



NARRATIVE REVIEW

Repositioning potentials of smallpox vaccines and antiviral agents in monkeypox outbreak: A rapid review on comparative benefits and risks

Md. Rabiul Islam¹  | Md. Jamal Hossain²  | Arpira Roy³ |
A. H. M. Nazmul Hasan¹ | Md. Ashrafur Rahman⁴ | Mohammad Shahriar¹ |
Mohiuddin Ahmed Bhuiyan¹

¹Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

²Department of Pharmacy, State University of Bangladesh, Dhaka, Bangladesh

³Department of Biotechnology, Sharda University, Greater Noida, India

⁴Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center (TTUHSC), Amarillo, Texas, USA

Correspondence

Md. Rabiul Islam, Department of Pharmacy, University of Asia Pacific, 74/A Green Rd, Farmgate, Dhaka-1205, Bangladesh.
Email: robi.ayaan@gmail.com

Abstract

Background and aims: There is a sought for vaccines and antiviral agents as countermeasures for the recent monkeypox outbreak. Here, we aimed to review and discuss the repurposing potentials of smallpox vaccines and drugs in monkeypox outbreaks based on their comparative benefits and risks. Therefore, we conducted this rapid review and discussed the repurposing potentials of smallpox vaccines and drugs in monkeypox infection.

Methods: Here, we searched Google Scholar and PubMed for relevant information and data. We found many articles that have suggested the use of smallpox vaccines and antiviral drugs in monkeypox outbreaks according to the study findings. We read the relevant articles to extract information.

Results: According to the available documents, we found two replication-competent and one replication-deficient vaccinia vaccines were effective against *Orthopoxvirus*. However, the healthcare authorities have authorized second-generation live vaccinia virus vaccines against *Orthopoxvirus* in many countries. Smallpox vaccine is almost 85% effective in preventing monkeypox infection as monkeypox virus, variola virus, and vaccinia virus are similar. The United States and Canada have approved a replication-deficient third-generation smallpox vaccine for the prevention of monkeypox infection. However, the widely used second-generation smallpox vaccines contain a live virus and replicate it into the human cell. Therefore, there is a chance to cause virus-induced complications among the vaccinated subjects. In those circumstances, the available *Orthopoxvirus* inhibitors might be a good choice for treating monkeypox infections as they showed similar efficacy in monkeypox infection in different animal model clinical trials. Also, the combined use of antiviral drugs and vaccinia immune globulin can enhance significant effectiveness in immunocompromised subjects.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Health Science Reports* published by Wiley Periodicals LLC.

Conclusion: Repurposing of these smallpox vaccines and antiviral agents might be weapons to fight monkeypox infection. Also, we recommend further investigations of smallpox vaccines and *Orthopoxvirus* inhibitors in a human model study to explore their exact role in human monkeypox infections.

KEYWORDS

antiviral agents, brincidofovir, cidofovir, drug repositioning, monkeypox, tecovirimat

1 | BACKGROUND

Monkeypox is spreading new worries around the world before the end of the Covid-19 epidemic. Covid-19 was a new type of virus that scientists had no idea about before the disease spread. Monkeypox is not a new disease. The disease was first reported in 1958.¹ In 1970, the first case of human monkeypox was reported in a central African country named the Democratic Republic of the Congo.¹ Afterward, monkeypox infections have been reported in several countries in West and Central Africa.² However, the prevalence of the disease outside Africa was not so high before May 2022. Since January 1, 2022 to June 15, 2022, a total of 2103 confirmed cases of monkeypox and one death have been reported from 42 European, American, and nonendemic countries.³ Monkeypox virus is a poxvirus that belongs to the *Orthopoxvirus* genus of the *Poxviridae* family.⁴ The initial symptoms of monkeypox infection include a high fever, headache, backache, swollen lymph nodes, and chickenpox-like rash.⁴ Most monkeypox symptoms are mild and patients recover within 2–4 weeks. The case fatality historically varies from 3% to 6% depending on the source of the monkeypox virus and the condition of the patients.⁵ Moreover, evidence-based proven therapeutic intervention for monkeypox infection is still absent. However, there are similarities between the monkeypox virus, variola virus (smallpox virus), and vaccinia virus (a component of orthopoxvirus vaccines). Therefore, smallpox vaccines and drugs are assumed to be effective in monkeypox infection. Moreover, we have seen drug repurposing and authorization for Covid-19 therapy.^{6,7} The healthcare authorities in many countries have started to offer or stockpile smallpox vaccines and drugs to control monkeypox outbreak. Here, we aimed to review and discuss the repurposing potentials of smallpox vaccines and drugs in monkeypox outbreaks based on their comparative benefits and risks. To do this, we searched Google Scholar and PubMed for relevant information for this rapid review. We found many articles have suggested the use of smallpox vaccines and antiviral drugs in monkeypox outbreak according to their study findings.

