

UPDATED ATAGI CLINICAL GUIDANCE ON VACCINATION AGAINST MONKEYPOX

Version 2.0
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Summary

- This guidance is on the use of smallpox vaccines for protection against monkeypox virus infection. This advice will continue to be updated as new information emerges during the current multi-country monkeypox outbreak.
- Monkeypox is usually a self-limiting illness, and most people recover within a few weeks. However, severe illness can occur, particularly in immunocompromised people.
- Two vaccines are available in Australia for prevention of monkeypox: the 3rd generation JYNNEOS[®] (MVA-BN: modified vaccinia Ankara vaccine-Bavarian Nordic) and the 2nd generation ACAM2000[™]
- Limited supplies of the 3rd generation JYNNEOS[®] have been secured by the Commonwealth and some States and Territories.
- JYNNEOS[®]:
 - JYNNEOS[®] is a highly-attenuated vaccine that is replication-deficient.
 - JYNNEOS[®] is administered in a 2-dose schedule by subcutaneous injection with a minimum dose interval between doses of 28 days.
 - JYNNEOS[®] is associated with fewer potential adverse events and is safe to use in people with immunocompromise or atopic dermatitis. JYNNEOS[®] may also be used in children or during pregnancy, after risk-benefit assessment.
- ACAM2000[™]:
 - ACAM2000[™] is a live-attenuated vaccine that is replication-competent.
 - Specialised training and methods are required to administer ACAM2000[™] by percutaneous scarification using a bifurcated needle, as a single dose.
 - Post-vaccination wound care is required for ACAM2000[™] to protect vulnerable contacts and prevent self-inoculation from the vaccination site.
 - ACAM2000[™] cannot be used in severely immunocompromised people, people with active atopic dermatitis, in pregnancy or in infants under 12 months of age. It is associated with rare but serious adverse events.
- Overall, JYNNEOS[®] is the preferred vaccine for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), due to its more favourable safety profile and comparative ease of administration. Supply considerations may affect availability of JYNNEOS[®]. For healthy non-pregnant adults, where JYNNEOS[®] is not suitable or not available, ACAM2000[™] has an established profile and may be considered for PrEP or PEP.
- The key risk groups recommended by Australian Technical Advisory Group on Immunisation (ATAGI) to receive vaccination are:
 1. Anyone categorised by public health authorities as a high risk monkeypox contact in the past 14 days.
 2. Gay, bisexual and other men who have sex with men (GBMSM) who are at the highest risk of monkeypox infection due to having a high number of sexual contacts. Risk criteria for infection may include:
 - Those living with HIV.
 - A recent history of multiple sexual partners, participating in group sex, or attending sex on premises venues.

- Other proxy markers, such as recent sexually transmitted infection or those being advised to take HIV PrEP due to number of sexual partners. Whilst many people prescribed HIV PrEP are monogamous with a HIV positive partner, this category can also capture those with multiple partners who are at high risk.
- Recommendation from other service providers, such as sexual health clinics.
- 3. Sex workers, particularly those whose clients are in high-risk categories.
- 4. Anyone in the above risk categories who is planning travel to a country experiencing a significant outbreak, with vaccination recommended 4-6 weeks prior to departure.
- 5. Immunisation providers who are administering the ACAM2000™ smallpox vaccine.
- The risk-benefit assessment discussion for individual vaccination is complex and depends on emerging epidemiology, exposure risk, contraindications and precautions, and alternative options to vaccination. Clinical resources are available to support this decision-making process.
- Healthcare workers who will be administering ACAM2000™ can be offered either vaccine if they have not previously received a smallpox vaccine.
- In those individuals who have received a smallpox vaccine in the past, a booster dose is recommended if the previous dose of a smallpox vaccine was given more than ten years prior. JYNNEOS® and ACAM2000™ are both suitable vaccines for a booster; options may be discussed as part of an individual risk-benefit assessment.

Background

The virus and transmission

Monkeypox virus is a DNA virus in the Orthopoxvirus genus, which also includes the variola virus (which causes smallpox) and vaccinia virus (which is used in smallpox vaccines). Monkeypox was first discovered in 1958 and since then multiple outbreaks have been reported, mostly in western and central African nations including the Democratic Republic of the Congo and Nigeria. In 2003, there was an outbreak in the United States of America (USA) caused by imported rodents from Africa, in which cases were reported in both humans and pet prairie dogs¹. There are two genomic clades: the West African clade which is usually less severe, and the Congo Basin (Central African) clade. Monkeypox causes less severe disease than smallpox.

Monkeypox virus can be transmitted from infected animals to people, or from person to person. The natural animal reservoir for monkeypox virus remains unknown. Monkeypox does not spread easily between people. Transmission between people occurs via:

- Close contact with lesions, body fluids,
- Respiratory droplets in prolonged face-to-face contact or
- Fomites (such as contaminated clothing or linen).

