

29

Smallpox and mpox

NOTIFIABLE

The disease

Smallpox

Smallpox is a highly transmissible disease which was one of the most severe infectious diseases affecting humans. Smallpox (variola) virus is a DNA virus, and a member of the genus *orthopoxvirus* of the Poxviridae family, which also includes vaccinia and mpox (formerly known as monkeypox). In December 1979, the Global Commission for the Certification of Smallpox Eradication declared the world free of smallpox and this declaration was ratified by the World Health Assembly in May 1980.

Mpox

Mpox is a rare disease that is caused by infection with the monkeypox virus. Monkeypox virus (MPXV) is related to but distinct from the viruses that cause smallpox (variola virus) and cowpox (vaccinia virus). The name monkeypox originates from the initial discovery of the virus in monkeys in a Danish laboratory in 1958.

Human mpox was first described in 1970 when regional elimination of smallpox revealed sporadic cases of a disease with similar presentation in rural areas of Democratic Republic of Congo (DRC). Outbreaks have since occurred in Nigeria, Republic of Congo, Sierra Leone, Liberia, Cameroon and the Central African Republic. MPXV is a zoonosis - an organism transmitted to humans from animals. The animal host is most likely a rodent, although the definitive reservoir has not been identified. Following the global eradication of smallpox in 1977, mpox has become the dominant cause of orthopox outbreaks in humans, possibly associated with waning orthopox immunity following cessation of smallpox vaccination (Rimoin *et al.* 2010).

Spread of MPXV may occur when a person comes into close contact with lesions, body fluids (including during intimate sexual contact), or respiratory droplets from an animal or human with the infection; or from contact with material contaminated with the virus e.g. bedding. The virus enters the body through broken skin, the respiratory tract or the mucous membranes.

The incubation period is 5 to 21 days, but typically 6 to 13 days following exposure. Most patients experience a mild, self-limiting illness, with spontaneous and complete recovery seen within 3 weeks of onset. However, severe illness can occur and sometimes results in death. The risk of severe disease is higher in children, pregnant women and severely immunosuppressed individuals.

There are two genetic groups of MPXV: Clade I (previously known as Central African or Congo basin Clade) and Clade II (previously known as West African Clade). These clades subdivide into multiple lineages. Clade I is associated with more severe disease in humans and a reported case fatality rate of up to 10%. By contrast, Clade II is associated with

milder disease, with a case fatality rate of 3-4%. Clade II was implicated in the 2022 outbreak in the UK (see below). MPXV was included in the national list of High Consequence Infectious Diseases (HCID) in the UK. Following the 2022 MPXV Clade IIb outbreak, mainly affecting gay, bisexual and other men who have sex with men (GBMSM), the Advisory Committee on Dangerous Pathogens (ACDP) recommended that all of Clade II MPXV should no longer be classified as HCID; but all of Clade I should remain an HCID. Until October 2024, there were no confirmed cases of mpox Clade I in the UK. As of 1 April 2025, 11 cases of clade Ib have been detected in the UK, with no deaths. The ACDP re-assessed evidence and advised that clade I mpox no longer met the criteria of an HCID. Therefore mpox is no longer managed as an HCID in healthcare settings. <https://www.gov.uk/guidance/derogation-of-clade-i-mpox>

History and epidemiology of the disease

Smallpox

Compulsory childhood smallpox vaccination of the UK population commenced in 1853. Smallpox ceased to be endemic in the UK by the 1930s, although importations continued to occur, with outbreaks in England in 1949 and Scotland in 1950. Smallpox vaccination remained routine in infants until 1962, although coverage of vaccination had declined to low levels in many areas. Vaccination as part of outbreak control was better accepted and vaccination of older schoolchildren and adults remained until 1971, when it was replaced with a selective risk group policy (Milward G, 2019).

The UK smallpox vaccination programme was part of the global smallpox eradication efforts in the latter half of the 20th century. At the end of the 1960s, smallpox was still endemic in Africa and Asia. Vaccination campaigns, surveillance and prevention measures that aimed to contain epidemic hotspots were intensified. One prevention strategy deployed was ring vaccination, where a geographically defined “ring” of people around each case and their contacts were vaccinated to protect those at greatest risk of contracting the disease. These vaccinated individuals also helped to form an immune buffer to prevent the spread of disease to neighbouring communities. This strategy relied on early diagnosis and reporting of cases to define the ring, and on rapid vaccine access, but less so on detailed contact-tracing. Ring vaccination with surveillance-containment was used successfully against smallpox as part of the final eradication phase in Africa in the 1970s.

After global eradication and in response to the threat of a bioterrorist release of smallpox in the UK, in 2003 the Department of Health published *Guidelines for smallpox response and management in the post- eradication era (smallpox plan)* ([\[ARCHIVED CONTENT\]](#) [Guidelines for smallpox response and management in the post-eradication era \(smallpox plan\) : Department of Health - Publications and statistics \(nationalarchives.gov.uk\)](#)). This outlined the role of vaccination of response teams who would safely manage and diagnose suspected cases of smallpox. In 2003–04 more than 300 healthcare and ambulance workers were vaccinated, along with a small number of staff in laboratories designated to receive specimens from suspected cases.

Mpox

Between 2018 and 2022 the UK experienced a small number of imported mpox cases, all Clade II, associated with travel to or from countries in West Africa where mpox is endemic. Spread was limited by rapid diagnosis, isolation and care of the cases in HCID centres and the quarantine and surveillance of close contacts. Vaccination of staff working in HCID

centres and post-exposure vaccination of contacts was advised, and no serious consequences of disease occurred.

In May 2022, following an increase in domestically acquired mpox cases largely affecting gay, bisexual and other men who have sex with men (GBMSM), a national incident was declared ([Monkeypox outbreak: technical briefings - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/publications/monkeypox-outbreak-epidemiological-overview)). By 31 December 2022, 3,732 confirmed and highly probable mpox cases had been reported in the UK, mainly in London, with the majority in males under 45 years of age; around 1% of cases were in women; there were no associated deaths (<https://www.gov.uk/government/publications/monkeypox-outbreak-epidemiological-overview>). The outbreak was associated with cases in similar populations worldwide (including North America and Europe) and led to WHO declaring it a Public Health Emergency of International Concern in July 2022.

During the 2022 mpox outbreak, UKHSA advised that pre-exposure vaccination should be extended beyond staff working in HCID units to a small group of designated healthcare staff in the additional hospital units that were stood up to care for mpox patients, and to designated staff in sexual health clinics who were identified to assess suspected cases. Advice for other health care staff, including those in front line roles, was to avoid exposure by ensuring that suspected mpox cases were triaged correctly and then assessed by those wearing appropriate personal protective equipment.

In June 2022, JCVI endorsed a reactive selective vaccination strategy with the aim of interrupting transmission in the subset of individuals at increased risk of exposure. JCVI advised that pre-exposure vaccination should be offered as soon as feasible to those GBMSM at highest risk of exposure. The initial priority was to deliver first doses to as many GBMSM at greatest risk of mpox as possible. The committee concluded that this would be best way to bring the current outbreak under control.

Due to restricted vaccine supplies and emerging evidence suggesting low effectiveness, post-exposure vaccination was limited to close contacts ideally within 4 days of last exposure, with use up to 14 days restricted to those who were at higher risk of complications from mpox.

The committee agreed that GBMSM at highest risk could be identified amongst those who attend sexual health services, using markers of risk to assess eligibility. These risk criteria included a recent history of multiple partners, participating in group sex, attending sex-on-premises venues or based on proxy markers such as recent bacterial sexually transmitted infection (in the past year).

