Prevention of monkeypox with vaccines: a rapid review

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The largest outbreak of monkeypox in history began in May, 2022, and has rapidly spread across the globe ever since. The purpose of this Review is to briefly describe human immune responses to orthopoxviruses; provide an overview of the vaccines available to combat this outbreak; and discuss the various clinical data and animal studies evaluating protective immunity to monkeypox elicited by vaccinia virus-based smallpox vaccines, address ongoing concerns regarding the outbreak, and provide suggestions for the appropriate use of vaccines as an outbreak control measure. Data showing clinical effectiveness (~85%) of smallpox vaccines against monkeypox come from surveillance studies conducted in central Africa in the 1980s and later during outbreaks in the same area. These data are supported by a large number of animal studies (primarily in non-human primates) with live virus challenge by various inoculation routes. These studies uniformly showed a high degree of protection and immunity against monkeypox virus following vaccination with various smallpox vaccines. Smallpox vaccines represent an effective countermeasure that can be used to control monkeypox outbreaks. However, smallpox vaccines do cause side-effects and the replication-competent, second-generation vaccines have contraindications. Third-generation vaccines, although safer for use in immunocompromised populations, require two doses, which is an impediment to rapid outbreak response. Lessons learned from the COVID-19 pandemic should be used to inform our collective response to this monkeypox outbreak and to future outbreaks.

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Introduction

Monkeypox virus is a DNA virus in the *Orthopoxvirus* genus, which also includes viruses such as vaccinia, cowpox, and variola.[1] Although monkeypox was originally described in monkeys in 1958, rodents are likely to be the natural reservoir of this virus with primates—including humans—being incidental hosts. Human infections were first identified in the Democratic Republic of the Congo in 1970. There are two distinct lineages of monkeypox virus, with the western Africa strain generally causing less severe disease than the central African—also known as the Congo Basin—strain (ie, 1–5% *vs* 10% case fatality).[2,3]

Human infections originate from contact with an infected animal or human. Subsequent human-to-human transmission can occur through large respiratory droplets or contact with a skin lesion (including through fomites).[1] The incubation period ranges from 7 days to 21 days with shorter incubation periods occurring with more invasive exposure (eg, bite *vs* scratch *vs* light touch).[4,5] Symptomatic cases are usually self-limited (ie, resolved by themselves without treatment) and the main symptoms are fever, chills, and malaise that precede the development of a centrifugal rash involving the palms of the hands and soles of the feet.[4] Although fever can last for up to a week, the rash evolves from maculopapular to vesicular to pustular to crusting over a period of 2–4 weeks.[4] Unlike smallpox, typical monkeypox infections are usually characterised by lymphadenopathy. Notably, it has become clear in the current outbreak that monkeypox can also present atypically without fever or rash, and with only one to a few skin lesions that can be asynchronous in appearance. Often these lesions are only present on the genitalia, oral mucosa, or rectal mucosa consistent with the points of skin contact in sexual settings. This association with sexual contact has led to misdiagnosed cases of monkeypox, and wrong or delayed treatment, and new clinical syndromes associated with monkeypox such as urethritis, rectal pain, and urinary retention. The consequences of monkeypox infection in pregnant women are unclear, though monkeypox virus can cross the placenta.[6] Additionally, initial reports from Germany and Italy of monkeypox-positive PCR assays of semen,[7,8] followed by a report from August, 2022 of infectious virus isolated from semen have surfaced raising concerns that monkeypox virus could also be sexually transmitted.[9]

Monkeypox outbreaks have occurred episodically in parts of Africa where the virus has become endemic,

Key messages

- Monkeypox cases are rapidly increasing, with the USA currently having the largest number of cases
- The major risk for infection currently is in the population of men who have sex with men; transmission within this community appears to be confined to skin-to-skin, oral, and rectal and perianal intimate contact, and possibly through semen
- The clinical phenotype now extends from typical monkeypox with widespread rash, fever, and lymphadenopathy, to just a single or a few lesions on the genitalia, or oral and rectal mucosa; therefore, careful physical examinations must be done, and thorough sexual histories retrieved
- The JYNNEOS vaccine is the safest vaccine available for pre-exposure and post-exposure use in preventing monkeypox; ACAM2000 and LC16m8 vaccines are also available in different countries; in addition, in some countries, antivirals might be available for treatment (eg, the USA)

