



National Immunisation Advisory Committee

RECOMMENDATIONS FOR THE USE OF MONKEYPOX MODIFIED VACCINIA
ANKARA VACCINES, IMVANEX OR JYNNEOS, BY THE INTRADERMAL ROUTE

NIAC | 22.08.2022

About NIAC

NIAC membership includes nominees from the RCPI, its Faculties and Institutes, the RCSI, the ICGP, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

[NIAC](#) meets to consider new evidence about vaccines and provide advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.

RECOMMENDATIONS

1. While vaccine supplies remain limited, monkeypox vaccine may be administered intradermally (ID) for those aged 18 years and older. Two 0.1ml doses no less than 28 days apart are required. Available data regarding ID administration are based on two doses of vaccine so it is important that the vaccine course is completed.
2. Vaccinees should be informed that there is an increased rate of local reactogenicity associated with ID vaccination which may last up to six months in a third of vaccinees.
3. The vaccine can be administered ID in those with immunocompromise, although the immune response may be lower than in those who are immunocompetent.
4. ID administration into the volar aspect of the forearm should be performed by health professionals appropriately trained in the correct administration of ID vaccines.
5. A person who has received their first vaccine dose subcutaneously (SC) may receive the second dose ID. Those whose 18th birthday occurs between their first and second dose may complete the series with the alternative ID dosing.
6. When vaccine supplies are adequate, those who received their first vaccine dose ID may receive the second dose SC.
7. Those who have had previous smallpox vaccination require one vaccine dose, which can be given SC or ID. Those who are immunocompromised require two vaccine doses no less than 28 days apart regardless of previous smallpox vaccination.
8. NIAC strongly encourages further research in Ireland on vaccine effectiveness against monkeypox as the exact level and duration of protection are unknown with either SC or ID administration in line with WHO recommendations.

These recommendations are an update to recommendations made on 27 May and 22 July 2022. They are made in the context of the current Public Health Emergency and limited availability of monkeypox vaccine. Adopting ID administration as an alternative to the standard SC administration will facilitate vaccination of a greater number as it could increase the numbers vaccinated five fold.

These recommendations reflect a dynamic vaccination programme strategy. Recommendations may be updated when more information becomes available.

1. BACKGROUND

Imvanex (Modified Vaccinia Ankara (MVA) – Bavarian Nordic Live virus) has been approved in the European Union since 2013 for subcutaneous (SC) administration for the prevention of smallpox.

On 27 June 2022 the European Medicines Agency (EMA) stated that the same vaccine is authorised for prevention of smallpox and monkeypox disease in those aged 18 years and older as Jynneos in the US and as Imvamune in Canada.¹ There are minor differences in the manufacturing processes and quality specifications between these three vaccines, which are due to differences in the datasets, but which do not affect the final quality of the vaccines. Jynneos could be used to provide protection against monkeypox disease in the EU.

On 22 July 2022 the EMA extended the indication of Imvanex to include protecting those aged 18 years and older from monkeypox disease.²

On 23 July 2022 the World Health Organization declared the escalating global monkeypox outbreak a Public Health Emergency of International Concern.³

On 9 August 2022 the Federal Drug Administration (FDA) issued an emergency use authorization to allow healthcare providers to use Jynneos by intradermal (ID) injection for individuals aged 18 years and older who are at high risk for monkeypox infection. The FDA considered the available safety and immunogenicity data as well as historical data regarding the use of live vaccinia virus smallpox vaccine.⁴

On 19 August 2022 the EMA advised that Imvanex can be administered by the ID route⁵ given the global demand for vaccine and the limited vaccine supply. In making their determinations, the EMA emergency task force considered the available evidence in support of antigen sparing vaccination strategies. No new safety signal with ID administration is identified however higher local reactogenicity is noted. The EMA has stated that in the ongoing emergency situation, the safety profile of the vaccine following the ID route can be considered acceptable.⁵

In Ireland monkeypox case numbers are increasing. Initial efforts to arrest the outbreak focused on increasing public awareness of monkeypox and its modes of transmission as well as targeted vaccination. Broadening population protection through wider use of pre-exposure prophylaxis for those at high risk could help to curtail the outbreak and is desirable. However vaccine supplies are limited. ID vaccination using a lower dose as an alternative to the standard SC administration would facilitate protection of more of those for whom the vaccine is recommended as a two dose schedule.

2. MONKEYPOX VACCINE

Imvanex (Modified Vaccinia Ankara (MVA) – Bavarian Nordic Live virus) is authorised in the EU for active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults. The recommended dosage is 0.5 ml SC at day 0 and a second 0.5ml dose no less than 28 days after the first dose.

There are no data available to indicate that one dose of Imvanex will provide long-lasting protection, which will be needed to control the current monkeypox outbreak.