UKHSA also advised that others who have frequent close and intimate contact with the GBMSM network at risk of mpox may also be vaccinated, irrespective of their identified gender. This included staff who work in GBMSM sex-on-premises venues, such as saunas, if they were regularly exposed to items (e.g. linen) or surfaces likely to be contaminated with body fluids or skin cells. It was also suggested that this offer could be combined with supplementary approaches to provide outreach vaccination for those who may not be in contact with sexual health services, estimated to be 37.4% of GBMSM at highest risk in 2021. ([Investigation into monkeypox outbreak in England: technical briefing 8 – GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/publications/investigation-into-monkeypox-outbreak-in-england-technical-briefing-8)).

In September 2022, based on the number of doses already delivered, the declining incidence of mpox and the available vaccine supply, JCVI agreed that the next priority was to offer a second dose to GBMSM at highest risk from around 2-3 months after their first

dose. Increasing the interval between doses is associated with higher peak antibody responses and durability of immunity (Berry *et al*, 2024), and so this strategy aimed to provide longer lasting protection and to protect this community against subsequent introduction from countries where the virus was still circulating at higher levels.

In June and September 2023, JCVI met to discuss the potential for a routine mpox immunisation programme. A model of the impact and cost-effectiveness of reactive (initiating a programme in response to an outbreak) and pre-emptive scenarios (offering vaccination as a routine programme) was reviewed (Zhang *et al*, 2024). In November 2023, JCVI recommended that a routine vaccination programme for protection of GBMSM at highest risk of exposure to mpox and offered through sexual health services, should be developed to prevent future outbreaks ([JCVI statement on mpox vaccination as a routine programme - GOV.UK \(www.gov.uk\)](#)).

In 2023, the Democratic Republic of Congo (DRC) reported a geographical expansion of mpox cases, with the highest ever annual number of Clade I MPXV cases and the first reports of sexual transmission of Clade I MPXV. In the first 7 months of 2024, suspected case numbers in DRC were similar to total cases in 2023. In addition, a new strain, Clade Ib, was identified, contributing to a high numbers of cases. Sexual transmission was confirmed among male partners, and through heterosexuals, including female sex workers, in outbreaks occurring in different geographical areas. Higher case fatality ratios have been reported in children (particularly infants) and in people with uncontrolled HIV infection.

While Clade I MPXV has historically only been reported in a few countries in Central Africa, during 2024 cases were also reported from several countries surrounding DRC including: Republic of Congo, Central African Republic, Burundi, Rwanda, Uganda, Kenya, Cameroon and Gabon. In August 2024, the Africa Centre for Disease Control (CDC) declared a Public Health Emergency of Continental Security and WHO declared a Public Health Emergency of International Concern in view of the upsurge of cases in the DRC and neighbouring countries and the emergence of the new strain (Clade Ib). By August 2024, single cases of Clade Ib mpox had also been reported in Sweden and in Thailand after acquisition in an affected country in Africa. Travel-associated cases of Clade Ib and since been reported in other countries including Germany, India, Kenya, Zimbabwe, Canada and the USA. The UK reported its first case of Clade Ib in October 2024 with three secondary cases in the same household. Further UK cases have occurred mainly in people returning from countries in Africa where community transmission is occurring.

The smallpox vaccination

First and second generation smallpox vaccines

Historically, first and second-generation smallpox vaccines were used for population-level and targeted occupational health-related immunisation programmes in the UK. These vaccines are no longer available in the UK.

First generation smallpox vaccines used during eradication were propagated in calf skin and purified from calf lymph. A successful vaccination produced a lesion at the site of administration. Second generation vaccines were propagated in tissue cell culture and produced using modern good manufacturing practices, thus having a lower risk of contamination with adventitious agents (Petersen *et al*. 2019).

First and second generation vaccines contain a live (replicating) vaccinia virus, mostly based on either the Lister or the New York City Board of Health (e.g. ACAM2000) strains.

Although these live vaccines were highly effective, they were also associated with risks of serious adverse events (Auckland C *et al*, 2005, Gallagher and Lipsitch 2019, Lane *et al*, 1968, Mora *et al*, 2009, Morgan *et al*, 2008). Previous data from Africa suggests that the live vaccines against smallpox may also be up to 85% effective in preventing mpox infection. None of these first and second generation vaccines for smallpox have been granted an indication for mpox.

Third generation smallpox vaccines

Newer, third generation, smallpox vaccines are now available which have a much-improved safety profile compared with first and second generation smallpox vaccines. Two of these smallpox vaccines have also been granted an indication for prevention of mpox (regardless of MPXV clade):

- LC16m8 (or LC16 “KMB”) vaccine: minimally replicating
- modified vaccinia Ankara (MVA-BN) (Imvanex®) vaccine: replication-defective

LC16m8 is an attenuated, minimally replicating strain of vaccinia virus developed in the early 1970s in Japan from the Lister clone. The virus used in the vaccine is attenuated through multiple passages in primary rabbit kidney cells. The vaccine is administered by inoculation (i.e. scarification) with a bifurcated needle, the same method used during the global smallpox eradication program during the 1970s. Japanese authorities licensed the vaccine to prevent smallpox in 1980. After evaluating evidence for safety and efficacy, WHO recommended stockpiling LC16m8 as part of global smallpox defence in 2013. Japan added prevention of mpox infection as an indication in August 2022. It is currently not licensed in the UK or in Europe.

The modified vaccinia Ankara (MVA-BN) (Imvanex®) vaccine contains a replication-defective (also known as replication-incompetent) virus. The virus used in the vaccine is attenuated through multiple passages in chicken embryo fibroblast cells, leading to a substantial loss of its genome including immune evasion and virulence factors. It demonstrates very limited replication capability and low neuropathogenicity in human and animal studies, while retaining immunogenic properties, including demonstrable protective immune responses against a variety of orthopoxviruses (Verheust C *et al*, 2002). MVA-BN was initially approved as a sub-cutaneous injection so does not require training in the scarification technique. As the virus cannot replicate in mammalian cells it does not produce a lesion at the site of vaccination and so there is no risk of auto-inoculation. Like vaccines that contain non-replicating vectors (such as the AstraZeneca COVID-19 vaccine), MVA-BN should be considered as an inactivated vaccine (see chapter 1).

MVA-BN (Imvanex®) was licensed by European Medicines Agency in 2013 for the prevention of smallpox. Data used for licensing was limited due to the eradication of smallpox in 1979 followed by the requirement for containment of the virus. Preclinical studies of MVA-BN have suggested that 2 doses of vaccine are immunogenic, generating antibody levels considered protective against smallpox, and by extrapolation, against mpox. Initial studies showed that MVA-BN protected non-human primates from lethal challenge with MPXV Clade I virus (Stittelaar *et al*, 2005, Earl *et al*, 2008; Jacobs *et al*, 2009, Kennedy *et al*, 2009, Hatch *et al*, 2013). Protection after a single dose was suggested from 6 days in Earl's study and 4 days in Stittelaar's study. In humans, while no serologic correlates of immunity for any orthopoxviruses have been established, MVA-BN has induced variola-neutralising antibodies

(Damon *et al*, 2009, Hughes *et al*, 2012), and MPXV-neutralising antibodies and cell-mediated responses including in children (Frey *et al*, 2021, Ladhani *et al*, 2023, Mazzotta *et al*, 2024, Otter *et al*, 2023, Priyamvada *et al*, 2022).

In September 2019, the Food and Drug Administration (FDA) in the US approved MVA-BN (Jynneos®) (the US labelled equivalent of Imvanex®) for the prevention of mpox as well as smallpox (FDA, 2019). In 2022, the vaccine was authorised for active immunisation against mpox in adults by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (<https://products.mhra.gov.uk/search/?search=IMVANEX>).