WHO has released guidelines for the consideration and use of vaccines to prevent monkeypox

For the **guidelines on vaccines to prevent monkeypox published by WHO** see https://www.who.int/publications/i/item/who-mpx-immunization-2022.1

most notably in the Democratic Republic of the Congo, Nigeria in 2017, and in other parts of central and western Africa over the past 5 years.[10] However, the number of infections occurring in endemic parts of Africa as well as outbreaks occurring in non-endemic parts of the world have been increasing. This rise could be related to a combination of factors, including the increasing number of people with no orthopoxvirus cross-protection due to the cessation of smallpox vaccination after eradication in 1980, and the growing ease and rapidity of global travel that allows previously isolated clusters to quickly become global epidemics.[10] For example, in the 2003 US outbreak there were 71 monkeypox cases stemming from the sale of pet prairie dogs that became infected through contact with illegally imported and infected rodents from Africa in a shared distribution centre.[11–13] Lastly, the effect of genetic changes in the virus on transmissibility needs to be evaluated.

Beginning in May, 2022, a large, multinational outbreak was identified, which at the time of writing this Review includes more than 52 090 PCR-confirmed cases across 100 countries, predominantly in networks of men who have sex with men (MSM).[1] Criteria such as little to no population-level immunity and evidence of infections across WHO regions, technically fit the definition of a pandemic.

Prevention with vaccines

Immune responses to one orthopoxvirus can recognise other orthopoxviruses and result in varying levels of protection depending on how closely related the different orthopoxviruses are. It has been hypothesised that the increase in monkeypox incidence since the cessation of smallpox vaccination is due to an increasingly immunologically naive population.[10,14–16] This immunological cross-reactivity has enabled researchers to develop various animal models of smallpox infection that were used to test vaccines and antivirals.[17] This cross-reactivity is primarily due to two factors. First, the high degree of sequence similarity between orthopoxviruses,[18] especially among immunologically relevant proteins, leading to a large number of shared immune epitopes.[19,20] Second, the wide breadth of the response, with antibodies targeting at least 24 membrane and structural proteins.[21–23] Similarly, T-cell responses recognise epitopes within a wide diversity of viral proteins, with CD4 T cells preferentially recognising structural proteins,[24] whereas CD8 T cells target proteins produced early (eg, virulence factors) in the viral lifecycle.[25,26] Neutralising antibody was established as a correlate of protection against smallpox (caused by the variola virus) in humans[27,28] and against other orthopoxviruses in animal models. Although T cells are not necessary for protection, they do contribute to viral clearance.

Some of the earliest evidence that vaccinia-specific immune responses can protect against monkeypox comes from studies done in the 1960s. In three separate studies involving chimpanzees, rhesus macaques, and cynomolgus macaques, respectively, vaccination with Dryvax (Wyeth Laboratories, PA, USA) or other first-generation smallpox vaccines provided complete protection against disease in almost all vaccinated animals. The single exception was an animal that did not develop a take (ie, a characteristic blister at vaccination site) after vaccination.[29–31] These early studies involved small numbers of animals but the results suggested that a large degree of cross-protective immunity was conferred by smallpox vaccination (table 1).

The USA currently has two licensed smallpox vaccines: ACAM2000 (Emergent Product Development Gaithersburg, MD, USA), and JYNNEOS (Bavarian Nordic, Hellerup, Denmark). ACAM2000 is only licensed to prevent smallpox, whereas JYNNEOS was approved for the prevention of smallpox and monkeypox in 2019. Both have been evaluated for protection against infection with monkeypox virus in animals. ACAM2000 is a second-generation vaccine derived from a single clonal viral isolate from Dryvax that exhibited reduced neurovirulence in animal models.[38] It is grown in cell culture rather than by the historical method of scarification on the sides of calves (*Bos taurus*). Immunogenicity testing showed non-inferiority to Dryvax and clinical trials showed a similar safety profile to Dryvax.[39,40]

Smallpox and monkeypox vaccines can be used in two situations: pre-exposure to prevent infection and disease or post-exposure to ameliorate infection and disease. Pre-exposure vaccination is warranted to protect those at the highest risk. This protection is best accomplished with a second-generation or third-generation vaccine (table 2). Post-exposure vaccination is ideally administered within 4 days of exposure to prevent infection, but it can be used up to 14 days after exposure to decrease the severity of disease. Post-exposure vaccination is also best accomplished with a second-generation or third-generation vaccine (table 2). Authorities in Montreal, QC, Canada released at least 3000 doses of vaccine for such purposes in July, 2022. In all cases, clinicians need to be aware of who might be eligible for vaccination, such that consultation can then occur with national health authorities in regard to releasing vaccines from national stockpiles. Smallpox vaccine is not available commercially or privately.