2 | SMALLPOX VACCINES

Scientists developed the smallpox vaccine as the first vaccine against any transmissible diseases. Vaccinia viruses are used to make smallpox vaccines that protect against smallpox disease. Smallpox

and monkeypox vaccines are being deployed in some countries to manage close contacts. However, vaccination precaution should be taken for those who have severe immunodeficiency. Globally, a massive vaccination drive was run by the World Health Organization (WHO) to eradicate smallpox from 1958 to 1977. The WHO officially stated a smallpox-free world on May 8, 1980.⁸ Therefore, a regular smallpox vaccination campaign is no longer carried out among the general population. However, there is a recommendation to vaccinate specific population samples who are at a higher risk of occupational contact with *Orthopoxvirus*.⁹ The first-generation standard smallpox vaccine (Dryvax) is no longer available to use. At present, replication-competent and replication-deficient smallpox vaccines are available to prevent the spreading of smallpox and monkeypox infections (Table 1). The live vaccinia virus vaccine (ACAM2000) and Aventis Pasteur smallpox vaccine (APSV) are second-generation replication-competent smallpox vaccines. The US FDA has approved the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine as a third-generation smallpox vaccine for the prevention of smallpox and monkeypox.^{10,12} Although complete protection was not throughout the lifespan, vaccine-induced immunity showed peak efficacy during the first 1–3 years following immunization.⁸ When the vaccine is administered before exposure occurred, the efficacy of the vaccine was about 100% and considerable protection might have continued for up to 15–20 years.^{8,13–15} Vaccination against smallpox showed efficacious even after exposure to smallpox in preventing and ameliorating disease conditions. Data extracted from the eradication period of smallpox indicate that vaccination to people after 3 days of infection to the virus showed less efficacy, but it might decrease the fatality rate.^{16–19} However, people who recovered from naturally acquired smallpox infection were found to have lifelong protection against the smallpox virus.^{10,20} Recent data suggested that smallpox vaccines are at least 85% effective to prevent monkeypox infection.¹² Pregnant women and lactating mothers, Pediatric and Geriatric Populations, People having known cardiovascular associated risk factors, and healthcare workers having previous smallpox infection or at a higher risk for smallpox infection should get vaccination with ACAM2000. Moreover, the above special group of the population having atopic eczema, HIV infection, or other associated health conditions should be grouped based on the relative risks rather than on their special category.¹⁰ A brief review and discussion of the therapeutic benefits and risks of each smallpox vaccine in smallpox and monkeypox infection are presented below.

TABLE 1 Summary of the antiviral agents that can be used to prevent monkeypox infection

Sl. agents	Antiviral names	Alternative names	Approval status	Primary use	Dose	Mode of action	Benefits	Limitations
1	Live vaccinia virus vaccine ¹⁰	ACAM2000	US FDA Approved (August 2007)	Active immunization against smallpox disease	<ul style="list-style-type: none"> A single dose of 0.0025 ml of vaccinia virus (live) containing $2.5-12.5 \times 10^5$ plaque forming units/dose Revaccination may be recommended in every 3 years 	Immunity induced by vaccinia virus cross-protects against variola virus	<ul style="list-style-type: none"> Replication-competent vaccinia virus vaccines are generally safe and effective Recombinant vaccinia viruses The vaccine does not contain variola virus and cannot cause smallpox Supplied as lyophilized powder reconstituted with packaged diluent 	<ul style="list-style-type: none"> Live, replication-competent vaccinia virus vaccine that can replicate in human cell. The risk of side effects in family contacts is similar to the vaccine recipient The high-risk population groups for severe adverse events are individuals with cardiac disease, eye disease topical steroids users, immunodeficiency, presence of severe skin conditions, infants below one year and pregnant women
2	Aventis Pasteur smallpox vaccine ¹⁰	APSV	US FDA authorized as IND/EUA	It is indicated in a case-by-case basis where ACAM2000 is unavailable or contraindicated	<ul style="list-style-type: none"> A single dose of 0.0025 ml of vaccinia virus (live) containing $2.5-12.5 \times 10^5$ plaque forming units/dose 	Immunity induced by vaccinia virus cross-protects against variola virus	<ul style="list-style-type: none"> Replication-competent vaccinia virus vaccines are generally safe and effective The vaccine does not contain variola virus and cannot cause smallpox It is estimated to be >95% effective when used as pre-exposure prophylaxis 	<ul style="list-style-type: none"> Live, replication-competent vaccinia virus vaccine that can replicate in human cell. The risk of side effects in household contacts is the same as those for the vaccine recipient Severe adverse reactions are more common in people who are being vaccinated for the first time and among young children below five years

(Continues)

TABLE 1 (Continued)

Sl. agents	Alternative names	Approval status	Primary use	Dose	Mode of action	Benefits	Limitations	
3	Modified vaccinia Ankara-Bavarian Nordic ¹⁰	MVA-BN/ JYNNEOS/ Imvamune/ Imvanex	US FDA Approved	For the prevention of smallpox and monkeypox	<ul style="list-style-type: none"> Two doses (0.5 ml each) separated by 4 weeks for individuals who have never been vaccinated against smallpox One dose (0.5 ml) for individuals previously vaccinated against smallpox 	Humoral and cellular immune responses to orthopoxviruses.	<ul style="list-style-type: none"> Live, attenuated, replication-deficient vaccine It can be used for vaccination of people with immune deficiencies Less side effects than others and no severe adverse events 	<ul style="list-style-type: none"> Not established by adequate human studies Clinical studies did not include sufficient numbers of subjects aged 65 and over Available human data on pregnant women are insufficient to inform vaccine-associated risks in pregnancy It is not known whether it is excreted in human milk. Safety and effectiveness have not been established in individuals aged below 18.
4	Vaccinia immune globulin (human) ¹¹	VIGI/VIGIV	US FDA Approved	Indicated for treatment of severe complications due to the active immunization by vaccinia vaccines.	Sterile solution available as 15 ml single-use vial containing a dose of $\geq 50,000$ U/vial	Provides passive immunity for individuals with complications to vaccinia virus vaccination. The exact mechanism of action is not known	<ul style="list-style-type: none"> Preparation of VIG suitable for IV use It can be used in patients with severe ocular complications other than isolated keratitis 	<ul style="list-style-type: none"> Pregnancy Category C Safety and effectiveness in the pediatric and geriatric population have not been established Risky for use in patients with renal insufficiency It is not recommended for those who have encephalitis or encephalomyelitis, myopericarditis, vaccinia cases, erythema multiforme, or isolated vaccinia keratitis