Estimates of real-world vaccine effectiveness for MVA-BN in preventing mpox infection have mainly been generated during the 2022 mpox outbreak (Mason *et al*, 2024, Pischel *et al* 2024, Berry *et al* 2024). In meta-analyses, vaccine effectiveness was estimated to be 76% and 82%, in the Pischel *et al* study, 78% and 83% in Mason *et al* study and 74% and 82% in the Berry *et al* study for one and two doses of MVA-BN respectively. Further studies since these reviews have reported similar estimates of vaccine effectiveness (Charles *et al*, 2024). There is some uncertainty about whether vaccine effectiveness may be affected by immune competence: slightly higher vaccine effectiveness was estimated in people not living with diagnosed HIV compared to those living with HIV (Yeganeh *et al*, 2024) and slightly lower vaccine effectiveness was estimated in people with an immunocompromising condition (Dalton *et al* 2023). However, in one review, vaccine effectiveness estimates in immunocompromised individuals, people living with HIV or people taking pre-exposure prophylaxis for HIV were similar to overall vaccine estimates, although with wide confidence intervals.

There is also evidence that pre-exposure vaccination may modify disease and thus reduce more severe presentations. Vaccine effectiveness against hospitalisation was estimated to be 67% in a meta-analysis of any dose of MVA-BN (Pischel *et al*, 2024). Other studies reported a milder disease course among MVA-BN recipients, including fewer lesions and body regions affected by a rash (Aparício Martins *et al*, 2024, Guagliardo *et al* 2024, Hazra *et al*, 2024, Eustaquio *et al*, 2023, Kroger *et al*, 2023).

There is accumulating evidence of durability of immunity of MVA-BN. Neutralising antibodies have returned to pre-vaccination baseline levels 24 months after vaccination (Ilchmann *et al*, 2023; Priyamvada *et al*, 2022); however, boosting with an additional dose of MVA-BN elevated neutralising antibody levels to peaks 10-fold or higher than those seen after one and two doses. This anamnestic response to boosting supports the presence of immunological memory induced by primary MVA-BN vaccination (Ilchmann *et al*, 2023). A model has predicted that increasing the interval between the two MVA-BN vaccine doses will lead to higher peak antibody response which remains above the one-dose peak for more than 10 years (Berry *et al*). This is consistent with modelling used by JCVI, where the observed data in 2023 fitted with a longer duration of protection – at least 5 years for one dose and 10 years for two doses of vaccine (Zhang *et al*, 2024).

There is growing evidence that MVA-BN has low effectiveness in preventing infection when given post-exposure. At day 14, the GMTs induced by a single MVA vaccination are equal to that induced by a live smallpox vaccine (ACAM2000), and the percentage of participants with seroconversion are similar (90.8% and 91.8%, respectively) (Pittman *et al*, 2019). Real world vaccine effectiveness post exposure is uncertain with most studies reporting negative vaccine effectiveness (Pischel *et al* 2024). Given the relatively short incubation period, any protection is likely to derive only where vaccine is given at a short interval after exposure

(Hazra *et al* 2024, Merad *et al* 2022, Thy *et al* 2022, Bertran *et al* 2023, Rosen *et al* 2024). Based on this evidence, rapid post-exposure vaccination may have the potential to prevent infection and/or to modify disease, but only if given promptly (see later section).

Results from a clinical study of immunocompetent individuals (Frey *et al*, 2015) have shown that a lower dose (0.1ml) of MVA-BN administered intradermally was immunologically non-inferior to the standard (0.5ml) dose given by subcutaneous administration. A US study estimated vaccine effectiveness by route of administration and found comparable protection by subcutaneous and intradermal administration routes (Dalton *et al*, 2023).

Presentation

The vaccine comes in packs of 10 or 20 single dose vials. The vaccine's normal appearance is a light yellow to pale white milky suspension.

Storage

MVA-BN is supplied frozen in packs of 10 or 20 vials. The remaining shelf life at clinic level will depend on previous storage temperature, please refer to documentation on the product.

Frozen vials should be transferred to 2°C to 8°C to thaw or may be thawed for 15 minutes at room temperature for immediate use. After thawing, vaccine can be stored for up to 8 weeks at 2°C to 8°C. Store in the original packaging in order to protect from light.

Where fractional doses are being used (see below), the contents of the vial can remain at room temperature for up to one hour whilst the five doses are used. Each dose should be drawn up and given immediately (as below).

Administration

The vaccine should be allowed to reach room temperature before use. Swirl the vial gently before use for at least 30 seconds. The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

Most vaccines are given by intramuscular (IM) injection (see chapter 4), but the MVA-BN Summary of Product Characteristics (SmPC) advises that the vaccine should be administered by the deep sub-cutaneous (SC) route. As there is published evidence suggesting an adequate immunological response (Vollmar *et al*, 2006) and extensive experience of using MVA containing vaccines given by the IM route, UKHSA advised that intra-muscular administration is an acceptable alternative. For adults, the preferred site for both IM and SC immunisation is the deltoid area of the upper arm; for small children the anterolateral aspect of the thigh is preferred (see chapter 4).

Fractional dose use

In August 2022, following the emergency use approval by the US Food and Drug Administration, JCVI endorsed the use of a fractional dose (0.1ml) of MVA-BN given by intradermal injection during periods of supply constraints. The approach was also advised by the European Medicines Agency Emergency Task Force. <https://www.ema.europa.eu/en/news/emas-emergency-task-force-advises-intradermal-use-imvanex-jynneos-against-monkeypox>

Where fractional doses are being used, after thawing and swirling, the first dose of 0.1ml should be withdrawn using the correct needle and syringe (see below). Appropriate

infection control and aseptic techniques should be used at all times and is particularly important when taking multiple doses from a single vial (see chapter 4).

A fractional dose intradermal injection for MVA-BN may be administered on the deltoid (the same site recommended for BCG - see chapters 32 and 4) or on the volar aspect (palm side) of the forearm around 2-4 inches below the ante-cubital fossa (the same site as normally used for Mantoux testing). Although the initial study in the USA was conducted using the forearm site (Frey *et al*, 2015), other vaccines (including influenza and rabies) have been tested with fractional intradermal dosing into the deltoid. The original live smallpox vaccine was also administered into the deltoid. UK healthcare professionals who have delivered BCG are more likely to be familiar with the deltoid site for intradermal administration, and early feedback from a pilot confirmed that this site was more acceptable to both the healthcare professional and to the vaccinees.

To administer the 0.1ml dose required, a graduated 1ml syringe should be used, the needle must be attached firmly and the intradermal injection administered with the bevel facing up. The immuniser should stretch the skin between the thumb and forefinger of one hand and with the other slowly insert the needle, with the bevel upwards, about 3mm into the superficial layers of the dermis almost parallel with the surface. The needle can usually be seen through the epidermis.

A correctly given intradermal injection results in a tense, blanched, raised bleb of around 7mm diameter with a 0.1ml injection. It is easier to administer intradermal injections correctly using a short (9-12 mm) 25G or 26G needle, ideally with a short bevel - see chapter 4. If little resistance is felt when injecting and a diffuse swelling occurs as opposed to a tense blanched bleb, the needle has been inserted too deeply. If this occurs, the needle should be withdrawn. A full intradermal dose should be repeated immediately (no minimum interval) and placed at least 2 inches (5cm) away from the incorrectly given dose.

Disposal

Equipment used for vaccination, including used vials, ampoules or syringes, should be disposed of by placing them in a proper, puncture-resistant 'sharps box' according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

MVA-BN (Imvanex®/Jynneos®/Imvamune®) contains an attenuated organism. Sharps waste and empty vials should be placed into yellow lidded waste bins and sent for incineration; there is no designation as genetically modified organism (GMO) waste.

Dosage and schedule

Pre-exposure vaccination of individuals previously not vaccinated against smallpox

Administer a course of two doses with at least a 28-day interval between doses (see table). A longer interval between first and second doses increases duration of protection.