Historical data on first-generation smallpox vaccines (eg, Dryvax) and more recent studies from the past 20 years looking at both first-generation and second-generation vaccines show an association with a number of common side-effects, both local and systemic, at similar rates. These side-effects included pain and swelling at the injection site, fatigue, and muscle pain in about half of recipients; lymphadenopathy and headache in 20–40% of recipients, fever in 20–40% of recipients; joint pain, backache, and abdominal pain or nausea in

	Pre-exposure indications	Post-exposure indications*	Administration	Common side-effects	Serious adverse events	Contraindications
Replication-competent vaccinia virus, second-generation (ACAM2000)	Research laboratory personnel working with orthopoxviruses; clinical laboratory personnel doing diagnostic testing for orthopoxviruses; designated response team members; health care-personnel who administer ACAM2000 or care for patients infected with orthopoxviruses; and not recommended for the general population as of June, 2022	Unprotected direct contact with an active orthopoxvirus lesion or fluid or a contaminated item; being within 2 m of an individual with an active orthopoxvirus case for 3 h or more	Single percutaneous dose with bifurcated needle	Pruritus, lymphadenopathy, administration site soreness, fever, headache, myalgia, rash, fatigue, and bacterial infection at the administration site	Myopericarditis and pericarditis, encephalitis, progressive vaccinia, erythema multiforme major, eczema, vaccinatum, generalised vaccinia, post-vaccinial encephalitis or encephalomyelitis, blindness due to autoinoculation, and fetal death in pregnant women	Atopic dermatitis†, active exfoliative skin conditions†, immunosuppression†, pregnancy†, age <1 year†, breastfeeding, serious vaccine component allergy, underlying heart disease, and ≥3 major cardiac risk factors
Attenuated, minimally replication-competent vaccinia virus, third-generation (LC16m18, available in Japan)	Same as above; preferred for those with contraindications for replicating vaccines, immune deficiencies, immunosuppression, or atopic dermatitis; not recommended for the general population as of June, 2022	Same as above; preferred for those with contraindications for replicating vaccines, immune deficiencies, or atopic dermatitis; preferred for pregnant women if modified vaccinia virus Ankara-Bavarian Nordic not available; licensed in Japan for use in children	Single percutaneous dose with bifurcated needle	Pruritus, lymphadenopathy, administration site soreness, fever, headache, myalgia, rash, and fatigue	None noted in clinical trials	Serious vaccine component allergy
Replication-deficient modified vaccinia Ankara, third-generation (JYNNEOS)	Same as above; preferred for those with contraindications for replicating vaccines, immune deficiencies, immunosuppression, or atopic dermatitis	Same as above; preferred for those with contraindications for replicating vaccines, immune deficiencies, or atopic dermatitis; preferred for pregnant women	Two subcutaneous doses, 28 days apart	Injection site reactions, myalgia, headache, fatigue, nausea, and chills	None	Serious vaccine component allergy

*Post-exposure vaccination is ideally provided within 4 days of exposure to prevent infection; however, vaccination within 4–14 days of exposure can reduce disease severity if infection were to occur. †Including household contacts with the condition.

Table 1: **Indications, administration, side-effects, and contraindications for smallpox and monkeypox vaccination**[32–37]

about 20% of recipients. More serious side-effects included generalised vaccinia, eczema vaccinatum, progressive vaccinia, post-vaccinial encephalopathy or encephalitis, and death. Historical data from the 1960s with Dryvax found that, per million primary doses, generalised vaccinia occurred at rates of 241·5, eczema vaccinatum at 38·5, progressive vaccinia at 1·5, post-vaccinial encephalopathy or encephalitis at 12·3, and death at around 1. More recent data from the early 2000s with Dryvax found lower rates per million vaccinees: 74·2 for generalised vaccinia, no eczema vaccinatum, no progressive vaccinia, 24·7 for post-vaccinial encephalopathy or encephalitis, and no deaths. Modern surveillance also found that myocarditis and pericarditis occurred at a rate of 519·5 per million doses. These cardiac events were not commonly reported in the 1960s.[32–34,49–53]