Transmission can be prevented using [infection control measures](#).

Increasing numbers of cases of human monkeypox have been reported sporadically in non-enzootic countries over the last 2 years. On 11 May 2022, the World Health Organization alerted member states to a multi-country outbreak of monkeypox, originating from the West African clade of virus². From the beginning of May to 4 July 2022, 6027 laboratory-confirmed cases have been reported in 59 countries, including Australia, across Europe, North America and South America³.

Although anyone can contract monkeypox, global data in 2022 to date show higher levels of transmission within – but not exclusive to – the sexual networks of gay, bisexual and other men who have sex with men (GBMSM).

Clinical features

The incubation period is between 5–21 days⁴. Monkeypox illness may begin with a prodrome of swollen lymph nodes, fever, headache, muscle aches, joint pain and back pain, followed by a [rash](#) within 1–3 days after fever onset. The rash tends to be more concentrated on face and extremities rather than the trunk and may occur in the genital, perianal and rectal areas. Proctitis, which may be painful, may occur⁵. The illness may also present without prodromal symptoms, with the rash being the first sign of infection⁶. The evolution of skin lesions progress through four stages: macular, papular, vesicular, and pustular, before scabbing over. A person with monkeypox may be infectious from the onset of any symptoms until all scabs have fallen off, leaving intact skin underneath. Resolution of skin lesions may take up to four weeks from prodrome onset.

Monkeypox is usually self-limiting and most people recover within a few weeks⁴. The risk of severe disease and complications such as secondary infection, sepsis, pneumonia and encephalitis is likely to be increased in people with immunocompromise, young children and pregnant women. Symptoms such as severe oropharyngeal or anorectal pain may also lead to hospitalisation⁷. Treatment with antiviral medication and vaccinia immunoglobulin (VIG) is available for people at risk of severe disease; refer to the [National Treatment Guidelines](#).

Vaccine information

Smallpox vaccines contain the vaccinia virus, a poxvirus related to both smallpox and monkeypox. Previous guidance in Australia and other countries on the use of smallpox vaccine has focused on protection against smallpox infection. Vaccines using the vaccinia virus for the prevention of smallpox are likely to be effective against monkeypox (refer to [Vaccine effectiveness below](#)).

There are two types of smallpox vaccine available in Australia for use against monkeypox:

- The third-generation vaccine: the replication-deficient modified vaccinia Ankara (MVA-BN) vaccine. The MVA-BN vaccine, known variously as JYNNEOS/Imvamune/Imvanex (Bavarian Nordic), is registered for use in USA, United Kingdom, Canada and other countries for prevention of smallpox and monkeypox. Limited supplies of JYNNEOS® have been secured by the Commonwealth and some States and Territories.
- The second-generation vaccine containing replication-competent live attenuated vaccinia virus: ACAM2000™ (Emergent BioSolutions) is available from the National Medical Stockpile on a request basis for State and Territory governments.

Table 1: Summary of vaccine characteristics

Category	ACAM2000™	JYNNEOS®
Manufacturer	Emergent BioSolutions	Bavarian Nordic
Approved age for use*	≥18 years	≥18 years*

Presentation	Multidose vial containing about 100 doses after reconstitution. Diluent supplied in separate vial.	Single dose vial containing 0.5mL each
Volume/strength	1.0-5.0 x 10 ⁸ plaque-forming units (PFU)/mL or 2.5-12.5 x 10 ⁵ PFU/dose	At least 0.5 x 10 ⁸ infectious U/ per 0.5 mL single dose/ per 0.5 mL single dose
Primary schedule	1 dose	2 doses, at least 28 days apart; the second dose does not need to be repeated if administered more than 28 days after the first dose.
Administration route	Percutaneous (scarification)	Subcutaneous (SC) injection
Ingredients	2.5-12.5 x 10 ⁵ plaque forming units of live vaccinia virus per dose	0.5 x 10 ⁸ to 3.95 x 10 ⁸ infectious units of live modified vaccinia Ankara-Bavarian Nordic virus
Excipients	<ul style="list-style-type: none"> • 6-8 mM HEPES buffer (pH 6.5-7.5) • 2% albumin USP • 0.5 – 0.7% sodium chloride USP • 5% mannitol USP Diluent: <ul style="list-style-type: none"> • 50% (v/v) Glycerol USP • 0.25% (v/v) Phenol USP • Water 	<ul style="list-style-type: none"> • 10 mM Tris (tromethamine) • 140 mM sodium chloride May contain residual amounts of chicken host-cell DNA (≤ 20 mcg), chicken protein (≤ 500 mcg), benzonase (≤ 0.0025 mcg), gentamicin (≤ 0.163 mcg) and ciprofloxacin (≤ 0.005 mcg).