Individuals who have previously been vaccinated with a live smallpox vaccination should only receive a single dose of MVA-BN. Live vaccine was only used routinely in the UK up to the 1970s, so apart from the healthcare workers vaccinated in 2003/4, vaccinated individuals will be older, and should have a distinctive scar (which normally looks like a circular 5 pence size dent in the left upper arm).

In the event of an outbreak or incident, it is highly unlikely that there will be sufficient time to offer pre-exposure vaccination with two doses for those at risk of occupational exposure. In this scenario, a single dose of vaccine should be offered immediately. Completion of the primary course with a second dose at least 28 days later should be considered if the individual is in an eligible group with clear ongoing risk of exposure. However, where supply is constrained the priority is to maximize first dose vaccination, and as protection from a single dose is high. Although it may take 14 days to respond to vaccination, individuals can commence work immediately after a single dose of MVA-BN, provided appropriate protective measures are available. As longer intervals between doses will help to extend protection, the second dose can be given later. Where the second dose of MVA-BN is given after 28 days, the first dose should not be repeated.

Table: Recommended Schedule for use of MVA-BN

	Individuals previously not vaccinated against smallpox	Individuals previously vaccinated against smallpox
Immunocompetent individuals (including people with atopic dermatitis) <i>This includes individuals living with HIV who are virally suppressed and have a CD4 count above 200 cells/mm³</i>	0.5 ml subcutaneous / intramuscular injection OR 0.1ml intradermal injection (during supply constraints) + 0.5 ml subcutaneous / intramuscular injection any time from 28 days OR 0.1ml intradermal injection at any time from 28 days	0.5 ml subcutaneous / intramuscular injection OR 0.1ml intradermal injection (during supply constraints)
Individuals who are immunosuppressed adults (as defined in chapter 28a), and those with a history of keloid scarring	0.5 ml subcutaneous / intramuscular injection + 0.5 ml subcutaneous / intramuscular injection at any time from 28 days	0.5 ml subcutaneous / intramuscular injection
Children under 18 years	0.5 ml subcutaneous / intramuscular injection + 0.5 ml subcutaneous / intramuscular injection at any time from 28 days <i>Intradermal vaccination (as above) is an acceptable alternative for localized outbreak use, during periods of supply constraints</i>	0.5 ml subcutaneous / intramuscular injection

Post-exposure of individuals of any age

Administer a 0.5ml SC/IM dose or a 0.1ml ID dose of MVA-BN.

There is growing evidence that post-exposure vaccination has low effectiveness in preventing symptomatic mpox, although it may attenuate disease severity. To maximise the chance of preventing infection, MVA-BN should be administered within 4 days from the date of exposure to MPXV. In certain groups at higher risk of complications (see later section on recommended use of vaccine), post-exposure vaccination may be extended to 14 days from exposure to potentially modify disease.

Those who have been primed with a single dose of MVA-BN or live smallpox vaccine, should make a more rapid response to a dose given after exposure. Exposed individuals should be given another dose of MVA-BN within the relevant period provided it is at least 28 days since they received their first dose. This post exposure dose can be considered their completing (second) dose.

Based on current available evidence, immunocompetent individuals who have previously received a two-dose course of MVA-BN, with the second dose given less than two years ago, a further dose is not needed after an exposure event. If their last dose was given more than two years ago, a further dose of vaccine should be offered after a recognized significant exposure. In individuals who are severely immunosuppressed, as defined in Chapter 28a, who may have a lower or less durable immune response, a post-exposure dose can be considered from six months after their second dose.

Booster vaccination

Although the SmPC states that boosters should be considered no less than two years after the two-dose primary course, there is currently insufficient evidence to support routine boosters in immunocompetent individuals.

Until further evidence is available a booster dose may only be considered in limited specific circumstances (see later section on reinforcing doses in recommended use of vaccine).

- administer 0.5ml SC/IM dose or a 0.1ml ID dose of MVA-BN

Recommendations for the use of MVA-BN smallpox vaccine**Pre-exposure immunisation**

The objective of immunisation is to provide protection in adults at high risk of exposure to mpox or other orthopoxviruses. In view of the similar vaccine effectiveness after one or two doses of vaccine, the priority should be to achieve high first dose coverage in those eligible.

GBMSM at high risk of exposure

In response to the JCVI advice, a routine programme in GBMSM delivered in sexual health services has been rolled out in phases aligned to vaccine supply with the full programme being launched from 1 August 2025. Eligibility for vaccination in the routine programme will be similar to that in the 2022 outbreak. GBMSM at highest risk should be identified amongst those who attend sexual health services, using markers of risk to assess eligibility. These risk criteria include a recent history of multiple partners, participating in group sex, attending sex-on-premises venues or based on proxy markers such as recent bacterial sexually transmitted infection (in the past year). Other individuals who have frequent close

and intimate contact with the GBMSM network at risk of mpox may also be vaccinated, irrespective of their identified gender. This would include staff who work in GBMSM sex-on-premises venues, such as saunas, if they are regularly exposed to items (e.g. linen) or surfaces likely to be contaminated with body fluids or skin cells.

People at occupational risk of exposure

Given the low incidence of infection in the UK, most health and social care workers are at very low risk of exposure to mpox, and do not require routine pre-exposure vaccination. Unvaccinated (and vaccinated) staff who are required to see suspected cases should wear appropriate personal protective equipment and avoid direct and close contact.

Individuals working in UK diagnostic laboratories, including those undertaking MPXV PCR and/or serology, should be using standard protective equipment and safety cabinets and therefore the risk of exposure, even in high incidence areas, should be minimal.

Staff who work in specialist roles where exposure to orthopox viruses is likely to be more frequent and prolonged, should be advised of the possible risk and offered vaccination based on an occupational health risk assessment. This would include:

- workers in laboratories where pox viruses (such as MPXV or genetically modified vaccinia) are handled or cultured, and others who work in highly specialist laboratories undertaking procedures with a significantly higher risk of exposure. (Advisory Committee on Dangerous Pathogens and the Advisory Committee on Genetic Modification, 1990)
- staff caring for in-patients with mpox in High Consequence Infectious Disease (HCID) units or Specialised Regional ID Centres (SRIDC), including those who clean areas where mpox patients have been cared for
- staff regularly undertaking environmental decontamination around cases of mpox
- UK health care and laboratory workers being deployed to respond to a MPXV outbreak or incident overseas
- UK humanitarian aid workers who will be living or working in close contact with the local population in areas affected by a MPXV outbreak or incident overseas

Pre-exposure vaccination may also be considered for those about to start providing prolonged or close care for a patient with confirmed mpox, or during wider outbreak response to protect health workers in settings or populations where an outbreak is happening (see section: vaccination during outbreaks and incidents).

In view of the similar effectiveness of one dose and two doses of MVA-BN, staff do not need to delay work or travel until the two-course schedule is completed. Although it may take 14 days to respond to vaccine, staff can commence work and travel immediately after the first dose of vaccine, provided appropriate infection control protection measures are available. Appropriate PPE and other measures should be used regardless of whether fully or partially vaccinated.

People travelling to countries experiencing outbreaks of mpox

For the current Clade I outbreak vaccination indications for pre-exposure travel vaccination are being reviewed by the JCVI travel sub-committee, but vaccination is not currently recommended for travellers. Eligible groups for vaccination will be kept under review as information about the current outbreak emerges. Current advice on avoiding exposure should be followed ([NaTHNaC – Mpox \(Monkeypox\) \(travelhealthpro.org.uk\)](https://www.travelhealthpro.org.uk)).