Abbreviations: APSV, Aventis Pasteur smallpox vaccine; EUA, emergency use authorization; IND, investigational new drug.

2.1 | Replication-competent vaccinia virus vaccines

ACAM2000 and APSV are examples of second-generation vaccines and are called replication-competent vaccinia virus vaccines due to their replication capacity in mammalian cells. The US FDA has licensed ACAM2000 and authorized APSV for active vaccination against smallpox disease in the population who are at a higher risk for smallpox infection.¹⁰ As replication-competent vaccines contain live vaccinia virus, it can replicate into the human cell that may cause some adverse effects, lesions, and spreading. The vaccinia virus may also cause rash, fever, headache, and body pain.¹⁰ The vaccinia virus-associated complications can be severe among immunocompromised individuals. People having severe immunodeficiency should avoid the smallpox vaccination due to the increased risk for severe adverse effects.¹⁰ Vaccinia virus can be spread from vaccinated people to unvaccinated individuals who are in close contact with vaccinated persons by replication-competent smallpox vaccine that contains vaccinia virus. The risk of side effects in domestic contact with the virus is expected to same as the recipient of the vaccine.¹⁰ Therefore, special care should be provided to the vaccination area to prevent the transmission of the virus.

2.1.1 | ACAM2000

ACAM2000 is a live vaccinia virus vaccine. African green monkey kidney (Vero) cells are used to grow it and test to know the presence of known adventitious agents.²¹ A single dose (~2.5 µl) of the vaccine is administered through the percutaneous route. The vaccine needs to administer to the upper arm over the deltoid muscle of the recipient.²² ACAM2000 showed immunogenic effect and efficacy against monkeypox infection. An animal model viral replication study showed no significant clinical signs attributable to monkeypox infection among nonhuman primates.²³

The results suggest that the vaccination of humans with a highly attenuated vaccinia virus vaccine (LC16m8) could induce long-term protection against monkeypox infection.²⁴ Another study suggests that LC16m8 can prevent lethal monkeypox in monkeys, and it may induce protective immunity against smallpox.²⁵ An animal model study showed that 2nd and 3rd-generation smallpox vaccines can reduce severity and mortality rates due to monkeypox infection among Prairie Dogs.²⁶ Moreover, another study showed that the severity of monkeypox infection was higher among the monkeys vaccinated with the ACAM2000 and concomitantly treated with tecovirimat as the antiviral drug affects the immunogenicity of ACAM2000 if administered concomitantly.²⁷

The safety of ACAM2000 was evaluated based on the serious adverse events defined by FDA such as lasting disability, hospitalization rate, life-threatening illnesses or associated complications, morbidity, and mortality rate. Myocarditis/pericarditis was considered the most common serious adverse event.¹⁰ Cardiac complications are linked to smallpox vaccination among the general

population and military workforce during recent vaccination programs with replication-competent smallpox vaccine in the United States.^{28,29} The safety study of ACAM2000 has not been done adequately in people with HIV infections who are considered at higher risk for serious vaccine complications.³⁰ The safety study of ACAM2000 has not been conducted on pregnant women.¹⁰ An immunization study among 376 women with 1st generation smallpox vaccine (Dryvax) has failed to explain the increased rates of pregnancy loss, preterm labor, low birth weight, or congenital birth defects.^{31,32} The frequently reported side effects were injection site pain, lymphadenitis, malaise, fatigue, headache, fever, and myalgia for the smallpox vaccine.¹⁰ The rare and serious adverse events associated with replication-competent smallpox vaccines are blindness, eczema vaccinatum, encephalitis, encephalomyelitis, encephalopathy, erythema multiforme major, fetal death, generalized vaccinia, myocarditis, pericarditis, ocular complications, progressive vaccinia, and severe vaccinal skin infections.¹⁰

2.1.2 | APSV

Another replication-competent vaccinia virus vaccine is known as APSV. The efficacy and safety profile of APSV are anticipated to be similar to ACAM2000. The APSV is produced from a vaccinia virus seed derived from the New York City Board of Health (NYCBOH) strain.²² The live vaccinia virus is supplied with 50% glycerol, 0.4% phenol, and 0.00017% Brilliant Green to formulate the vaccine. APSV vaccine is more than 95% effective among the poxvirus-naïve population.⁸ The safety profile of APSV and ACAM2000 is expected to be similar. The chances of occurring severe adverse events due to the smallpox vaccine from the NYCBOH strain of vaccinia virus is lower, however, it can happen among the young individuals who received 1st dose of the vaccine.³³ Encephalitis, progressive vaccinia, and eczema vaccinatum are the most common serious complications due to vaccination.³³ The risk of occurring myopericarditis due to APSV was anticipated similar to ACAM2000. US FDA authorized APSV as an investigational new drug (IND) or emergency use authorization (EUA) for use on a case-by-case basis in situations where ACAM2000 is unavailable or contraindicated.³⁴