*JYNNEOS[®] is available for use in Australia under s18A (emergency use provision) of the Therapeutic Goods Act 1989. It is approved for use by the US FDA, UK MHRA and other regulatory bodies for use from ≥18 years.

Vaccine recommendations

Vaccination with either JYNNEOS[®] or ACAM2000[™] may be used for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) against monkeypox. A shared clinical decision-making approach is appropriate, based on a joint assessment of individual risks, benefits and vaccine availability.

Overall, JYNNEOS[®] is the preferred vaccine for both PrEP and PEP, due to its more favourable safety profile and comparative ease of administration. For healthy non-pregnant adults, where JYNNEOS[®] is not suitable or not available, ACAM2000[™] may be considered for PrEP or PEP.

ACAM2000[™] is associated with rare but serious adverse events and cannot be used in severely immunocompromised people, in pregnancy, people with active eczema or in infants below 12 months of age. JYNNEOS[®] is associated with fewer potential adverse events and is safe to use in people with immunocompromise. JYNNEOS[®] should be used in preference to ACAM2000[™] for people with a history of eczema, in pregnancy and breastfeeding, and in children on an off-label basis, based on a risk-benefit assessment.

PEP should be considered as soon as possible after first exposure to a confirmed monkeypox case. Refer to the [CDNA National Guidelines for Public Health Units](#). Vaccination within 4 days of first exposure to an infectious case will provide the highest likelihood of prevention of disease. Vaccination between 4 to 14 days is anticipated to attenuate disease.

Vaccination as pre-exposure prophylaxis (PrEP)

In general, JYNNEOS® is preferred over ACAM2000™ for use for PrEP. Prioritisation for PrEP should take into account supply considerations, with at-risk population groups receiving priority over other groups, such as healthcare workers and laboratory workers, if supply is constrained.

Vaccination is recommended for healthcare workers who will be providing ACAM2000™ vaccination to others and who have not received a smallpox vaccine in the past. Those who have previously received a smallpox vaccine are likely to have some residual protection (see [Vaccine effectiveness](#)) but may consider receiving a dose of JYNNEOS® as a booster dose. Healthcare workers who will only be administering the JYNNEOS® vaccine and otherwise have no anticipated occupational exposure to monkeypox or other replication-competent Orthopoxviruses are not routinely recommended a smallpox vaccine.

Vaccination may also be considered for PrEP for healthcare workers likely to see patients with monkeypox, including primary care, sexual health clinics, hospital staff, and any others at high risk of exposure based on an assessment of their risk of exposure to the monkeypox virus. The risk of transmission should be also minimised by using [infection control measures](#).

Laboratory workers working with smallpox or monkeypox virus, identified through local laboratory risk assessments, may also be considered for PrEP. Refer to the [PHLN Laboratory case definition](#) document. Individuals working in these environments should review their own history of smallpox vaccination, as booster doses may be appropriate for those with new or ongoing risk of exposure to monkeypox⁸.

Previously vaccinated healthcare workers and laboratory workers with ongoing risk of occupational exposure may be considered for a booster. Supply of smallpox vaccines may impact on the availability of specific brands of vaccine for those at occupational risk, with either of the current vaccines appropriate for this indication following an individual risk-benefit discussion. A booster dose should be administered if the previous dose of a smallpox vaccine was given more than ten years prior. Subsequent boosters for those at continuing occupational risk should be given at ten-yearly intervals.

ATAGI recommends JYNNEOS® vaccination for:

- GBMSM (age ≥16) at highest risk of infection with monkeypox virus due to a high number of contacts. Risk criteria for infection may include:
 - Those living with HIV
 - A recent history of multiple sexual partners, participating in group sex, attending sex on premises venues.
 - Other proxy markers, such as recent sexually transmitted infection or those being advised to take HIV PrEP due to the number of sexual partners. While many people prescribed HIV PrEP are monogamous with a HIV positive partner, this category can also capture those with multiple partners who are at high risk.
 - Recommendation from other service providers, such as sexual health clinics.
- Sex workers, particularly those whose clients belong to high-risk categories.
- Anyone in the above risk categories who is planning travel to a country experiencing a significant outbreak.

- Immunisation providers who are administering the ACAM2000™ smallpox vaccine

Wider vaccination of low-risk GBMSM or the general population is not recommended at this time, due to the current epidemiology, low risk of infection and limited vaccine supply.

Vaccination for post-exposure prophylaxis (PEP)

Close contacts of monkeypox cases may be considered for vaccination for PEP. These may include high-risk contacts who may be healthcare workers, household contacts, sexual contacts, or contacts in other settings where a risk for transmission has been identified.