Vaccination during outbreaks and incidents

The objective of reactive immunisation is to provide protection to adults and children at higher risk of exposure following an imported case of MPXV Clade I or a cluster/outbreak of mpox. Outbreak control would include a single dose of MVA-BN vaccine for those eligible for vaccination, regardless of age (using the age specific advice in the table above).

Vaccination is an adjunct to the cornerstones of mpox outbreak response: prompt detection, diagnosis, isolation and treatment of patients, tracing of contacts, effective personal protective equipment for healthcare workers and other frontline staff.

In situations where there is an introduction of Clade I infection, or evidence of community transmission in the UK, MVA-BN should also be considered for use in a wider population at high risk of exposure, following expert public health advice. Post-exposure vaccination should be considered for close contacts of cases to prevent secondary spread (see section on post-exposure vaccination below).

The vaccination strategy may also be expanded to include household contacts of individuals who have had a significant exposure to Clade I MPXV. Targeting a wider “ring” within which the case occurred, aims to prevent tertiary cases and further waves of transmission in that population. Defining a wider group eligible for vaccination should be based on the available epidemiological data, and an assessment of whether standard infection control measures (such as self-isolation, contact tracing and monitoring) is challenging (for example in pre-school settings) and/or likely to be ineffective (for example where there are multiple unidentified and/or anonymous contacts). There may also be a lower threshold for intervention where most of the exposed population is vulnerable to severe disease (such as children under five years of age), and/or marginalized and less able to access care (such as people experiencing homelessness).

A local risk assessment by the Health Protection Team and incident management team should be undertaken, allowing for varied modes of transmission, local epidemiology and flexibility of response actions. Populations where a wider ring vaccination approach may be considered, and a single dose of vaccine offered after a case or cluster of Clade I MPXV is detected include:

- members of a sexual network with multiple casual sexual partners, such as sex workers and their clients working from an identified property or other specific street/location; a semi-closed sexual network associated with a specific venue; or sexual networks of individuals using sex-on-premises or other public/semi-public sites, regardless of gender or sexual orientation
- individuals in on-going regular attendance at venues where close contact is expected (such as schools and pre-school settings, daycare settings, and contact sports clubs)
- individuals in congregate closed settings, such as an extended household, a prison or other detained setting, a boarding school, care home or residential facility (noting that the risk of spread is lower for older people who may have immunity from prior smallpox vaccination), and homeless shelters/hostels
- members of a geographically defined area or community with a documented high risk of exposure to mpox (e.g. a village or defined postcode area), including and/or prioritizing children in that community

A wider outbreak response should be accompanied by considering an extension of pre-exposure vaccination recommendations to protect health workers in settings or with populations where an outbreak is happening. This may need to be limited to a small numbers of designated healthcare staff who will be directly assessing and/or managing suspected mpox cases.

If multiple unlinked clusters are observed in specific settings or populations, then this should prompt review to determine whether a pre-exposure programme in these populations would be more effective.

Post exposure vaccination

The objectives of post exposure immunisation are to provide protection against infection and to modify disease severity in individuals following an identified exposure. There is growing evidence of the low effectiveness of post-exposure vaccination using MVA-BN, so vaccination should be prioritized to those most likely to benefit.

Post-exposure vaccination for community or occupational contacts should be considered for those with the highest exposure risks defined in the [contact tracing guidance](#) for mpox. Post exposure vaccine is currently offered to those who have had a category 3 (high risk) exposure to any mpox clade. Since derogation of mpox as an HCID, post-exposure vaccination is no longer routinely recommended for category 2 (medium risk) exposure but may be considered if: (a) there is a high concern about respiratory transmission (e.g. the case has lesions in the upper respiratory tract or respiratory symptoms); and (b) the contact is at higher risk of severe mpox complications (immunosuppressed, pregnant or aged under 5 years).

If in an eligible exposure category, post exposure vaccination with MVA-BN should be given within 4 days of exposure, although it may be offered up to 14 days post exposure to potentially modify disease in those who are at higher risk of the complications of mpox – this includes children (below the age of five years), pregnant women and individuals with severe immunosuppression (see chapter 28a). People living with HIV who are virally suppressed and have a CD4 count greater than 200 cells/mm³, are not considered to be severely immunosuppressed for this purpose.

For individuals with prolonged exposures, the benefits of post exposure vaccination are likely to be limited when the first exposure was more than four days earlier. Where the exposure level is high, or may have increased over the period, then offering vaccination at a later interval may be considered.

For adult immunocompetent contacts who are identified too late for effective post exposure intervention, then vaccination should be considered for household members of the exposed individual, particularly if the exposure is significant and if the household member is at higher risk of complications (as above).

In addition, any exposure event may be an opportunity to offer a first or second dose of vaccine to unvaccinated individuals who are eligible for pre-exposure vaccination, for example GBMSM at risk of mpox and certain health care workers.

Previous incomplete vaccination

If the MVA-BN course is interrupted or delayed, it should be resumed using the same vaccine but the first dose does not need to be repeated.

Evidence suggests that those who have previously received a live smallpox vaccine make an antibody response to their first dose of MVA-BN as good or better than after a second

dose of MVA-BN in naïve individuals. Anecdotal reports during management of the early imported mpox cases reported in the UK suggests that healthcare workers vaccinated with the Lister/Elstree vaccine in 2003/4 experienced a higher rate of the common side effects, particularly local reactions, after their first dose of MVA-BN. This suggests that live vaccines prime very effectively for immunity and that a single dose of MVA-BN is sufficient to complete a primary course, regardless of interval since receipt of the live vaccine.

Reinforcing vaccination

There are limited data to determine the need and appropriate timing of booster doses. Studies two years after the second primary dose showed a decline in antibody levels and a fall in the proportion of people with neutralising antibody (Priyamvada *et al*, 2022, Ilchmann *et al*, 2023). A booster dose given two years after the primary course, however, increases the proportion of recipients with measurable antibody, suggesting an anamnestic response and development of immune memory from the primary course. Modelling combining immunogenicity and vaccine effectiveness data predicts that the duration of protection after two doses is around 10 years (Berry *et al*, 2024). This is consistent with modelling in England in which observed case numbers in 2023 fitted best with an assumption of 10-years duration of protection (Zhang *et al*, 2024).

In individuals who have received a dose of live vaccine followed by a single dose of MVA-BN, the need for further boosting has not been established.

Therefore, a booster dose may be considered in either of the following circumstances:

- immunocompetent eligible health care workers at ongoing risk whose primary course was completed more than 10 years ago
- severely immunosuppressed (as defined in Chapter 28a) individuals eligible for pre-exposure immunisation whose primary course was completed more than 2 years ago. People living with HIV who have a current CD4 count of less than 200 cells/mm³ or who are not virally suppressed, are considered to be severely immunosuppressed

Where boosting is considered necessary a single dose should be administered, at least two years after the primary course. If boosting is following a significant exposure a single dose of vaccine should be administered within 4 days.

Co-administration with other vaccines and prophylaxis

Although no data for co-administration of MVA-BN vaccine with other vaccines exists, in the absence of such data first principles would suggest that interference between inactivated (non-replicating) vaccines with different antigenic content is likely to be limited (see Chapter 11). Based on experience with other vaccines, any potential interference is most likely to result in a slightly attenuated immune response to one of the vaccines. There is no evidence of any safety concerns, although it may make the attribution of any adverse events more difficult. Inactivated (or non-replicating) vaccines such as MVA-BN can also be co-administered with live vaccines and in those on HIV PrEP.

As the non-replicating MVA-BN is considered inactivated, where individuals in an eligible cohort present having recently received one or more inactivated or another live vaccine, MVA-BN vaccination should still be given. The same applies for most other live and inactivated vaccines where MVA-BN vaccination has been received first or where a patient presents requiring two or more vaccines. It is generally better for vaccination with any

required vaccines (including MVA-BN, hepatitis A, hepatitis B and HPV) to proceed to avoid any further delay in protection and to reduce the risk of the patient not returning for a later appointment.