2.2 | Replication-deficient smallpox vaccine (MVA-BN)

MVA-BN is a highly attenuated 3rd generation live vaccinia virus vaccine. MVA-BN is a replication-deficient vaccinia vaccine approved to prevent smallpox and monkeypox infections.^{35,36} MVA-BN has been approved for the prevention of monkeypox infection in the United States and Canada. For people who are at a higher risk for vaccination-associated complications involving systemic viral transmission; replication-deficient vaccines were introduced for them. The safety profile of the vaccine is expected to have favorable in humans compared with replication-competent smallpox vaccines.³⁷⁻³⁹

MVA-BN can be given to healthy individuals and persons with immune deficiencies, HIV infections, atopic dermatitis, or allergic rhinitis. The vaccine is administered through a subcutaneous route.³⁶ A total of 0.5 ml of MVA-BN is administered in two doses at 0- and 4-weeks intervals for the primary vaccine compared to ACAM2000.⁴⁰ A single 0.5 ml shot is administered to people previously vaccinated against smallpox. The visible cutaneous reaction is not produced following the administration of MVA-BN doses.³⁶

The effectiveness of MVA-BN against smallpox is still unproven due to limited studies among human participants. However, several clinical investigations evaluate the efficacy of MVA-BN to produce an immune response.³⁷⁻⁴¹ MVA-BN is a well-tolerated vaccine except for mild to moderate pain at the site of injection.⁴¹ Studies did not find any vaccine-related serious adverse events and transient local reactogenicity was more frequently seen at the higher dose of this highly attenuated poxvirus vaccine.³⁸ The doses of MVA-BN displayed a favorable safety profile with local reactions as the most frequent side effect.³⁷ A study suggested that an increased variola neutralizing antibody response might be produced due to subcutaneous administration of MVA-BN in comparison with the standard 1st generation smallpox vaccine.⁴² Generally, the safety profile of MVA-BN was found similar in subjects with HIV infections compared to uninfected subjects. The safety profile of MVA-BN has not been established among pregnant women by human study. Studies did not report myopericarditis following the vaccination with MVA-BN. The efficacy and safety of MVA-BN vaccines have been investigated in persons aged over 18 years.

3 | ANTIVIRAL DRUGS

Smallpox vaccines may cause some serious and life-threatening complications as they contain live attenuated vaccinia virus as a component of the vaccine.⁴³⁻⁴⁵ Therefore, antiviral drugs are required as countermeasures for the intentional release of smallpox (variola) and naturally occurring monkeypox infection.^{2,46} Antiviral countermeasures showed effectiveness in the infected people to survive in the above circumstances. So far, we have now three *Orthopoxvirus* inhibitors as a countermeasure for smallpox and monkeypox infections (Table 2). The available authorized poxvirus inhibitors are cidofovir, brincidofovir (CMX001), and tecovirimat (ST-246). All these three antiviral drugs showed good efficacy against *Orthopoxvirus* in animal models.⁵⁰ However, their effectiveness in immunocompromised subjects is limited since severe infections occurred due to *Orthopoxvirus* in immunodeficient humans and animals.^{44,51} In the later part of this article, we have briefly discussed each antiviral based on their comparative benefits and risks to control smallpox and monkeypox infections.

3.1 | Cidofovir (CDV)

CDV is a nucleotide analog that converts to a cytidine triphosphate analog in the cell and inhibits the DNA polymerase of poxvirus.⁵²

There is no proven data available on the efficacy of CDV in the treatment of human monkeypox infection. However, the molecule showed activity against poxviruses in several studies.^{53,54} It is not established yet whether not patients having severe monkeypox infection will be benefitted from the treatment with CDV. Furthermore, CDV is used to treat molluscum contagiosum poxvirus infection in humans.⁵⁵

3.1.1 | Brincidofovir (BCV)

BCV is a lipid conjugate derivative of CDV. BCV has improved cellular uptake and conversion rate to the active form than CDV.⁵⁶ BCV is an orally bioavailable drug that allows tablets and suspensions for better patient compliance. Also, BCV has a better renal safety profile than CDV.⁵⁷ Several *Orthopoxvirus* animal model studies revealed promising results in the case of BCV.^{58,59} A recent study reported that BCV 200 mg once a week orally might elevate liver enzymes among patients with monkeypox infection. BCV might have an enhanced safety profile compared to CDV. Serious adverse effects were absent during the treatment of cytomegalovirus infection with BCV. Furthermore, BCV can be used in molluscum contagiosum poxvirus in humans.⁶⁰ BCV showed good efficacy against monkeypox infection in an animal model study when administered as a regimen started on the day of infection.⁶¹ However, the effectiveness of BCV in the treatment of monkeypox in humans has not been established by adequate human model studies. *One study administered BCV 200 mg once a week orally for monkeypox infection, and patients developed elevated liver enzymes resulting in cessation of therapy.*⁶² Although BCV was found effective against poxviruses in several nonhuman model studies.^{58,59} So, there is an urgent need for prospective human model studies on BCV in monkeypox infection.