For guidance on who should consider receiving a smallpox vaccine (ACAM2000™ or JYNNEOS®) for PEP, seek the advice of the local Public Health Unit and refer to the [CDNA National Guidelines for Public Health Units](#).

JYNNEOS® is the preferred vaccine for PEP. Where a decision is made to provide PEP, and JYNNEOS® is to be used, a single dose of JYNNEOS® should be given. If monkeypox infection has not occurred and there is an ongoing exposure risk, the second dose of JYNNEOS® should be given from at least 28 days after the first, as completion of a primary course for long-term protection. A single dose is recommended if ACAM2000™ is used for PEP, noting the contraindication to this vaccine if the individual is immunosuppressed.

Risk-benefit considerations for vaccination

A recommendation for vaccination should be based on shared decision-making between the patient and clinician. When considering vaccinating for either PrEP or PEP, the following factors should be considered:

- Severity of monkeypox: Monkeypox in humans is generally self-limiting and is less severe than smallpox. Overall case fatality rates ranged from around 3-10% in a recent review of outbreaks in the West and Central African settings⁹. As of 19 July 2022, there had been no deaths in any of the 10,604 cases reported in European Union/European Economic Area countries¹⁰.
- Individual risk factors for severe monkeypox, noting that some conditions may also be absolute or relative contraindications to vaccination with ACAM2000™, e.g. immunocompromise, pregnancy.
- Availability of other options with possible effectiveness as PEP, such as vaccinia immune globulin or pre-emptive antiviral therapy; refer to [National Treatment Guidelines](#).
- Availability of treatment for monkeypox such as antiviral therapy or vaccinia immune globulin; refer to [National Treatment Guidelines](#).
- Individual risk factors for adverse events from vaccination, especially with ACAM2000™ e.g., immunocompromise, eczema, cardiac disease, pregnancy, young age (refer to [Contraindications and Precautions](#)).
- Frequency and severity of adverse events after vaccination with either of the vaccines, noting evidence suggesting a lower rate of adverse events following JYNNEOS® compared to ACAM2000™, and availability of treatment for adverse events related to the vaccine.
- Prior vaccination with a smallpox vaccine and the potential benefit of revaccination or a booster dose (refer to [vaccine effectiveness](#) section).
- Relatively more direct evidence demonstrating effectiveness in disease prevention from replication-competent vaccine (such as ACAM2000™) compared with JYNNEOS®.

- Timing when maximum protection is conferred after a primary dose/series (about 4 weeks after a single dose of ACAM2000™, compared with about 2 weeks after the second dose of JYNNEOS®)
- Timing of first and last exposure to the monkeypox virus, if considering PEP.

Key vaccine characteristics relevant to decision-making are summarised in Table 2.

Table 2: Key characteristics of ACAM2000™ and JYNNEOS® relevant to shared decision making

Characteristic	ACAM2000™	JYNNEOS®
Safety in people with immunocompromise	Contraindicated – contains live replication-competent virus	Considered safe to use
Safety in pregnancy	Contraindicated – contains live replication-competent virus	Considered safe to use
Safety in children	Not formally studied in children aged <18 years, however, there was widespread use of first generation live attenuated vaccinia vaccines in the past in this age group. Contraindicated for age <1 year.	Not formally studied in children <18 year (and not registered for use in children in regions where JYNNEOS® is registered), however, there are trial data on safety in children on MVA used as the vector for a small number of childhood vaccines; can be considered in this age group using risk-benefit assessment, especially for individuals in high-risk groups ≥16 years of age.
Safety in people with eczema / atopic dermatitis	Absolute contraindication in people with active atopic dermatitis. Relative contraindication in people with a past history of atopic dermatitis but without current disease activity – Risk of serious adverse events	Safe to use
Safety in people with vulnerable close contacts	Precaution – risk of serious adverse events	Safe to use
Risk of myocarditis or pericarditis	Yes – refer to Adverse Events	Insufficient data to assess risk Not reported in clinical studies*
Risk of other serious adverse events	Yes – refer to Adverse Events	No other notable serious adverse events based on available data
Co-administration	In people at risk of myo/pericarditis, for PrEP purposes only, consider separating ACAM2000™ and mRNA COVID-19 vaccine by several weeks	Considered safe to co-administer*

*One case of possible pericarditis, with suggestive evidence of an alternative viral infection as the potential cause, was identified among >7800 recipients of MVA-BN vaccines (including JYNNEOS®) across multiple clinical studies

During the shared clinical decision making and consent process, patients should also be informed of the following:

For either ACAM2000™ or JYNNEOS® vaccination

- Potential serious and mild adverse events (refer to [Adverse Events](#) below)

For ACAM2000™ only:

- Expected vaccine reaction, including permanent scar
- Aftercare instructions, including wound care
- Precautions to minimise risk of autoinoculation or transmission of vaccine virus to others
- For women of childbearing potential: the need to avoid pregnancy for 28 days following vaccination. If ACAM2000™ is inadvertently given to a pregnant woman, seek expert advice via your state or territory health department.