Contraindications

The vaccine should not be routinely given to individuals who have previously had a sudden life-threatening allergic reaction to a dose of MVA-BN or to any ingredient of MVA-BN. MVA-BN includes trace residues of chicken protein, benzonase, gentamicin and ciprofloxacin from the manufacturing process.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Observation following vaccination

There is no routine requirement for observation following MVA-BN administration but individuals should be observed for any immediate reactions whilst they are receiving any verbal post vaccination information and exiting the centre. Facilities for management of anaphylaxis should be available at all vaccination sites (see chapter 8). As fainting can occur following vaccination, all those vaccinated with MVA-BN should be advised to not drive for 15 minutes after vaccination.

Pregnancy

Although MVA-BN has not formally been evaluated in pregnancy, animal studies (three studies in female rats) identified no vaccine related fetal malformations. Experience of use of MVA-BN in pregnant women is limited to less than 300 pregnancies without leading to any adverse events on pregnancy. As it is a non-replicating vaccine, there is no theoretical reason for concerns in pregnancy and the adverse events profile would be expected to be similar to that in non-pregnant vaccinees. Whilst it is not routinely recommended for use in pregnancy, any theoretical concern needs to be weighed against the maternal risks from mpox infection in pregnancy (such as a risk of more severe disease from viral infections in the third trimester) and any consequent fetal risks from maternal infection in early pregnancy.

Breastfeeding

It is not known whether MVA-BN is excreted in human milk, but this is unlikely as the vaccine virus does not replicate effectively in humans. Individuals who are breast feeding and have a significant exposure to mpox should therefore be offered vaccination, after discussion about the risks of mpox to themselves and to the breast-fed child.

Individuals with underlying medical conditions

Individuals with atopic dermatitis are known to have developed more site-associated reactions and generalized symptoms following MVA-BN vaccination. Individuals in this group therefore need to have a risk assessment before being offered vaccination. The assessment should consider the risk of exposure, the risk of side effects from vaccination and the potential use of alternative preventive interventions.

Individuals with a history of developing keloid scarring should be offered a 0.5ml SC/IM dose of MVA-BN in preference to a fractional dose intradermally.

Current or previous mpox infection

If an individual is acutely unwell, including those with symptoms or signs of possible mpox infection, immunisation should be postponed until they have fully recovered. This is to both reduce risks of exposing others and to avoid wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Whether prior mpox infection protects against future infection is unclear, but based on analogy from smallpox infection and from live smallpox vaccine, it is likely that re-infection will be unusual, particularly in the short term. A very small number of possible reinfections have been reported globally (Hasra *et al*, 2024, Li *et al*, 2024). Although previous mpox infection is not a contra-indication to vaccination, in a situation of constrained vaccine supply, it is recommended that vaccination of confirmed cases is deferred. If supply allows, vaccination may be considered in those at on-going risk once fully recovered.

Children and young people

Although the MVA-BN vaccine is not licensed in children, several paediatric studies of other vaccines using MVA as a vector (often at a considerably higher dose than used in MVA-BN) have been undertaken with a reassuring side effect profile. This includes a TB vaccine trial of approximately 1500 infants, aged approximately 5 to 6 months, and a trial of 200 Gambian infants who received an MVA malaria vaccine with an acceptable safety profile (Tameris *et al*, 2013, Oto *et al*, 2011, Afolabi *et al*, 2016). The adverse event profile with MVA-BN would be expected to be identical to the profile with these TB and malaria candidate vaccines and therefore provides some reassurance of its use in children, including infants.

During the 2022 mpox Clade II outbreak, 87 English children (median age 5 years) received one MVA-BN dose as post-exposure vaccination. None developed any serious adverse events or developed mpox disease after vaccination. Of survey respondents, 36% reported no symptoms, 40% reported injection-site reactions only, and 24% reported systemic symptoms with or without local reactions (Ladhani *et al*, 2023). The vaccine should therefore be offered to children considered to be at risk, as children seem to have a more severe presentation of mpox. As there is no evidence on the use of intradermal fractional doses in children, administration of MVA-BN in children under 18 years should ideally be through the subcutaneous or intramuscular route. The exception is where wider vaccination is being offered in a localized outbreak setting and during supply constraints, when intradermal fractional doses may be given.

Immunosuppression including HIV infection

MVA-BN is a replication-defective virus and should pose no risk to those who are immunosuppressed. The safety and immunogenicity of a full dose of MVA-BN in persons living with HIV infection (with CD4 cell counts above 100 cells/mm³) has been demonstrated (Greenberg *et al*, 2013). However, the immune response to the vaccine could be reduced in severely immunosuppressed individuals. Vaccination should proceed using a 0.5ml SC/IM dose in individuals with immunosuppression (including people living with HIV and with a CD4 count of less than 200 cells/mm³) as they are at significant risk of the complications of mpox and data on intradermal administration is absent in this population. Specialist medical advice on other measures may be required and additional doses should be considered for those at ongoing-risk of exposure.

Adverse Reactions

Data from multiple clinical trials shows that MVA-BN has a favourable adverse event profile compared with first and second generation smallpox vaccines (WHO 2013, Frey *et al*, 2007, Vollmar *et al*, 2006, von Krempelhuber *et al*, 2010, Greenberg *et al*, 2013).

Common adverse events include local site reactions and influenza-like symptoms. These events were mainly mild to moderate in intensity and resolved without intervention within seven days following vaccination. Adverse event rates reported after any vaccination dose (1st, 2nd or booster) were similar, but anecdotally the frequency of adverse events, particularly local site reactions, appears to be higher in those who had received previous live smallpox vaccine.

Unlike the live vaccine, there have been no reports to date of myocarditis/pericarditis or encephalitis after these vaccines.

Intradermal (ID) injection was associated with a higher rate of itchiness and local reactions such as redness and induration when compared to subcutaneous injection (Frey *et al*, 2015; and Frey *et al* 2023), although pain at the injection site was less common than after subcutaneous administration. Some of the local reactions persisted for longer in the ID group and some subjects developed small nodules or discoloration at the injection site that were still present six months after infection. Systemic reactions were generally similar across both groups.

Live smallpox vaccine

No live smallpox vaccine is licensed for use in the UK, and there is no current indication for live smallpox vaccination for any individual. In response to the threat of a bioterrorist release of smallpox, in 2003 the Department of Health published guidelines for smallpox response and an information pack for non-emergency vaccination of first responders.

The pack includes information on administration and types of vaccine. It also has guidance on pre-vaccination screening and exclusion criteria and on work restrictions following vaccination ([\[ARCHIVED CONTENT\] Guidelines for smallpox response and management in the post-eradication era \(smallpox plan\) : Department of Health - Publications and statistics \(nationalarchives.gov.uk\)](#)).

Vaccination with live vaccination is no longer recommended for people exhuming bodies in crypts, since the theoretical risk involved poses less risk than the live vaccine.

Reporting anaphylaxis and other allergic reactions

Anaphylaxis is a very rare, recognised side effect of most vaccines and suspected cases should be reported via the Yellow Card Scheme (www.yellowcard.mhra.gov.uk). Chapter 8 of the Green Book gives detailed guidance on distinguishing between faints, panic attacks and the signs and symptoms of anaphylaxis. If a case of suspected anaphylaxis meets the clinical features described in Chapter 8, this should be reported via the Yellow Card Scheme as a case of 'anaphylaxis'. Cases of less severe allergic reactions (i.e. not including the clinical features of anaphylaxis) should not be reported as anaphylaxis but as 'allergic reaction'.

