomfort, redness, and swelling are possible negative effects. Vaccination is contraindicated in patients with a severe allergy to any of the vaccine's components, including gentamicin, ciprofloxacin, or egg protein. Patients with HIV and eczema can receive JYNNEOS safely. There is no evidence of teratogenic effects in animal studies. There are no risks associated with pregnancy or breastfeeding.[11,51]

In a recent study, third generation smallpox vaccine IMVANEX® has been found effective against MPX in risk groups but has not completely prevented infection.[52]

Fourth-generation MPX vaccines

Vaccines built from genetic code and protein scaffolds are currently in the midst of intensive research and development, marking the beginning of what could be dubbed the fourth generation of vaccines. Pure protein ectodomains of A33 and B5, generated from EV, with L1 and A27, derived from mature virus, and the adjuvants Alhydrogel and CpG, were shown to provide complete protection against deadly MPXV in a study involving nonhuman primates. Two doses of an adjuvanted protein subunit vaccine provided protection in nonhuman primates.[53] An additional study discovered that rhesus macaques were better protected from severe MPX infection when

vaccinated using a recombinant vaccination mode (DNA plus proteins) rather than DNA or proteins alone. An effective vaccine against live VACV would be useful; however, it is not feasible when screening large populations to determine who is at most risk for complications. In addition, it could be used to immunize those who are unwilling to receive the VACV vaccination and provide safe baseline poxvirus immunity.[54-56]

Major progress in developing MPX vaccines including smallpox vaccine between the years 1700 and 2022 is presented in Figure.

Non-human primate studies

Although mice, prairie dogs, ground squirrels, African dormice, and African pouched rats have all been used to test vaccinations and antivirals for MPX, it is generally agreed that non-human primates are better models of human illness. Numerous studies have shown that protection from first-generation vaccinations is superior. The vast majority of animals have complete immunity and show no signs of clinical disease.[28,33,40] When a rash and other symptoms do occur, they tend to be milder and resolve more quickly than they do with previous-generation vaccines, and the rash itself is always more localized (i.e., it covers a smaller percentage of the body and has fewer lesions).[6] Low-level, temporary viraemia is detected seldom. The protection offered by the ACAM2000 second-generation vaccine is comparable to that offered by the first-generation vaccines. MVA and LC16m8 also offer substantial protection; however, breakthrough disease is more common and, when present, the rash is more noticeable than with first- or second-generation vaccines. Animals inoculated with either a first- or second-generation smallpox vaccine have shown comparable or slightly greater antibody titres in investigations of immunogenicity. The results of these animal studies demonstrate unequivocally that smallpox vaccines stimulate immunological responses that can provide substantial and, in many cases, full protection against MPX infection.[11,40,49,50]

Human studies

Many studies have reported the use of smallpox vaccines during outbreaks of MPX, adding to the information gathered from animal models. Studies like this add to the growing body of evidence in favor of cross-protective immunity. Surveillance data collected in Zaire (now the Democratic Republic of the Congo) between 1980 and 1984 shows that the incidence of MPX is greater in those who have not been vaccinated against smallpox. Immunization against smallpox in the past is considered to be 85% effective.[3,44] Surveillance data gathered during the 2006-2007 outbreaks in the DRC revealed that 38% of MPX cases had evidence of prior smallpox vaccination, compared to 26% of the general population. Immunization was associated with a 521-fold lower incidence of MPX in people born before smallpox vaccination was discontinued, with an estimated vaccine efficacy of 80.7%. Six of the 29 people studied who contracted smallpox during the 2003 outbreak in the United States showed signs of having been vaccinated as children, demonstrating that remote immunization offers some protection but not necessarily complete immunity to symptomatic disease.[14,19,24,39,42] In reality, multiple findings suggest that the condition is altered by prior smallpox vaccination, with vaccinated persons typically experiencing milder symptoms and a less severe rash and fewer lesions. In 2017, researchers in the DRC began testing the safety and efficacy of JYNNEOS in healthcare workers who were at high risk of exposure to the MPXV.[5,11,25,36] The study's results have not been released yet, but they promise to contribute to the existing body of real-world evidence demonstrating the value of smallpox immunization in high-risk populations. Note that sexual contact is a likely transmission route in this outbreak. In addition, a significant prevalence of genital lesions was reported during a human MPX outbreak in Nigeria in 2017-2018. This finding was unprecedented in previously published outbreaks. This previously reported high incidence, in addition to the clear association between sexual activity and the incidence of genital lesions during the 2022 outbreak, may suggest either a new route of transmission or a lower threshold for infection through sexual activity compared to transmission from non-sexual contact.[6,22,23,30,35,41,50]