Vaccine Contraindications and Precautions

CONTRAINDICATIONS

JYNNEOS®

Contraindications include anaphylaxis to a previous dose or to a component of the vaccine.

JYNNEOS® contains benzonase, gentamicin and ciprofloxacin and may contain trace residues of chicken egg protein.

See [JYNNEOS® consent template](#).

ACAM2000™

Absolute contraindications to ACAM2000™ include:

- Anaphylaxis to previous dose or to a component of the vaccine (including neomycin or polymyxin B sulfate)
- Severe immunocompromise, particularly defects in cellular immunity. For detailed guidance on which conditions and medications cause severe immunocompromise, refer to prior [ATAGI guidance](#).
- Pregnancy (women of child-bearing age should avoid pregnancy for 28 days after vaccination)
- Age under 12 months
- Presence of active dermatitis (including eczema) or other active exfoliative skin conditions

People in the following groups should be viewed as having relative contraindications, depending on their detailed clinical history and the risks for vaccine-related adverse events (as well as from the risk for monkeypox):

- Mild or moderate immunocompromise, including secondary to treatment or disease
- Eye disease treated with topical steroids
- Age 12 months to <18 years

- Past history of atopic dermatitis or other exfoliative skin conditions, without current disease activity. People with inactive atopic dermatitis may be administered ACAM2000™, followed by careful monitoring and active follow up. Refer to the [National Treatment Guidelines](#) for treatment of serious vaccine-related complications.

PRECAUTIONS

JYNNEOS®

Specific points to note:

- People who are pregnant or breastfeeding. JYNNEOS® has not been formally evaluated in pregnant or lactating women, but there are no theoretical safety concerns relating to its use in these groups.
- Children under 18 years of age. JYNNEOS® has not been approved for use in individuals under 18 years of age in regions/countries where it is registered. There are limited safety data for this age group. However, paediatric studies of other vaccines using MVA as a vector have not demonstrated significant safety concerns¹¹⁻¹³. In the current outbreak, people in high-risk GBMSM groups ≥16 years of age are recommended to receive vaccination as potential benefits outweigh potential risks.
- Individuals with atopic dermatitis reported a higher frequency of local and general symptoms after vaccination compared with those without this condition.
- Lower immune response has been observed in HIV infected individuals compared to healthy individuals, but clinical relevance is unknown. There are no data on the immune response to JYNNEOS® in other immunosuppressed individuals¹⁴.

ACAM2000™

The risk for adverse events may be higher for the following individuals (refer to [Adverse Events](#)) or their household contacts, and this needs to be considered in the risk-benefit assessment.

- People who are breastfeeding, where the risk is to the infant via documented vaccinia virus shedding through breastmilk
- People with cardiac disease/cardiac risk factors. Major cardiac risk factors include hypertension, diabetes mellitus, hypercholesterolemia, heart disease at age ≤50 years in a first-degree relative, and smoking. The presence of three or more of these factors is considered a relative contraindication to primary vaccination with ACAM2000™.
- People with vulnerable household contacts (e.g., immunocompromised, people with eczema active exfoliative skin conditions, pregnant individuals), noting the risk of onward transmission to others can be minimised (refer to [Aftercare](#)).

Vaccine administration and aftercare

JYNNEOS®

JYNNEOS® is administered by subcutaneous (SC) injection, via two doses (0.5 mL each) at least 28 days apart. Each dose (0.5 mL) is supplied in a single-dose vial. No specialised aftercare is required. Refer to

[Product Information](#). The second dose does not need to be repeated if given later than 28 days after the first dose.

ACAM2000™

Detailed information on ACAM2000™ administration and aftercare is available in the [Product Information](#) and the [Consumer Medicines Information sheet](#), accessible at the TGA website.

ACAM2000™ is supplied in multi-dose vials, each containing approximately 100 doses after reconstitution. Specialised trained vaccinators administer ACAM2000™ with a bifurcated needle using a technique called scarification. The virus replicates at the injection site, causing a localised infection (“pock”) around 10 days after inoculation. The vaccine has “taken”, or been successful, if a red itchy spot is present 4 days following vaccination. A blister then develops and forms a scab that falls off in the third week, leaving a small scar. When choosing the vaccination site, consider the practicality of keeping the area covered.