3.1.2 | Tecovirimat (TCV)

TCV has been approved by the European Medicines Agency (EMA), Health Canada, and the US-FDA for the treatment of smallpox. The European Union (EU) has approved TCV for treatment of monkeypox.³ It blocks the last step of viral replication by preventing the transmission of the virus within the body.^{63,64} TCV showed good efficacy against monkeypox infection in an animal model study when administered as a regimen began on the day of infection.⁶¹ However, adequate supporting information is not available about the efficacy of TCV for the treatment of monkeypox infection in humans. However, several nonhuman model studies showed the effectiveness of TCV in treating *Orthopoxvirus*-induced infections. TCV was found to be safe and well-tolerable with few side effects according to human clinical trials. TCV 200 mg twice daily for 2 weeks orally showed no adverse effects and a shorter duration of hospital stay compared to others.⁶² An earlier study reported that TCV equally inhibits variola and monkeypox viruses by reducing the production and release of enveloped *Orthopoxvirus* in severe systemic infections.⁶⁵ TCV may

TABLE 2 Summary of the antiviral drugs that can be used in monkeypox infection

Sl.	Antiviral drugs names	Alternative names	Approval status	Primary use	Dose	Mode of action	Benefits	Limitations
1	Cidofovir ⁴⁷	VISTIDE	US FDA Approved	Indicated for the treatment of cytomegalovirus reinitis in AIDS patients	The recommended dose of cidofovir is 5 mg/kg body weight (IV) once weekly.	Cidofovir suppresses human cytomagalovirus replication by selective inhibition of viral DNA synthesis	<ul style="list-style-type: none"> Cidofovir has been shown to be effective against the virus that causes smallpox It is also effective in treating animals that had diseases similar to smallpox It has broad-spectrum activity against DNA viruses, including herpes-, adeno-, polyoma-, papilloma- and poxviruses 	<ul style="list-style-type: none"> The safety and efficacy of cidofovir have not been established in patients with hepatic disease, pediatric patients, and geriatric patients. It should be used with lower the risk of blindness and other vision problems. Only IV dosage form is available
2	Brincidofovir ⁴⁸	CMX001/ TEMBEXA	US FDA Approved	For the treatment of human smallpox disease	<ul style="list-style-type: none"> Patients weighing 48 kg or above: 200 mg once weekly for two doses Patients weighing 10 kg to less than 48 kg: 4 mg/kg once weekly for two doses Patients weighing less than 10 kg: 6 mg/kg once weekly for two doses 	Brincidofovir is an orthopoxvirus nucleotide analog DNA polymerase inhibitor against variola virus	<ul style="list-style-type: none"> It can be used in adult and pediatric patients, including neonates It is available as oral suspension and tablets Several animal model studies showed that brincidofovir is effective in monkeypox infection 	<ul style="list-style-type: none"> The effectiveness of brincidofovir for treatment of monkeypox infection has not been determined in humans Efficacy may be reduced in immunocompromised patients based on studies in immune deficient animals
3	Tecovirimat ⁴⁹	ST-246/ TPOXX	US FDA Approved (July 2018)	Indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg	<ul style="list-style-type: none"> Patients weighing 40 kg or above: 600 mg twice daily for 14 days Patients weighing 25 kg to less than 40 kg: 400 mg twice daily for 14 days Patients weighing 13 kg to less than 25 kg: 200 mg twice daily for 14 days 	Tecovirimat is a novel tricyclonene compound that inhibits orthopoxvirus VP37 protein	<ul style="list-style-type: none"> It can be used in adult and pediatric patients It is available as oral capsule Several animal and human model studies showed that tecovirimat is effective in monkeypox infection 	<ul style="list-style-type: none"> The effectiveness of tecovirimat for treatment of smallpox disease has not been determined in humans by adequate and well-controlled clinical trials Tecovirimat efficacy may be reduced in immunocompromised patients based on studies in immune deficient animals

affect immunogenicity when concomitantly administered with ACAM2000.²⁷

4 | OTHER DRUGS

Vaccinia immune globulin (VIG) is produced from the pooled blood of the vaccinated population by the smallpox vaccine. The antibody was developed in response to the smallpox vaccine in these individuals are withdrawn and purified. VIG can be used intravenously to treat individuals with progressive vaccinia following smallpox vaccination.⁶⁶ It was also used with CVD as concomitant therapy for the management of the 2003, Midwest monkeypox outbreak to lessen the serious side effects of the smallpox vaccine.⁶⁷ Antiviral drugs in combination with VIG significantly enhance the efficacy of VIG in the treatment of progressive cutaneous vaccinia virus infections in immunosuppressed cases. However, VIG therapy is costly, and its supply is limited.⁶⁸ Adequate data is not available supporting the effectiveness of VIG for treating monkeypox complications in humans. There is no proven benefit of VIG in treating smallpox complications and it is used under an IND.

5 | CONCLUSION

Still, the evidence-based preventive and therapeutic agents are absent for monkeypox infection.⁶⁹ According to the present report, we assume that smallpox vaccines and antiviral drugs can control monkeypox outbreaks. Therefore, we recommend repurposing of these smallpox vaccines and antiviral agents in the recent monkeypox outbreak. Moreover, we recommend further investigations of smallpox vaccines and *Orthopoxvirus* inhibitors in a human model study to explore their exact role in human monkeypox infections. The WHO can deploy experts to review vaccines and antivirals of smallpox and monkeypox to provide guidelines to the countries about their usages to prevent monkeypox infection. In addition to the repurposing of antismallpox agents, public awareness, appropriate preventive measures, rapid identification and isolation of cases, contact tracing, and proper treatment may control monkeypox outbreaks.