JYNNEOS is a third-generation vaccine based on the non-replicating modified vaccinia virus Ankara (MVA) strain with deletion of approximately 10% of its genome. JYNNEOS is produced in chicken egg fibroblasts using serum-free medium, purified using tangential flow filtration, and supplied as a frozen-liquid suspension containing 5×10^7 50% tissue culture infectious dose per dose[35] and administered subcutaneously in two doses, 28 days apart. At the time of writing this Review, the US Food and Drug Administration (FDA) is considering allowing the use of the vaccine as two intradermal doses—at 20% of the usual dose—on day 0 and 28. This decision is based on data showing equivalent antibody titres using this and the approved regimens.[54] With two doses, immunogenicity is similar to that seen with ACAM2000, but with fewer adverse events.[35,55] MVA-based vaccines do not elicit the characteristic take but are associated with many of the same common, mild side-effects including pain at site of injection (85% of recipients); redness, swelling, itching, and induration at site of injection (40–60%); fatigue, muscle pain, and headaches (20–40%); nausea (17%), chills (10%). Fever is rare, with only around 2% of recipients reporting it. Similarly, cardiac events were only reported in around 2% of recipients and myopericarditis was not found in any vaccine recipients.[456,57]

LC16m8 is another third-generation vaccine containing a virus derived from the Lister strain used in first-generation vaccines. Multiple passages in tissue culture and selection for an attenuated phenotype resulted in the LC16m8 strain that does not have a full-length, functional B5 membrane protein.[58] The vaccine is produced in cell culture using rabbit kidney cells. The vaccine received a full licence by Japanese regulatory authorities in 1980 and is currently manufactured by Kaketsuken (Kumamoto, Japan). VaxGen holds marketing rights for LC16m8 in the USA,[59] although no biological licence application for this vaccine has been received by the FDA to date. The virus in this vaccine is attenuated, undergoing restricted replication in vaccine recipients.[60] LC16m8 elicits a similar immune response to the parental Lister vaccine[61,62]

	Vaccine and dose groups	Schedule and route	Viral strain, dose, and timing	Outcome
McConnell et al (1968)[30]				
Chimpanzees	Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Utrecht 65-32: intravenous 1·0 mL at $10^{6{\cdot}8}$ $TCID_{50}$ 29 days after vaccination	Two of three animals had no visible signs of infection; the remaining had no response to vaccination and developed skin lesions after challenge
Chimpanzees	Unvaccinated	..	..	Three of four animals developed lesions by day 7; one animal died 10 days after challenge
McConnell et al (1964)[29]				
Rhesus macaques	Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Strain 7-61: intravenous 1·5 mL at $10^{5{\cdot}5}$ $TCID_{50}$ 35 days after vaccination	Five of six animals did not develop any symptoms or rash; one animal developed bloody diarrhoea and died on day 9 from an unrelated illness—necropsy indicated no pathology of monkeypox
Rhesus macaques	Unvaccinated	..	..	Five (100%) animals developed severe monkeypox by day 9; all animals were viraemic; one animal died on day 8
Gispen et al (1967)[31]				
Cynomolgus macaques	Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Utrecht 65-32: scarification (one animal), intranasal (one animal), dose not reported, and animals challenged 28 days after vaccination	Neither of the two animals developed a rash or local reaction
Cynomolgus macaques	Cowpox: dose unknown	Percutaneous or scarification using a bifurcated needle	Utrecht 65-32: scarification (one animal), intranasal (one animal), and dose not reported 28 days after vaccination	Neither of the two animals developed a rash or local reaction
Cynomolgus macaques	Unvaccinated	..	..	Two (100%) animals developed a generalised vesicular rash
Earl et al (2004)[41]				
Cynomolgus macaques	MVA: 1×10^9 pfu and then MVA: 1×10^9 pfu	Intramuscular, given 56 days apart	Zaire-79: intravenous 5×10^7 pfu 56 days after final vaccination	Six of eight animals developed a rash (1–36 lesions) on days 9–15; the lesions were small, atypical, and non-progressive in those six animals; and no animals died
Cynomolgus macaques	MVA: 1×10^9 pfu and then Dryvax: $2{\cdot}5 \times 10^5$ pfu	Intramuscular and then percutaneous or scarification using a bifurcated needle, given 56 days apart	Zaire-79: intravenous 5×10^7 pfu 56 days after final vaccination	None of the eight animals developed a rash or any clinical symptoms
Cynomolgus macaques	Mock vaccine containing PBS and then Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle, given 56 days apart	Zaire-79: intravenous 5×10^7 pfu 56 days after final vaccination	None of the eight animals developed a rash or any clinical symptoms
Cynomolgus macaques	Unvaccinated	..	..	Eight (100%) animals developed a rash (>500 lesions) on days 3–6; eight animals were moribund on days 15–18; and two of eight animals died by day 18
Edghill-Smith et al (2005)[42]				
Rhesus macaques	Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: intravenous 5×10^7 pfu 28 days after final vaccination	None of the four animals developed a rash; no animals had detectable viraemia; anti-CD20 antibody treatment to deplete B cells before vaccination abrogated protection; and anti-CD8 antibody treatment to deplete cytotoxic T lymphocytes before challenge had no effect on protection
Marriott et al (2008)[43]				
Cynomolgus macaques	ACAM2000: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: intravenous $3{\cdot}8 \times 10^7$ pfu 61 days after final vaccination	None of the eight animals developed a rash or fever; and no animals had viraemia
Cynomolgus macaques	Dryvax: $2{\cdot}5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: intravenous $3{\cdot}8 \times 10^7$ pfu 61 days after final vaccination	None of the eight animals developed a rash or fever; none of the animals had viraemia; and three of the animals had low amounts of virus transiently detectable in the oral cavity
Cynomolgus macaques	Unvaccinated	..	..	Eight (100%) animals developed a rash; and eight animals succumbed to disease by day 9