Aftercare following ACAM2000™ administration

Prior to vaccination, vaccine recipients should be informed about expected reactions and aftercare. They should also be informed about the potential for serious adverse events and how to seek care if concerning symptoms develop (refer to [Adverse Events](#)).

- The expected reaction to vaccination is a papule (small bump) at the vaccination site on day 2 to 5 post vaccination, which progresses to a vesicle (blister), then pustule (blister with pus), and then a scab.
- The scab typically separates within 14-21 days, leaving a pitted scar.
- The vaccination site wound is infectious until scabbing occurs and must be covered with a gauze bandage secured with adhesive tape, to prevent a risk of auto-(self) inoculation onto skin in other sites or transmission of the vaccinia virus to others. An occlusive dressing can be used to minimise risk of transmission to vulnerable close contacts.
- Wound dressings should be changed every 1 to 3 days disposed of in sealed plastic bags and can then be disposed of in general rubbish.
- Avoid contact with individuals at high risk of serious adverse effects of vaccinia virus, for instance, those with eczema or other exfoliative skin lesions, immunodeficiency states including HIV infection, pregnant persons or infants less than 12 months of age.
- Vaccinated healthcare workers should avoid contact with immunocompromised patients and high-risk areas (e.g., haematological oncology and transplant wards) until the scab has separated. When caring for patients, ensure the vaccination site is well covered with an occlusive wound dressing and follow good hand washing technique.
- Blood and organ donation should be avoided for at least 30 days following vaccination.
- Pregnancy should be avoided for at least 28 days following vaccination.
- Refer to [Product Information](#) and the [Consumer Medicines Information sheet](#) for further information.

Co-administration of ACAM2000™ or JYNNEOS® with COVID-19 or other vaccines

There is a rare risk of associated myocarditis and/or pericarditis following either ACAM2000™ or mRNA COVID-19 vaccines, respectively, especially in people under 40 years of age and in males. Based on the theoretical risk of myocarditis and pericarditis, when used as PrEP, spacing ACAM2000™ and an mRNA COVID-19 vaccine apart by several weeks may be considered. This may theoretically reduce the risk of myocarditis and pericarditis, but there is no evidence to confirm this.

Whether JYNNEOS® is associated with a risk of myocarditis is uncertain. For PrEP purposes only, spacing JYNNEOS® and an mRNA COVID-19 vaccine apart by several weeks may be considered for people with increased risk of myocarditis and/or pericarditis following an mRNA COVID-19 vaccine, such as young adult males.

Adverse events

JYNNEOS®

JYNNEOS® vaccine is associated with fewer adverse events than ACAM2000™. A phase 3 trial showed fewer minor and serious adverse events in participants who received JYNNEOS® than in those who received ACAM2000™ (17 out of 220 versus 64 out of 213 participants with adverse events of grade 3 or higher, P<0.001)¹⁵.

Safety data for JYNNEOS® are available from a pooled analysis of 22 clinical studies which included over 7800 participants who received an MVA-BN vaccine¹⁶. Adverse events in persons previously vaccinated with a smallpox vaccine compared with those never vaccinated occurred at similar frequencies after MVA-BN was given (Table 3)¹⁶.

Table 3 - Adverse events following vaccination with MVA-BN (JYNNEOS®)¹⁶

	Frequency in vaccine-naïve individuals	Frequency in previously vaccinated individuals
Common local adverse events		
Injection site pain	85%	80%
Injection site redness	61%	81%
Injection site swelling	51%	67%
Induration	45%	70%
Injection site itch	43%	32%
Common systemic adverse events		
Muscle aches	43%	22%
Headache	35%	28%
Fatigue	30%	34%
Nausea	17%	10%
Chills	10%	0.7%
Fever	2%	0.5%

ACAM2000™

Adverse events after ACAM2000™ in clinical studies were common but were generally mild to moderate. (Refer to the [Product Information](#) for further information.)

Common local adverse events included:

- A permanent pitted scar at the injection site is universal following successful inoculation
- Injection site itch (92%)
- Injection site redness (74%)

Common systemic adverse events included:

- Headache (50%)
- Fatigue (48%)
- Muscle aches (46%)
- Malaise (37%)
- Feeling hot (32%)

- Injection site pain (67%)
- Lymph node pain (57%)
- Injection site swelling (48%)
- Nausea (19%)
- Diarrhoea (16%)

Serious adverse events

ACAM2000™ is associated with a risk of myocarditis and pericarditis. The risk is highest in young adults and in males, with overall incidence of around 1 in 5000 to 1 in 12,800 doses based on post-licensure passive surveillance in military personnel^{17,18}. Of the 180 cases reported in one cohort study, 21% were subclinical myopericarditis, 22% were myocarditis, 27% were pericarditis and 29% were clinical myopericarditis¹⁷. In a case series of 18 cases, the mean time to onset was 10 days¹⁸.