AUTHOR CONTRIBUTIONS

Conceptualization: Md. Rabiul Islam, Md. Jamal Hossain, and Arpita Roy. **Literature search and information collection:** Arpita Roy, Md. Ashrafur Rahman, and Md. Jamal Hossain; **Writing—original draft:** Md. Rabiul Islam and A. H. M. Nazmul Hasan; **Writing—review and editing:** Md. Rabiul Islam, Mohammad Shahriar, and Mohiuddin Ahmed Bhuiyan. All authors reviewed and approved the final submission.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are within the manuscript.

TRANSPARENCY STATEMENT

The lead author (Md. Rabiul Islam) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Md. Rabiul Islam  <https://orcid.org/0000-0003-2820-3144>

Md. Jamal Hossain  <https://orcid.org/0000-0001-9706-207X>

REFERENCES

- Mahase E. Monkeypox: what do we know about the outbreaks in Europe and North America. *BMJ*. 2022;377:o1274. doi:10.1136/bmj.o1274
- Islam MR, Asaduzzaman M, Shahriar M, Bhuiyan MA. The spreading of monkeypox in nonendemic countries has created panic across the world: could it be another threat? *J Med Virol*. 2022. doi:10.1002/jmv.27919
- The World Health Organization. *Multi-Country Monkeypox Outbreak: Situation Update*. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393>
- Gavi. *Five Things You Need to Know About Monkeypox*. https://www.gavi.org/vaccineswork/five-things-you-need-know-about-monkeypox?gclid=CjwKCAjw4ayUBhA4EiwATWYBrrd1cTgCWqNhTOA5qaSHYCq6F6TBdJiemwdqNOQFcx0zc2zuq8ZsixoCt94-QAvD_BwE.
- The Guardian. *Monkeypox Outbreak Could be Just 'The Peak of the Iceberg'*, *WHO Warns*. <https://www.theguardian.com/world/2022/may/28/monkeypox-outbreak-could-be-just-the-peak-of-the-iceberg-who-warns?fbclid=IwAR07kTXQZ9sMVwlyt-MGR-YxYalUZf4NTLUz7brLZAqTMzkUvEJ7CO-F66Q>
- Sohan M, Hossain MJ, Islam MR. The SARS-CoV-2 omicron (B.1.1.529) variant and effectiveness of existing vaccines: what we know so far. *J Med Virol*. 2022;94(5):1796-1798. doi:10.1002/jmv.27574
- Islam T, Hasan M, Rahman MS, Islam MR. Comparative evaluation of authorized drugs for treating Covid-19 patients. *Health Sci Rep*. 2022;5(4):e671. doi:10.1002/hsr2.671
- Fenner F, Henderson D, Arita I, Jezek Z, Ladnyi I. *Smallpox and its Eradication*. World Health Organization; 1988.
- Henderson DA, Inglesby TV, Bartlett JG, et al. Working group on civilian biodefense. Smallpox as a biological weapon: medical and public health management. *JAMA*. 1999;281:2127-2137.
- Petersen BW, Damon IK, Pertowski CA, et al. Clinical guidance for smallpox vaccine use in a postevent vaccination program. *MMWR Recomm Rep*. 2015;64(RR-02):1-26.
- Lustig S, Maik-Rachline G, Paran N, et al. Effective post-exposure protection against lethal orthopoxviruses infection by vaccinia immune globulin involves induction of adaptive immune response. *Vaccine*. 2009;27(11):1691-1699. doi:10.1016/j.vaccine.2009.01.038
- CDC. Newly licensed smallpox vaccine to replace old smallpox vaccine. *MMWR Morb Moratal Wkly Rep*. 2008;57:207-208.
- Mandell GL, Bennett JE, Dolin R. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Churchill Livingstone/Elsevier; 2010.
- Hammarlund E, Lewis MW, Carter SV, et al. Multiple diagnostic techniques identify previously vaccinated individuals with protective immunity against monkeypox. *Nat Med*. 2005;11:1005-1011.
- Taub DD, Ershler WB, Janowski M, et al. Immunity from smallpox vaccine persists for decades: a longitudinal study. *Am J Med*. 2008;121:1058-1064.