Ring vaccination to counteract MPX outbreak and limit virus spread

Of note, ring vaccination strategy has been opined to combat the ongoing MPX outbreaks by

limiting the virus transmission and spread, and this can be of potential benefits during mass gathering events. The success of ring vaccination, or the immunization of close contacts of confirmed patients, depends on the rapid diagnosis of infected cases. The extent and length of controlled outbreaks are highly unpredictable due to the intrinsic randomness of epidemic outbreaks. The Ebola virus was previously eliminated via a ring vaccination method. The spread of MPX can be stopped by immunizing close contacts of an infected person.[57] The United States of America (USA) and a number of European countries have already begun implementing the plan. The Union Ministry of Health and Family Welfare in India has recently decided to implement the ring vaccination technique in an effort to control the disease. Several countries have tried ring vaccination in response to recent epidemics. For this strategy to work, vaccination must occur within 1-4 days following exposure.[5,23,57] Specifically, for the MPX outbreak, and because of the slow transmission and long incubation time of the disease, ring vaccination offers a possible approach. Health officials benefit from the strategy's simplicity, efficiency in making use of scarce resources (vaccines and personnel), less likelihood of spread, fewer vaccines needed to complete the ring, and higher effectiveness in geographically distinct towns with smaller populations.[55-5]7 The IMVANEX vaccine, a third-generation smallpox vaccine, was well tolerated and did not cause side effects in an observational study conducted by researchers at Universite Paris Cite. The study compared high-risk close contacts of confirmed cases with and without vaccination. Twelve people out of 276 who were immunized experienced a breakthrough illness, and another dozen close contacts became ill 5 days after immunization. Two other people became infected 22 and 25 days later. The authors found that the vaccine reduced the chance of infection but was unable to eliminate the disease entirely.[57]

The ring vaccination method needs to be used with prudence. Firstly, this method is dependent on thorough testing and contact tracing, which is difficult in places where stigma persists and may prove tough to infiltrate since MPX can potentially spread through sexual contact among males who have sex with other men (MSM). Due to religious, cultural, and legal reasons, MSM can feel ashamed and discriminated against, especially in countries where such behavior is illegal. Therefore, it may be challenging to trace these individuals and their sexual relationships, which may put the ring vaccination method at risk.[58] Concurrently, these communities require public education initiatives, medical facilities equipped to handle cases of sexually transmitted diseases, and emotional and social welfare programs. Secondly, logistical, manufacturing, and financial barriers may prevent impacted countries from implementing ring vaccination immediately. Finally, it can be challenging to persuade the public to get vaccinated because some of the currently available vaccinations have been linked to uncommon but substantial adverse outcomes. Thus, education efforts across the country will be necessary to assist and speed up the process of introducing ring vaccination. In conclusion, there is an immediate need to create novel vaccinations that precisely target MPXV to effectively manage this disease, as well as genomic surveillance for MPXV in human and animal populations. Efforts made at the international level to standardize vaccine production and disperse them fairly are crucial.[57-63]

Of note, other recent advances in designing specific MPX vaccines by exploring modern vaccine development platforms and technologies comprise of developing newer, novel and next-generation vaccines, multiple-epitope vaccine employing pan-genome and reverse vaccinology, multi-epitope and multi-valent peptide-based vaccines approaches using molecular biology, bioinformatics, immunoinformatics, vaccinomics approaches, and formulating nucleic acid-based universal MPX vaccine candidates.[63-75] Such progresses in formulating novel MPX vaccines would certainly aid in countering MPX outbreaks and facilitate future preparedness plans.

CONCLUSION AND THE FUTURE

Dangers to human health from MPX are significant owing to its global public health concerns. The disease's transmission patterns and clinical presentation are clearly evolving, especially outside of Africa. Infants and young children (under the age of eight), pregnant women, and

people with impaired immune systems are likely to be at the greatest risk. The United States now maintains smallpox MPX vaccinations in its Strategic National Stockpile, in addition to two potential antiviral treatments. There are not many other countries that have taken these kinds of precautions. A major choice, when to deploy antivirals and vaccinations, is currently being examined on a national and WHO scale. Given the extremely low risk of infection in the general population, the most rational application will not be mass immunization but rather in individuals at elevated risk as a result of behaviour, occupation, or close contact. Given the rate of dissemination so far, a ring vaccination campaign is necessary. Furthermore, we propose that healthcare facilities think about keeping core teams of healthcare workers who are regularly updated on training and immunizations to treat patients with high-consequence infectious diseases like MPX. ACAM2000, MVA-Bavarian Nordic, LC16m8, and other vaccines all have different risks and advantages, uses, and availability that play a role in vaccination selection. Note that the risk-benefit analysis may vary over time and amongst populations.