Other serious adverse events have been historically associated with replication-competent smallpox vaccines, including the first-generation vaccine Dryvax, and are listed below. Accurate rate estimates of these adverse events for ACAM2000™ are not available given its limited use, but they are a potential risk. Recommendations for treatment of serious adverse events with VIG and/or antiviral agents are outlined in the [National Treatment Guidelines](#).

- Accidental autoinoculation is the unintentional transfer of vaccinia virus from the vaccination site to elsewhere on the body, which can produce a vaccinia rash at distant sites.
- Autoinoculation of the eye may result in vaccinia keratitis. There are no current disease-specific treatment options available for the management of vaccinia keratitis¹⁹.
- Eczema vaccinatum involves widespread pustular/erosive lesions from the vaccinia virus, occurring particularly in areas affected by eczema/atopic dermatitis.
- Generalised vaccinia results from viraemia and presents with a generalised vaccinia virus rash and can be accompanied by fever, myalgia and headache; but is self-limiting in immunocompetent hosts. Generalised vaccinia is thought to be rare but has been reported after ACAM2000™²⁰.
- Progressive vaccinia presents with delayed/absent local wound healing and widespread lesions emanating from the inoculation site that can become necrotic. The incidence of this during the smallpox vaccination era was 1 per million doses²¹. The risk is highest in people with severe immunocompromise, particularly those with defective cell-mediated immunity.
- Fetal vaccinia resulting from vaccination during pregnancy, which can result in stillbirth or perinatal death.
- Serious neurological adverse events including encephalitis, post-vaccinia encephalopathy (PVE) and encephalomyelitis (PVEM).

As there are limited safety data from large population-based programs for ACAM2000™ and JYNNEOS®, it is important to ensure there is ongoing phase IV (post marketing) vaccine safety monitoring for both vaccines, utilising Australian adverse event surveillance systems. ATAGI recommends that these reports be collated at a jurisdictional and national level, utilising international frameworks for smallpox vaccine reporting²².

Individuals who develop any adverse events following immunisation (AEFI) with a smallpox vaccine should be encouraged to report data on the event(s) to their healthcare provider, who in turn report to the State/Territory and the [TGA](#). Active surveillance for AEFI with smallpox vaccines is also encouraged, using established systems such as AusVaxSafety.

Vaccine effectiveness

There is evidence that demonstrates the effectiveness of replication-competent smallpox vaccines (such as Dryvax or ACAM2000™) against smallpox or monkeypox, when used for pre-exposure or post-exposure prophylaxis. There are no direct data on the effectiveness of JYNNEOS® against smallpox or monkeypox. Vaccine effectiveness is inferred from indirect evidence, particularly immunogenicity data.

Effectiveness of ACAM2000™ and JYNNEOS® for pre-exposure prophylaxis against monkeypox

Active monkeypox surveillance data from the Democratic Republic of the Congo (DRC) in 2005–2007 demonstrated that among individuals born before 1980 (when the official national mass smallpox vaccination program ended), people vaccinated against smallpox had a 5.2-fold lower risk of monkeypox than those unvaccinated (0.78 vs. 4.05 per 10,000), giving a smallpox pre-exposure vaccine effectiveness against monkeypox of 80.7% (95% CI: 68.2–88.4%)²³.

Vaccine efficacy against smallpox by first generation smallpox vaccines such as Dryvax has not been assessed in randomised controlled studies. After administration of a standard dose of smallpox (vaccinia virus) vaccine, >95% of primary vaccinees exhibit neutralising or hemagglutination inhibition antibody against smallpox at a titre of $\geq 1:10$ ^{24,25}. Additionally, clinical effectiveness of first-generation smallpox vaccines, leading to global eradication of smallpox, has been shown. Immunogenicity data for the second-generation vaccine, ACAM2000™, assessed immune responses following inoculation against smallpox virus rather than monkeypox virus, and in randomised controlled trials ACAM2000™ demonstrated similar cellular immune responses against smallpox virus as Dryvax. On the basis of all immunogenicity results, ACAM2000™ is considered to be non-inferior to Dryvax against smallpox²⁵ and can be inferred to be similarly effective against other poxviruses including monkeypox.

Vaccine effectiveness for the third generation MVA-BN vaccine (including JYNNEOS®) against smallpox was inferred by comparing the immunogenicity of MVA-BN to that of ACAM2000™ using plaque reduction neutralization testing (PRNT) against vaccinia virus. In a phase 3 trial of 440 participants randomised to two doses of MVA-BN followed by ACAM2000™ versus one dose of ACAM2000™, the immune responses in the MVA-BN group, after two doses of MVA-BN and prior to the challenge with ACAM2000™, were similar to those who had received one dose of ACAM2000™ only^{14,15}.