16. Massoudi MS, Barker L, Schwartz B. Effectiveness of postexposure vaccination for the prevention of smallpox: results of a delphi analysis. *J Infect Dis.* 2003;188:973-976.
17. Rao AR, Jacob ES, Kamalakshi S, Appaswamy S, Bradbury BD. Epidemiological studies in smallpox. A study of intrafamilial transmission in a series of 254 infected families. *Indian J Med Res.* 1968;56:1826-1854.
18. Heiner GG, Fatima N, McCrumb FR, Jr. A study of intrafamilial transmission of smallpox. *Am J Epidemiol.* 1971;94:316-326.
19. Sommer A. The 1972 smallpox outbreak in Khulna municipality, Bangladesh. II. effectiveness of surveillance and containment in urban epidemic control. *Am J Epidemiol.* 1974;99:303-313.
20. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med.* 2002;346:1300-1308.
21. Greenberg RN, Kennedy JS. ACAM2000: a newly licensed cell culture-based live vaccinia smallpox vaccine. *Expert Opin Investig Drugs.* 2008;17:555-564.
22. Talbot TR, Stapleton JT, Brady RC, et al. Vaccination success rate and reaction profile with diluted and undiluted smallpox vaccine: a randomized controlled trial. *JAMA.* 2004;292:1205-1212.
23. Marriott KA, Parkinson CV, Morefield SI, Davenport R, Nichols R, Monath TP. Clonal vaccinia virus grown in cell culture fully protects monkeys from lethal monkeypox challenge. *Vaccine.* 2008;26(4):581-588. doi:10.1016/j.vaccine.2007.10.063
24. Iizuka I, Ami Y, Suzaki Y, et al. A single vaccination of nonhuman primates with highly attenuated smallpox vaccine, LC16m8, provides long-term protection against monkeypox. *Jpn J Infect Dis.* 2017;70(4):408-415. doi:10.7883/yoken.JJID.2016.417
25. Saijo M, Ami Y, Suzaki Y, et al. LC16m8, a highly attenuated vaccinia virus vaccine lacking expression of the membrane protein B5R, protects monkeys from monkeypox. *J Virol.* 2006;80(11):5179-5188. doi:10.1128/JVI.02642-05
26. Keckler MS, Salzer JS, Patel N, et al. IMVAMUNE[®] and ACAM2000[®] provide different protection against disease when administered postexposure in an intranasal monkeypox challenge prairie dog model. *Vaccines (Basel).* 2020;8(3):396. doi:10.3390/vaccines8030396
27. Russo AT, Berhanu A, Bigger CB, et al. Co-administration of tecovirimat and ACAM2000[™] in non-human primates: effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. *Vaccine.* 2020;38(3):644-654. doi:10.1016/j.vaccine.2019.10.049
28. Redfield RR, Wright DC, James WD, Jones TS, Brown C, Burke DS. Disseminated vaccinia in a military recruit with human immunodeficiency virus (HIV) disease. *N Engl J Med.* 1987;316:673-676.
29. Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States, January-October 2003. *JAMA.* 2005;294:2734-2743.
30. Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. *Vaccine.* 2005;23:2078-81.
31. US FDA. Food and Drug Administration. Acambis I. ACAM2000 Smallpox Vaccine: Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing document. Food and Drug Administration; 2007. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4292b2-02.pdf>
32. Ryan MA, Seward JF. Smallpox vaccine in pregnancy registry team. pregnancy, birth, and infant health outcomes from The National Smallpox Vaccine in Pregnancy Registry, 2003-2006. *Clin Infect Dis.* 2008;46(Suppl 3):S221-S226.
33. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J Infect Dis.* 1970;122:303-309.
34. CDC. Vaccines; 2019. <https://www.cdc.gov/smallpox/clinicians/vaccines.html>
35. CDC. *Monkeypox and Smallpox Vaccine Guidance*; 2022. <https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html>
36. Kennedy JS, Greenberg RN. IMVAMUNE: modified vaccinia Ankara strain as an attenuated smallpox vaccine. *Expert Rev Vaccines.* 2009;8:13-24.
37. von Krempelhuber A, Vollmar J, Pokorny R, et al. A randomized, double-blind, dose-finding phase II study to evaluate immunogenicity and safety of the third generation smallpox vaccine candidate IMVAMUNE. *Vaccine.* 2010;28(5):1209-1216. doi:10.1016/j.vaccine.2009.11.030
38. Walsh SR, Wilck MB, Dominguez DJ, et al. Safety and immunogenicity of modified vaccinia Ankara in hematopoietic stem cell transplant recipients: a randomized, controlled trial. *J Infect Dis.* 2013;207(12):1888-1897. doi:10.1093/infdis/jit105
39. Greenberg RN, Overton ET, Haas DW, et al. Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. *J Infect Dis.* 2013;207:749-758.
40. Frey SE, Winokur PL, Salata RA, et al. Safety and immunogenicity of IMVAMUNE smallpox vaccine using different strategies for a post event scenario. *Vaccine.* 2013;31:3025-33
41. Vollmar J, Arndt N, Eckl KM, et al. Safety and immunogenicity of IMVAMUNE, a promising candidate as a third generation smallpox vaccine. *Vaccine.* 2006;24(12):2065-2070. doi:10.1016/j.vaccine.2005.11.022
42. Damon IK, Davidson WB, Hughes CM, et al. Evaluation of smallpox vaccines using variola neutralization. *J Gen Virol.* 2009;90:1962-1966.
43. Bray M. Pathogenesis and potential antiviral therapy of complications of smallpox vaccination. *Antiviral Res.* 2003;58(2):101-114.
44. Bray M, Wright ME. Progressive vaccinia. *Clin Infect Dis.* 2003;36(6):766-774.
45. Reed JL, Scott DE, Bray M. Eczema vaccinatum. *Clin Infect Dis.* 2012;54(6):832-840.
46. Cleri DJ, Porwancher RB, Ricketti AJ, Ramos-Bonner LS, Vernaleo JR. Smallpox as a bioterrorist weapon: myth or menace? *Infect Dis Clin North Am.* 2006;20(2):329-357.
47. Access Data. *Full Prescribing Information for Cidofovir.* https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf
48. Access Data. *Full Prescribing Information for Brincidofovir.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000_214461s000lbl.pdf
49. Access Data. *Full Prescribing Information for Tecovirimat.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf
50. Smeets DF. Orthopoxvirus inhibitors that are active in animal models: an update from 2008 to 2012. *Future Virol.* 2013;8(9):891-901. doi:10.2217/fvl.13.76
51. Neyts J, Clercq E. Efficacy of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine for the treatment of lethal vaccinia virus infections in severe combined immune deficiency (SCID) mice. *J Med Virol.* 1993;41(3):242-246.
52. Duraffour S, Andrei G, Topalis D, et al. Mutations conferring resistance to viral DNA polymerase inhibitors in camelpox virus give different drug-susceptibility profiles in vaccinia virus. *J Virol.* 2012;86(13):7310-7325.
53. Smeets DF, Sidwell RW. A review of compounds exhibiting anti-orthopoxvirus activity in animal models. *Antiviral Res.* 2003;57(1-2):41-52.
54. Smeets DF. Progress in the discovery of compounds inhibiting orthopoxviruses in animal models. *Antivir Chem Chemother.* 2008;19(3):115-124.
55. Erickson C, Driscoll M, Gaspari A. Efficacy of intravenous cidofovir in the treatment of giant molluscum contagiosum in a patient with