(Table 2 continues on next page)

with lower frequencies of minor adverse events and no serious adverse events.[63–65] Lymphadenopathy was the most common side-effect, occurring in 15·5% of recipients. Fever was reported in 2·6%, while headaches, itching, myalgia, joint pain, and fatigue were all reported in less than 1% of recipients. No cases of myopericarditis have been reported in clinical trials of LC16m8.[64,65]

Non-human primate studies

Although there are various rodent models (eg, mice, prairie dogs, ground squirrels, African dormice, and African pouched rats) of monkeypox infection that have been used to test vaccines and antivirals,[66–74] the general consensus is that non-human primates are better models of human disease. All three of these licensed vaccines

	Vaccine and dose groups	Schedule and route	Viral strain, dose, and timing	Outcome
(Continued from previous page)				
Stittelaar et al (2005)[44]				
Cynomolgus macaques	MVA: 1×10^8 pfu and then MVA: 1×10^8 pfu	Subcutaneous, given 28 days apart	Strain MSF#6: intratracheal 1×10^6 or 1×10^7 pfu 15 weeks after final vaccination	One of six animals developed a rash, it received 1×10^7 pfu monkeypox virus, rash was less extensive and the lesions resolved more quickly compared with unvaccinated animals; no animals died
Cynomolgus macaques	MVA: 1×10^8 pfu and then Elstree-RIVM: $2{\cdot}5\times10^5$ pfu	MVA-subcutaneous and Elstree-RIVM-percutaneous or scarification using a bifurcated needle 28 days later	Strain MSF#6: intratracheal 1×10^6 or 1×10^7 pfu 15 weeks after final vaccination	None of the six animals developed a rash; and no animals died
Cynomolgus macaques	Elstree-RIVM: $2{\cdot}5\times10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Strain MSF#6: intratracheal 1×10^6 or 1×10^7 pfu 15 weeks after final vaccination	None of the six animals developed a rash; and no animals died
Cynomolgus macaques	Elstree-BN: $2{\cdot}5\times10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Strain MSF#6: intratracheal 1×10^6 or 1×10^7 pfu 15 weeks after final vaccination	None of the six animals developed a rash; and no animals died
Cynomolgus macaques	Unvaccinated	..	..	Three (100%) animals receiving 1×10^6 pfu developed a rash by day 11 and disease resolved in all animals by day 28; all animals receiving 1×10^7 pfu developed a severe rash by day 8; and all animals died: one (33%) on day 15, two (67%) by euthanasia on day 19 due to deteriorating clinical conditions
Hatch et al (2005)[45]				
Cynomolgus macaques	ACAM2000: $2{\cdot}5\times10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: aerosol 5×10^7 pfu 28 days after final vaccination	All six animals survived with little to no evidence of disease (average lesion count was three); this is the only group not to have any evidence of pulmonary oedema
Cynomolgus macaques	MVA: 1×10^8 pfu	MVA-subcutaneous	Zaire-79: aerosol 5×10^7 pfu 28 days after final vaccination	Two of six animals developed clinical symptoms and a rash by day 9 and succumbed to disease. The other four animals had minimal disease (average lesion count was ten)
Cynomolgus macaques	MVA: 1×10^8 pfu and then MVA: 1×10^8 pfu	Subcutaneous, given 28 days apart	Zaire-79: aerosol 5×10^7 pfu 28 days after final vaccination	All six animals survived with minimal symptoms (average lesion count was seven)
Cynomolgus macaques	Unvaccinated	..	..	All six animals developed an extensive rash (average lesion count was 51) with severe symptoms and died or required euthanasia by day 6
Saijo et al (2006)[46]				
Cynomolgus macaques	LC16m8: $2{\cdot}5\times10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Liberia strain: intranasal 1×10^6 pfu; and Zr-599: subcutaneous 1×10^6 pfu 5 weeks after vaccination	Intranasal: none of the three animals developed a rash, none had clinical illness or detectable viraemia; MVA-subcutaneous: none of the three animals developed a rash, and three (100%) animals had transient, low-level viraemia on days 3–6
Cynomolgus macaques	Lister: $2{\cdot}5\times10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Liberia strain: intranasal 1×10^6 pfu; and Zr-599: subcutaneous 1×10^6 pfu 5 weeks after vaccination	Intranasal: none of the three animals developed a rash, none had clinical illness or detectable viraemia; MVA-subcutaneous: none of the two animals developed a rash, none had clinical illness or detectable viraemia
Cynomolgus macaques	Unvaccinated	..	..	Intranasal: two (100%) animals developed a small rash, clinical illness, and had detectable viraemia, both animals survived; MVA-subcutaneous: two (100%) animals developed extensive, progressive rash by day 7, viraemia by day 3, and were euthanised on day 14 and 18