Pre-exposure prophylaxis (PrEP) of people at high risk of exposure is the most efficient strategy to deploy immunizations to contain an MPX outbreak if contact tracing fails to discover a significant percentage of infected contacts. Vaccination plans should give first priority to men who have intercourse only with other men, as well as frontline health workers who are at high risk of occupational exposure. Health care workers, members of public health response teams, and those working in research and clinical laboratories that diagnose MPXV should all ideally be immunized. Individuals who take all reasonable precautions, including wearing protective gear, pose no sufficient risk of infection to require post-exposure prophylaxis (PEP). People who have been exposed to MPXV but who have not received a smallpox vaccination within the past three years should also be inoculated. All people are not at high risk for MPX, hence there is no need for a widespread vaccination campaign against it right now. Several countries with MPX epidemics have amassed supplies of second-generation vaccinations. Pregnant women, young children, the immunocompromised, and people with skin conditions like eczema are advised against using the vaccines currently in storage due to the risk of adverse reactions. Third-generation vaccinations have fewer side effects but are less widely available, which could improve vaccination rates. There may be a need to revise the risk-benefit analysis if the virus spreads to high-risk populations like pregnant women or young children, or if the death toll is higher than anticipated. Rather of vaccinating everyone against smallpox, a ring vaccination strategy targeting those at highest risk should be implemented in light of the ongoing MPX epidemic. In light of this, the immunization program faces a significant difficulty in identifying the best group to focus on in terms of providing easy access to immunizations, taking into account both risks and benefits. The epidemiological status of the jurisdiction and the most recent results on the transmission dynamics, severity, and mortality of the MPXV should also be considered when evaluating the target population.

The potential for evolution of the MPXV genome to boost transmissibility, augment virulence, or degrade antiviral efficacy by modifying the genetic sequence for proteins blocked and targeted by antivirals, such as the VP37 protein and tecovirimat, is also a major issue today. Such worries are reasonable and should be planned for in light of the precarious state of affairs surrounding COVID-19, climate change, shaky economies, the growing prospect of conflict, and continued troubles with the supply chain. Meanwhile, it is crucial to educate public health officials, healthcare providers, and the general public on the ongoing danger posed by emerging illnesses. It is imperative that countries re-evaluate their level of preparedness for pandemics like MPX and create their own strategic national stockpiles for the benefit of international security. The funding for education, avoidance, analysis, and treatment cannot be sporadic. The lessons of the COVID-19 pandemic are clear: preparedness is an ongoing process and a wise investment in the health of the population and the prosperity of the nation's economy. Education is crucial key in this area, and a system of classes, exams, tracking, and treatment should be implemented broadly.

Those most at risk of MXV infection must be reached, and vaccination rates must

be maintained, globally through targeted health promotion activities. Herd immunity must be ensured against this virus, which necessitates more clinical research and pharmacovigilance monitoring in vulnerable populations. Enhanced monitoring and diagnosis, better infection prevention and control in healthcare facilities, and social and safety containment measures are urgently needed now. The most vulnerable, including the poor and the wealthy living on the margins, as well as those living in the areas hardest hit by the outbreak, will need to be the focus of global efforts to ensure widespread access to vaccines, effective contextual risk communication, rising awareness, and public engagement strategies. A comprehensive immunization strategy needs to be created before MPX cases continue to climb exponentially, posing a pandemic threat in the midst of the current COVID-19 epidemic.

Unfortunately, there are not yet any scientifically-backed prophylactic or therapeutic strategies for MPX. A human model study investigating the effects of smallpox immunizations and Orthopoxvirus inhibitors on human MPX infections is also recommended. To combat the spread of MPX, the WHO can dispatch teams of experts to assess the efficacy of smallpox and MPX vaccinations and antivirals, and then provide member states with guidance on how to implement those recommendations. Public education, prevention initiatives, rapid case discovery and isolation, contact tracing, and treatment may all play a role in controlling MPX outbreaks.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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