- human immunodeficiency virus. *Arch Dermatol*. 2011;147(6): 652-654.
56. Hostetler KY, Beadle JR, Trahan J, et al. Oral 1-O-octadecyl-2-O-benzyl-sn-glycero-3-cidofovir targets the lung and is effective against a lethal respiratory challenge with ectromelia virus in mice. *Antiviral Res*. 2007;73:212-218. doi:10.1016/j.antiviral.2006.10.009
57. Tippin TK, Morrison ME, Brundage TM, Mommeja-Marin H. Brincidofovir is not a substrate for the human organic anion transporter 1: a mechanistic explanation for the lack of nephrotoxicity observed in clinical studies. *Ther Drug Monit*. 2016;38:1-786. doi:10.1097/FTD.0000000000000353
58. Rice AD, Adams MM, Lampert B, et al. Efficacy of CMX001 as a prophylactic and presymptomatic antiviral agent in New Zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. *Viruses*. 2011;3:63-82. doi:10.3390/v3020063
59. Israely T, Paran N, Lustig S, et al. A single cidofovir treatment rescues animals at progressive stages of lethal orthopoxvirus disease. *Virology*. 2012;9:119. doi:10.1186/1743-422X-9-119.
60. Cohen JI, Davila W, Ali MA, et al. Detection of molluscum contagiosum virus (MCV) DNA in the plasma of an immunocompromised patient and possible reduction of MCV DNA with CMX-001. *J Infect Dis*. 2012;205(5):794-797.
61. Stabenow J, Buller RM, Schriewer J, West C, Sagartz JE, Parker S. A mouse model of lethal infection for evaluating prophylactics and therapeutics against monkeypox virus. *J Virol*. 2010;84(8):3909-3920. doi:10.1128/JVI.02012-09
62. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. 2022;S1473-S3099(22):00228-6. doi:10.1016/S1473-3099(22)00228-6
63. Yang G, Pevear DC, Davies MH, et al. An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. *J Virol*. 2005;79(20):13139-13149.
64. Jordan R, Leeds JM, Tyavanagimatt S, Hruby DE. Development of ST-246[®] for treatment of poxvirus infections. *Viruses*. 2010;2(11): 2409-2435.
65. Smith SK, Olson VA, Karem KL, Jordan R, Hruby DE, Damon IK. In vitro efficacy of ST246 against smallpox and monkeypox. *Antimicrob Agents Chemother*. 2009;53(3):1007-1012. doi:10.1128/AAC.01044-08
66. He Y, Sultana I, Takeda K, Reed JL. Cutaneous deficiency of filaggrin and STAT3 exacerbates vaccinia disease in vivo. *PLoS One*. 2017;12(1):e0170070. doi:10.1371/journal.pone.0170070
67. Wharton M, Strikas RA, Harpaz R, et al. Recommendations for using smallpox vaccine in a pre-event vaccination program. supplemental recommendations of the advisory committee on immunization practices (ACIP) and the healthcare infection control practices advisory committee (HICPAC). *MMWR Recomm Rep*. 2003;52(RR-7):1-16.
68. Smee DF, Dagley A, Downs B, Hagloch J, Tarbet EB. Enhanced efficacy of cidofovir combined with vaccinia immune globulin in treating progressive cutaneous vaccinia virus infections in immunosuppressed hairless mice. *Antimicrob Agents Chemother*. 2015;59(1): 520-526. doi:10.1128/AAC.04289-14
69. Islam MR, Hasan M, Rahman MS, Rahman Md. A. (2022). Monkeypox outbreak—No panic and stigma: only awareness and preventive measures can halt the pandemic turn of this epidemic infection. *The International Journal of Health Planning and Management*. doi:10.1002/hpm.3539

How to cite this article: Islam MR, Hossain MJ, Roy A, et al. Repositioning potentials of smallpox vaccines and antiviral agents in monkeypox outbreak: a rapid review on comparative benefits and risks. *Health Sci Rep*. 2022;5:e798. doi:10.1002/hsr2.798