(Table 2 continues on next page)

have been tested for protection against monkeypox virus challenge in non-human primates and are summarised in table 2. These studies have repeatedly showed that first-generation vaccines provide the strongest protection. Most animals have sterilising immunity and no evidence of clinical illness. When rash and other symptoms are present, the rash is always more limited (ie, with fewer lesions and covering a much smaller area of the body), and symptoms are milder with an accelerated course of resolution than with other-generation vaccines. Rarely, there is detection of low-level, transient viraemia.

Protection with the ACAM2000 second-generation vaccine is essentially the same as with first-generation vaccines. MVA and LC16m8 also provide strong protection; however, breakthrough disease is more common and, when present, the rash is more pronounced compared with first-generation or second-generation vaccines. In studies of immunogenicity, antibody titres are similar between groups or are slightly higher in animals vaccinated with first-generation or second-generation smallpox vaccines. The animal study data clearly show that smallpox vaccines elicit immune

	Vaccine and dose groups	Schedule and route	Viral strain, dose, and timing	Outcome
(Continued from previous page)				
Gordon et al (2011)[47]				
Cynomolgus macaques	Dryvax: $2 \cdot 5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: intranasal 5×10^7 pfu 60 days after final vaccination	Four (100%) animals developed a small rash with fewer lesions than unvaccinated conterparts (lesion count: 1–39) that resolved by day 9; viraemia was present in all animals, but 5 logs lower than unvaccinated animals
Cynomolgus macaques	LC16m8: $2 \cdot 5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zaire-79: intranasal 5×10^7 pfu 60 days after final vaccination	14 (100%) animals developed a progressive rash (lesion count: 12–146) that resolved in all animals on day 9–12; and viraemia was present in all animals but 3 logs lower than unvaccinated animals
Cynomolgus macaques	Unvaccinated	..	..	Six (100%) animals developed rapidly progressing rash (lesions too numerous to count) by day 6 with high viral loads in the blood; all animals succumbed to disease by day 12
Iizuka et al (2017)[48]				
Cynomolgus macaques	Lister: $2 \cdot 5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zr-599: subcutaneous 5×10^7 pfu 6 or 12 months after final vaccination	Two of four animals developed a rash at first timepoint, and the other two did at the second timepoint; none of the four animals had detectable viraemia
Cynomolgus macaques	LC16m8: $2 \cdot 5 \times 10^5$ pfu	Percutaneous or scarification using a bifurcated needle	Zr-599: subcutaneous 5×10^7 pfu 6 or 12 months after final vaccination	None of the two animals developed a rash at either timepoint; two of the three 6-month-infected animals had transient viraemia (one on day 3 and the other on day 7); and none of the two 12-month-infected animals had detectable viraemia
Cynomolgus macaques	Unvaccinated	..	..	Four (100%) animals developed a characteristic rash (lesion count=95–1150) and detectable viraemia by day 3–4