As this vaccine is labelled with a black triangle, all adverse reactions occurring in individuals of any age after vaccination should be reported to the MHRA using the Yellow Card Scheme. Anyone can report a suspected adverse reaction to the Medical and Healthcare

products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (www.yellowcard.mhra.gov.uk). Any adverse reaction should also be documented in accordance with local procedures.

Management of suspected cases and contacts

Further guidance on the management of contacts and cases of mpox can be found at: <https://www.gov.uk/government/collections/monkeypox-guidance>

Supplies

Imvanex® in Europe, Jynneos® in the USA and Imvamune® in Canada is manufactured by Bavarian Nordic. Vaccine is supplied to designated healthcare providers from UKHSA. Post-exposure vaccination can be accessed by reporting the case to your local health protection team.

References

- Advisory Committee on Dangerous Pathogens and Advisory Committee on Genetic Modification (1990) Vaccination of laboratory workers handling vaccinia and related pox viruses in infectious situations for humans. London: TSO.
- Afolabi MO, Tiono AB, Adetifa UN *et al.* (2016) Safety and Immunogenicity of ChAd63 and MVA ME-TRAP in West African Children and Infants. *Mol Ther.* 24(8): 1470-7.
- Aparício Martins I, João AL, Neves JM, Fernandes C. Mpox after vaccination: a case series. *Sex Transm Infect.* 2024 Feb 19;100(2):120. doi: 10.1136/sextrans-2023-056055. PMID: 38135495.
- Auckland C, Cowlishaw A, Morgan D *et al.* (2005) Reactions to small pox vaccine in naïve and previously-vaccinated individuals. *Vaccine.* 23(32): 4185-7.
- Berry MT, Khan SR, Schlub TE, Notaras A, Kunasekaran M, Grulich AE, MacIntyre CR, Davenport MP, Khoury DS. Predicting vaccine effectiveness for mpox. *Nat Commun.* 2024 May 8;15(1):3856. doi: 10.1038/s41467-024-48180-w
- Bertran M, Andrews N, Davison C, Dugbazah B, Boateng J, Lunt R, Hardstaff J, Green M, Blomquist P, Turner C, Mohammed H, Cordery R, Mandal S, Campbell C, Ladhani SN, Ramsay M, Amirthalingam G, Bernal JL. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis.* 2023 Jul;23(7):828-835. doi.org/10.1016/S1473-3099(23)00057-9.
- Charles H, Thorley K, Turner C, *et al.* Post-peak mpox in England: epidemiology, reinfection, and vaccine effectiveness – data from 2023. medRxiv 2024 24303362 [accessed 2024 June 18] <https://www.medrxiv.org/content/10.1101/2024.02.26.24303362v1>
- Dalton AF, Diallo AO, Chard AN, Mouilia D *et al.* Estimated Effectiveness of Jynneos Vaccine in Preventing Mpox: A Multijurisdictional Case-Control Study — United States, August 19, 2022–March 31, 2023. *MMWR Morb Mortal Wkly Rep.* 2023 May 19;72(20):553-558. Doi.org/10.15585/mmwr.mm7220a3. www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm7220a3-H.pdf
- Department of Health (2003) Guidelines for smallpox response and management in the post-eradication era (smallpox plan). Available at: <https://webarchive.nationalarchives.gov.uk/ukgwa/20130107105354/http://www.dh.gov.uk/assetRoot/04/07/08/32/04070832.pdf>
- Department of Health (2003) Smallpox vaccination of Regional Response Groups: information for health care workers administering or receiving the smallpox vaccine. Available at: <https://webarchive.nationalarchives.gov.uk/ukgwa/20031117030644/http://www.doh.gov.uk:80/smallpox/vaccination/index.htm>
- Earl JL, Americo PL, Wyatt LS, *et al.*, 2008. Rapid protection in a monkeypox model by a single injection of a replication-deficient vaccinia virus. *Proc. Natl. Acad. Sci. U. S. A* 105: 10889–10894.
- Eustaquio PC, Salmon-Trejo LAT, McGuire LC, Ellington SR. Epidemiologic and Clinical Features of Mpox in Adults Aged >50 Years—United States, May 2022–May 2023. *MMWR Morb Mortal Wkly Rep.* 2023;72:893-6. www.cdc.gov/mmwr/volumes/72/wr/mm7233a3.htm
- Frey SE, Newman FK, Kennedy JS *et al.* (2007) Clinical and immunologic responses to multiple doses of IMVAMUNE(R) (Modified Vaccinia Ankara) followed by Dryvax(R) challenge. *Vaccine.* 25: 8562-73
- Frey SE, Wald A, Edupuganti S *et al.* Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. *Vaccine* 2015 33: 5225-5234. <https://doi.org/10.1016/j.vaccine.2015.06.075>.
- Gallagher T and Lipsitch M. (2019) Post exposure Effects of Vaccines on Infectious Diseases. *Epidemiol Rev.* 41(1): 13-27
- Greenberg RN, Overton ET, Haas DW *et al.* (2013) Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. *J. Infect. Dis.* 207: 749-58.
- Guagliardo SA, Kracalik I, Carter RJ, Braden C, Free R, Hamal M, Tuttle A, McCollum AM, Rao AK. Monkeypox Virus Infections After 2 Preexposure Doses of JYNNEOS Vaccine — United States, May 2022–May 2024. *MMWR Morb Mortal Wkly Rep* 2024;73:460– 466.
- Hatch GJ, Graham VA, Bewley KR, Tree JA, Dennis M, Taylor I, Funnell SG, Bate SR, Steeds K, Tipton T, Bean T, Hudson L, Atkinson DJ, McLuckie G, Charlwood M, Roberts AD, Vipond J. Assessment of the protective effect of Imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques. *J Virol.* 2013 Jul;87(14):7805-15. doi.org/10.1128/JVI.03481-12.
- Hazra A, Zucker J, Bell E, *et al.* Mpox in people with past infection or a complete vaccination course: a global case series. *Lancet Infect Dis.* 2024 Jan;24(1):57-64. doi.org/10.1016/S1473-3099(23)00492-9