Additionally, evidence for the use of smallpox vaccines against monkeypox was informed by challenge studies in macaques. In one study, three groups of macaques were vaccinated using 1 dose of ACAM2000™, 1 dose of MVA-BN or 2 doses of MVA-BN. After challenge with a lethal dose of monkeypox virus at 28 days following the last vaccine dose, vaccine efficacy against death compared to an unvaccinated control group was 100% for the ACAM2000™ and 2-dose MVA-BN groups, and 67% for the 1-dose MVA-BN group²⁶.

A systematic review on duration of immunity published in 2019 suggests that some protection against smallpox virus may persist for greater than 20 years after smallpox vaccination²⁷. It is unclear how these data can be extrapolated to infer the duration of protection against monkeypox.

Clinical studies have shown evidence of protection against the vaccinia virus at 2 years following a primary course of the MVA-BN vaccine¹⁴. A single booster dose of MVA-BN at 2 years led to a slight improvement in immune response another 2 years later, among people who had also received a primary course of the

MVA-BN vaccine. The duration of protection after 1 primary dose of MVA-BN is currently not known beyond 4 weeks.

Vaccine effectiveness for post-exposure prophylaxis (PEP)

Vaccination with a smallpox vaccine following exposure to monkeypox may prevent or attenuate the infection, based on extrapolation from low-quality historical data of protection against smallpox, animal models, and more recent use in isolated outbreaks of monkeypox in non-endemic countries.

A 2019 review of human smallpox outbreak data from year 1882 to 1973 calculated an overall effectiveness of PEP against smallpox with any smallpox vaccine of 45% (IQR 25.5% to 64.5%), noting wide variation in timing of vaccination after exposure²⁸. A study obtaining consensus opinions from experts using the Delphi technique estimated the effectiveness of post-exposure smallpox vaccination in preventing disease at 1–3 days after exposure to be 80%²⁹.

There are insufficient data to specifically estimate effectiveness against monkeypox, though a range of first, second and third-generation smallpox vaccines have been used as PEP for monkeypox in outbreaks of monkeypox in non-endemic countries since 2003³⁰⁻³³. Breakthrough monkeypox cases have occurred after PEP vaccination of high-risk contacts with Dryvax and with MVA-BN.

The effectiveness of post-exposure use of ACAM2000™ and JYNNEOS® against monkeypox was compared directly in one animal study only, using prairie dogs. At day 7 following vaccination, animals vaccinated with one dose of ACAM2000™ one day after exposure to the monkeypox virus had higher antibody titres than those receiving one dose of JYNNEOS® one day after exposure, suggesting a more rapid immune response after ACAM2000™. While the difference in antibody titres was not statistically different at day 14 following vaccination, no correlate of protection in this species is known³⁴.

This comparable immunogenicity after a single dose of MVA-BN (including JYNNEOS®) with that of ACAM2000™ (for which there is indirect evidence for effectiveness when used for PEP), indirectly suggests some effectiveness can be expected after a single dose of MVA-BN given as PEP. Various animal studies with the monkeypox (and mousepox) viruses, using mostly the MVA-BN vaccine, corroborate the finding that vaccine effectiveness as PEP begins to decline over time (e.g. when given at 3 days post-exposure, effectiveness is lower than when given at 1 day post-exposure).

Vaccine storage and handling

JYNNEOS®

(Refer to the [Product Information](#) for further information.)

Packaging

JYNNEOS® is supplied in packages of 20 single-dose vials.

Storage

Guidance on storage conditions and shelf life of the vaccine product that will be used in Australia will be provided when confirmatory information from the manufacturer becomes available.

ACAM2000™

(Refer to the [Product Information](#) for further information.)

Packaging

The live vaccinia virus component of the ACAM2000™ vaccine is supplied in multiple-dose 3 mL clear glass vials containing lyophilised powder (freeze-dried vaccine). Diluent for ACAM2000™ is supplied in 3 mL clear glass vials containing 0.6 mL of diluent. Bifurcated needles are supplied in boxes (5 x 5 x 1 in) containing 100 needles. 1 mL tuberculin syringes with 25-gauge x 5/8” needles are supplied for vaccine reconstitution.

Storage

ACAM2000™ should be stored in a freezer with an average temperature of -15°C to -25°C. After reconstitution, ACAM2000™ vaccine may be administered during 8 hours at +20°C to +25°C. Reconstituted ACAM2000™ vaccine may be stored in a refrigerator at +2°C to +8°C for no longer than 30 days, after which it should be discarded. Diluent for ACAM2000™ should be stored at +15°C to +30°C. ACAM2000™ contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open.

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