MVA=modified vaccinia virus Ankara. PBS=phosphate-buffered saline. PFU=plaque forming units.$TCID_{50}$=50% tissue culture infectious dose.

Table 2: **Non-human primate studies testing smallpox vaccine-induced protection against monkeypox**

responses capable of substantial—and in many cases complete—protection against monkeypox infection. The data from Hatch and colleagues contributed to the approval of JYNNEOS for the prevention of monkeypox by the FDA in 2019.[45]

Human studies

In addition to the animal model data, several studies have reported on the use of smallpox vaccines during monkeypox outbreaks. These studies provide additional supporting evidence of cross-protective immunity. Surveillance data from Zaire (now Democratic Republic of the Congo) in 1980–84 indicate that monkeypox attack rates are higher in individuals without previous smallpox vaccination than in those with previous vaccination. Previous smallpox immunisation results in an estimated protective efficacy of 85%.[75] Subsequent surveillance data from the 2006–07 outbreaks in the Democratic Republic of the Congo[14] indicate that 3·8% of monkeypox cases had previous evidence of smallpox vaccination compared with 26·4% of the overall population. In individuals born before smallpox vaccination ceased, vaccination was linked to a 5·21-fold reduced risk of monkeypox, with vaccine effectiveness estimated at 80·7% (95% CI 68·2–88·4). In a separate study of 29 infected individuals from the 2003 outbreak in the USA, six of the patients had evidence of childhood smallpox vaccination, suggesting that remote vaccination provides some protection but not necessarily full protection against symptomatic disease.[76] In fact, numerous reports indicate that the disease is modified by previous smallpox vaccination, with vaccinated individuals generally having less extensive rash, fewer lesions, and milder symptoms than their unvaccinated counterparts.[77–81] Finally, in 2017 a study of the safety and effectiveness of JYNNEOS in health-care personnel in the Democratic Republic of the Congo with a high risk of exposure to monkeypox virus was initiated.[82] The results from this study are not yet available but should provide additional real-world information regarding the utility of smallpox vaccination in at-risk groups when available. It is important to note that the current outbreak involves transmission during sexual activity. Additionally, a human monkeypox outbreak in Nigeria in 2017–18 noted a high incidence of genital lesions, which was not described in previous outbreaks. This previously reported high incidence coupled with the clear association of sexual activity and incidence of genital lesions in the 2022 outbreak, could implicate a new route of transmission or reduced threshold for infection through sexual activity compared with transmission from non-sexual contact.[83,84] These scenarios have not been evaluated in any of the human or animals studies described here.

Concerns and hypotheses

As of Sept 2, 2022, the human monkeypox outbreak recognised in May, 2022, now involves over 52 090 confirmed cases across 100 countries outside of Africa—the largest known outbreak of monkeypox so far. Most cases are in adult males, with a median age of

38 years, similar to the age range seen in outbreaks in Africa over the past 5 years.[83] The changing epidemiology of human monkeypox infections is of great concern. In part it exposes challenges that directly confront us regarding climate change, exotic and rapid global travel, human behaviours—including sexual behaviour; rapid testing, diagnosis, and treatment; availability and use of prevention; and the trade in exotic animals.

Features of the changing epidemiology that probably directly facilitated the current monkeypox outbreak include human behaviour (eg, travel to countries with different infectious disease threats as well as rapid spread among sexual networks), absence of previous smallpox vaccination, and the ability to depart high-risk areas before symptom onset and arrive in international destinations within hours. A feature of the current outbreak has been the rapid and unanticipated spread of monkeypox infection within weeks. One possibility for why this rapid spread is occurring includes viral mutation such that transmissibility but not virulence has been enhanced. To date, the evidence suggests two viral variants are present in the USA with an unanticipated accumulation of mutations suggesting longer-term subclinical transmission, but no evidence of enhanced transmissibility. This longer-term subclinical transmission, along with numerous and rapid sexual contacts could have facilitated transmission,[85] and could explain transmission to those who did not travel to Africa, are not MSM, and had only casual exposure. Viral sequencing done so far suggests that the causative virus is from the west African clade—a clade with documented milder disease and lower case-fatality rates than other clades. In the 2003 US monkeypox outbreak involving 71 known individuals, none were treated with antivirals, vaccinia immune globulin, or vaccine, and all survived. One individual (a 6-year-old child) did, however, develop encephalitis.[79]