- Ilchmann H, Samy N, Reichhardt D, Schmidt D, Powell JD, Meyer TPH, Silbernagl G, Nichols R, Weidenthaler H, De Moerloose L, Chen L, Chaplin P. One- and Two-Dose Vaccinations with Modified Vaccinia Ankara-Bavarian Nordic Induce Durable B-Cell Memory Responses Comparable to Replicating Smallpox Vaccines. *J Infect Dis.* 2023 May 12;227(10):1203-1213. doi.org/10.1093/infdis/jiac455
- Jacobs BL, Langland JO, Kibler KV, Denzler KL, White SD, Holechek SA, Wong S, Huynh T, Baskin CR. Vaccinia virus vaccines: Past, present and future. *Antiviral Res.* 2009 Oct;84(1):1-13. doi.org/10.1016/j.antiviral.2009.06.006.
- Kennedy JS, Greenberg RN. IMVAMUNE: modified vaccinia Ankara strain as an attenuated smallpox vaccine. *Expert Rev Vaccines.* 2009 Jan;8(1):13-24. doi.org/10.1586/14760584.8.1.13
- Kröger ST, Lehmann MC, Treutlein M, Fiethe A, Kossow A, Küfer-Weiß A, Nießen J, Grüne B. Mpox outbreak 2022: an overview of all cases reported to the Cologne Health Department. *Infection.* 2023 Oct;51(5):1369-1381. doi: 10.1007/s15010-023-01997-x. Epub 2023 Feb 14. PMID: 36787016; PMCID: PMC9926425.
- Ladhani SN, Dowell AC, Jones S, Hicks B, Rowe C, Begum J, Wailblinger D, Wright J, Owens S, Pickering A, Shilltoe B, McMaster P, Whittaker E, Zuo J, Powell A, Amirthalingam G, Mandal S, Lopez-Bernal J, Ramsay ME, Kissane N, Bell M, Watson H, Ho D, Hallis B, Otter A, Moss P, Cohen J. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara-Bavaria Nordic vaccine against mpox in children: a national outbreak response. *Lancet Infect Dis.* 2023 Sep;23(9):1042-1050. doi.org/10.1016/S1473-3099(23)00270-0.
- Lane JM, Ruben FL, Neff JM *et al.*, 1969. Complications of smallpox vaccination, 1968. *N. Engl. J. Med* 281 (22): 1201–1208.
- Li T, Li Z, Xia Y, Long J, Qi L. Mpox reinfection: A rapid systematic review of case reports. *Infect Med (Beijing).* 2024 Feb 25;3(1):100096. doi: 10.1016/j.imj.2024.100096. PMID: 38586545; PMCID: PMC10998266.
- Mason LMK, Betancur E, Riera-Montes M, Lienert F, Scheele S. MVA-BN Vaccine Effectiveness: A Systematic Review of Real-World Evidence in Outbreak Settings. *medRxiv* 24306078, 2024 April 26 Doi.org/10.1101/2024.04.25.24306078.
- Mazzotta V, Cozzi Lepri A, Matusali G, *et al* Immunogenicity and reactogenicity of modified vaccinia Ankara pre-exposure vaccination against mpox according to previous smallpox vaccine exposure and HIV infection: prospective cohort study. *EClinicalMedicine.* 2024 Jan 12;68:102420. doi.org/10.1016/j.eclim.2023.102420.
- Merad Y, Gaymard A, Cotte L, *et al.* Outcomes of post-exposure vaccination by modified vaccinia Ankara to prevent mpox (formerly monkeypox): a retrospective observational study in Lyon, France, June to August 2022. *Euro Surveill.* 2022 Dec;27(50):2200882. doi.org/10.2807/1560-7917.ES.2022.27.50.2200882.
- Milward G. *Vaccinating Britain: Mass vaccination and the public since the Second World War.* Manchester University Press; 2019. <https://www.ncbi.nlm.nih.gov/books/NBK545998/>
- Mora LF, Khan AH, Sperling LS, (2009). Cardiac complications after smallpox vaccination. *South Med. J* 102 (6): 615–619.
- Morgan J, *et al.*, (2008). Myocarditis, pericarditis, and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, January-October 2003. *Clin. Infect. Dis* 46 (Suppl 3), S242–S250.
- Ota MO, Odutola MM, Owiafe PK *et al.* (2011) Immunogenicity of the tuberculosis vaccine MVA85A is reduced by coadministration with EPI vaccines in a randomized controlled trial in Gambian infants. *Sci Transl Med* 3 88ra56.
- Otter AD, Jones S, Hicks B, Bailey D *et al.*, Monkeypox virus-infected individuals mount comparable humoral immune responses as Smallpox-vaccinated individuals. *Nat Commun.* 2023 Sep 23;14(1):5948. Doi.org/10.1038/s41467-023-41587-x
- Petersen BW, Kabamba J, McCollum AM *et al.* (2019) Vaccinating against monkeypox in the Democratic Republic of the Congo. *Antiviral Research.* 162: 171-177
- Pischel L, Martini BA, Yu Y, Cacesse D, Tracy M, Kharbanda K, Ahmed N, Patel K, Grimshaw AA, Malik AA, Goshua G, Omer SB. Vaccine effectiveness of 3rd generation mpox vaccines against mpox infection and disease severity: A systematic review and meta-analysis. *Vaccine,* 2024 <https://doi.org/10.1016/j.vaccine.2024.06.021>
- Pittman PR, Hahn M, Lee HS, Koca C, Samy N, Schmidt D and others. 'Phase 3 efficacy trial of modified vaccinia ankara as a vaccine against smallpox.' 2019, *New England Journal of Medicine* 2019: volume 381, pages 1,897 to 1,908
- Priyamvada L, Carson WC, Ortega E *et al.* Serological responses to the MVA-based Jynneos monkeypox vaccine in a cohort of participants from the Democratic Republic of Congo. *Vaccine.* 2022 Nov 28;40(50):7321-7327.doi.org/10.1016/j.vaccine.2022.10.078.

Rimoin AW, Mulembakani PM, Johnston SC *et al.* (2010) Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. *Proc Natl Acad Sci U S A.* 107(37): 16262-7

Rosen JB, Arciuolo RJ, Pathela P, Boyer CB, Baumgartner J, Latash J, Malec L, Lee EH, Reddy V, King R, Edward Real J, Lipsitch M, Zucker JR. Jynneos™ effectiveness as post-exposure prophylaxis against mpox: Challenges using real-world outbreak data. *Vaccine.* 2024 Jan 25;42(3):548-555. doi.org/10.1016/j.vaccine.2023.12.066.

Stittelaar KJ, van Amerongen G, Kondova I, Kuiken T, van Lavieren RF, Pistor FH, Niesters HG, van Doornum G, van der Zeijst BA, Mateo L, Chaplin PJ, Osterhaus AD. Modified vaccinia virus Ankara protects macaques against respiratory challenge with monkeypox virus. *J Virol.* 2005 Jun;79(12):7845-51. Doi.org/10.1128/JVI.79.12.7845-7851.2005

Tameris MD, Hatherill M, Landry BS *et al.* (2013) Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet.* 381: 1021-28

Thy M, Peiffer-Smadja N, Mailhe M, Kramer L, Ferré VM, Houhou N, Tarhini H, Bertin C, Beaumont AL, Garé M, Le Pluart D, Perrineau S, Rahi M, Deconinck L, Phung B, Mollo B, Cortier M, Cresta M, De La Porte Des Vaux C, Joly V, Lariven S, Rioux C, Somarriba C, Lescure FX, Charpentier C, Yazdanpanah Y, Ghosn J. Breakthrough Infections after Postexposure Vaccination against Mpox. *N Engl J Med.* 2022 Dec 29;387(26):2477-2479. doi.org/10.1056/NEJMc2211944.

US Food and Drug Administration (FDA). JYNNEOS October 2019 available from: <https://www.fda.gov/vaccines-blood-biologics/jynneos>

Verheust C, Goossens M, Pauwels K, *et al.* (2002) Biosafety aspects of modified vaccinia virus Ankara (MVA)-based vectors used for gene therapy or vaccination. *Vaccine.* 30: 2,623 to 2,632

Vollmar J, Arndtz N, Eckl KM *et al.* (2006) Safety and immunogenicity of Imvamune, a promising candidate as a third generation smallpox vaccine. *Vaccine.* 24: 2065-70

Von Krempelhuber A, Vollmar J, Prokorny R *et al.* (2010) A randomized, double-blind, dose-finding Phase II study to evaluate immunogenicity and safety of the third generation smallpox vaccine candidate IMVAMUNE. *Vaccine.* 28: 1209-16

World Health Organisation (WHO) (2013) Summary report on first, second and third generation smallpox vaccines. Geneva.

Yeganeh N, Yin S, Moir O, Danza P, Kim M, Finn L, Fisher R, Kulkarni S, Perez M, Poortinga K, Garland W, Foo C, Haddix M, Archer R, Frey N, Balter S, Singhal R, Kim A. Effectiveness of JYNNEOS vaccine against symptomatic mpox disease in adult men in Los Angeles County, August 29, 2022 to January 1, 2023. *Vaccine.* 2024 Aug 13;42(20):125987. Doi.org/10.1016/j.vaccine.2024.05.035.

Zhang X-S, Niyomsri S, Mandal S, Mohammed H *et al.*, (2024) Cost-effectiveness of vaccinations strategies to control future mpox outbreaks in England. Pre-print. medRxiv 2024.08.20.24312301; doi: <https://doi.org/10.1101/2024.08.20.24312301>