A major concern is the possibility that monkeypox virus could establish an animal reservoir outside of west or central Africa. This viral reservoir could occur in the rodent, prairie dog, or exotic small pet trade. If this animal reservoir was established, it would mean the disease could not be eliminated, and would add a new and continuing risk to the population. In turn, this could require enhanced detection, surveillance, and vaccination efforts in high-risk areas.

Conclusions and the future

Human monkeypox represents a substantial health risk to the human population. It is evident that the epidemiology and clinical phenotype of the disease is changing—primarily outside of Africa. The highest risks are likely to be in infants and young children (aged <8 years), pregnant women, and those who are immunocompromised. The USA currently has both smallpox and monkeypox vaccines available in its Strategic National Stockpile, as well as two antivirals that could be used. Few other countries have taken such preparatory steps.

When to deploy antivirals and vaccines is an important decision, and one currently being reviewed nationally and at the WHO level.[86] The most logical use will not be mass immunisation given the extremely low risk of infection in the general population, but rather in those with increased risk due to behaviour, occupation, or close contact. A ring vaccination effort is warranted given the rapid spread so far. We would further suggest that consideration should be given to health-care organisations maintaining core teams of health-care providers who maintain training and are immunised to care for high consequence infectious diseases including monkeypox cases. The risks and benefits, as well as utility and availability of the ACAM2000, MVA-Bavarian Nordic, LC16m8, and other vaccines vary and impact such decision making. It is important to note that the risk–benefit calculations will probably change in different populations and might also change over time.

Another concern nowadays is that of potential evolution of the monkeypox virus genome to create one or more of the following effects: increase transmissibility, augment virulence, or to degrade antiviral efficacy by altering the genetic sequence for the proteins inhibited and targeted by antivirals such as the VP37 protein and tecovirimat. Given the tenuous state of the continuing challenges around COVID-19, climate change, fragile economies, the looming threat of war, and continuing supply chain issues, such concerns are warranted and should be planned for.

In the meantime, public health officials, health-care providers, and the general public need to be educated in regard to the continuous nature of the threat of emerging diseases. Nations need to reassess their preparedness for outbreaks such as monkeypox and establish their own strategic national stockpiles to ensure global safety. Resources for training, prevention, diagnosis, surveillance, and treatment cannot continue to be on again, off again. If we have learned anything from the

Search strategy and selection criteria

MEDLINE and PubMed databases were searched for primary research articles in English published between Jan 1, 1967 and Aug 8, 2022. Search terms included: "monkeypox", "smallpox vaccine", "animal studies", and "challenge studies". These terms were used individually and in various combinations. Bibliographies of identified publication were also searched for additional sources to reference. Each article was reviewed by the three authors (GAP, RBK, and PKT) for inclusion. Articles were included if they contained clinical or epidemiological information relevant to the current monkeypox virus outbreak, historical information to establish context, human smallpox vaccine effectiveness data versus monkeypox infection, or data from animal monkeypox challenge studies using smallpox vaccines.

COVID-19 pandemic it is that preparedness must be continuous, and should be seen as an investment in the well-being of the population and national economies. In this regard, education is paramount, and a framework of teaching, testing, tracing, and treating should be widely established.

Contributors

GAP, RBK, and PKT contributed equally to the conceptualisation, writing of the original draft, review, and editing of this Review.

Declaration of interests

GAP offers consultative advice on vaccine development to Merck, Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, Eli Lilly, Affinivax, Novavax, Bavarian Nordic, AstraZeneca, Exelixis, Regeneron, Janssen, Vyriad, Moderna, and Genevant Sciences. GAP holds patents related to vaccinia and measles peptide vaccines. RBK and GAP hold a patent related to vaccinia peptide vaccines. GAP and RBK have received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. RBK has received funding from Merck Research Laboratories to study waning immunity to mumps vaccine. PKT declares no competing interests.

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