The vaccine was initially developed specifically as an alternative for use in immunocompromised individuals in the event of a smallpox outbreak. It has been tested in individuals with immunocompromise (HIV and atopic dermatitis) and was safe and effective in the trials that were performed to support approval.^{6,7}

A 2010 study with another MVA vaccine, ACAM3000, showed that administration by the ID route resulted in significantly higher local adverse reactions (i.e., erythema, induration) than the SC route, with most lasting at least 30 days, and higher rates after the second vaccine dose.⁸

A 2015 clinical study of the MVA vaccine evaluated the safety and immunogenicity of a two-dose series of 0.1ml given ID compared to 0.5ml given SC.⁹ The proportion of those with erythema (redness) and/or induration (hardness) was significantly higher after ID vaccination compared to SC and the reactions lasted longer in the ID group. Over a third had mild injection site skin discoloration lasting ≥ 6 months. The same study demonstrated comparable humoral immunogenicity with ID and SC administration.⁹

The exact level and duration of protection against monkeypox are unknown with either SC or ID administration. As the 2015 study was in healthy people, it is unknown if the reduced ID dose will be immunologically non inferior to the standard SC dose in specific groups such as the immunocompromised or those living with HIV.

ID delivery of vaccines, allowing antigen sparing, with comparable immunogenicity has been shown with a reduced ID dose of rabies or influenza vaccine compared with IM administration.^{10,11}

3. INTERNATIONAL RECOMMENDATIONS

EMA

The EMA has stated that national authorities may decide as a temporary measure to use Imvanex as an ID injection at a lower dose to protect at-risk individuals during the current monkeypox outbreaks while supply of the vaccine remains limited.

US

Jynneos vaccine is licensed under emergency use authorisation for a series of two doses administered 28 days (4 weeks) apart.

The standard regimen involves 0.5 ml by SC administration. In the context of the current national Public Health Emergency (PHE) in the US, the FDA has authorised an alternative regimen with an ID dose of 0.1ml.

UK

The UK Health Security Agency (UKHSA) and the Joint Committee on Vaccination and Immunisation (JCVI) have reviewed the evidence in ID administration and agree that changing the method of administration will potentially enable an up to five fold increase in the number of people that can be offered vaccination with the same amount of vaccine and the same immunological protection. Small scale piloting of ID dosing of monkeypox vaccination will begin in the coming days (personal communication).

4. INTRADERMAL USE OF MONKEYPOX VACCINE

While vaccine supplies remain limited, monkeypox vaccine may be administered ID for those aged 18 years and older. Two 0.1ml doses no less than 28 days apart are required.

There is an increased rate of local reactogenicity associated with ID vaccination which may last up to six months in a third of vaccinees.

Available data regarding ID administration are based on two doses of vaccine so it is important that the vaccine course is completed.

The vaccine can be administered ID in those with immunocompromise, although the immune response may be lower than in those who are immunocompetent.

ID administration into the volar aspect of the forearm should be performed by health professionals appropriately trained in the correct administration of ID vaccines.

A person who has received their first vaccine dose SC may receive the second dose ID. Those whose 18th birthday occurs between their first and second dose may complete the series with the alternative ID dosing.

When vaccine supplies are adequate, those who received their first vaccine dose ID may receive the second dose SC.

Those who have had previous smallpox vaccination require one vaccine dose, which can be given SC or ID. Those who are immunocompromised require two vaccine doses no less than 28 days apart regardless of previous smallpox vaccination.

NIAC strongly encourages further research in Ireland on vaccine effectiveness against monkeypox as the exact level and duration of protection are unknown with either SC or ID administration in line with WHO recommendations.

Directions for intradermal administration¹²⁻¹⁵

When possible, low dead volume syringes and/or needles should be used to extract up to five doses (0.1 mL each) from a single vial. If standard syringes and needles are used, there may not be sufficient volume to obtain five doses from a single vial.

- The vaccine should be allowed to reach room temperature before use.
- Hold the vaccine vial upright and swirl gently for at least 30 seconds before each use.
- The suspension should be visually inspected for particulate matter and discoloration before each use. In the event of any damage to the vial, foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.
- Clean the vaccine vial stopper with a single-use antiseptic swab before each use.
- Using a 1ml syringe and a 25-27G, 10-16mm needle carefully withdraw 0.1 ml of vaccine.
- Do NOT combine residual vaccine from multiple vials.
- Administer the vaccine by ID injection into the volar aspect (inner side) of the forearm.
- Using the finger and thumb of the non dominant hand, stretch the skin at the mid point of the volar (palmar) side of the forearm.
- Insert the needle into the dermis with the bevel facing upwards, at an angle of 5-10 degrees, to a distance of 2-3 mm. The bevel should be covered by skin and visible through the epidermis.
- Slowly inject 0.1ml. When given correctly, an ID injection should raise a blanched bleb or wheal.¹⁶ If no resistance is felt when the needle is inserted, the needle may be in SC tissue. In this case, withdraw the needle and repeat the injection at a new site.

- Once the vial is punctured and all the contents are not used, the vial should be stored at +2°C to +8°C and used within eight hours of the first puncture.
- A person who presents for their second ID vaccine dose who is still experiencing erythema or induration at the site of first dose intradermal vaccine administration may have the second dose administered intradermally in the contralateral forearm.

It may be helpful to view the CDC video [‘How to administer a JYNNEOS vaccine intradermally’](#).¹⁶

Contraindications and precautions

In addition to the contraindications and precautions listed in [Chapter 13a](#), ID administration is not recommended for those with a history of keloid scar formation. They should receive SC vaccination.

REFERENCES

1. European Medicines Agency (2022). Possible use of the vaccine Jynneos against infection by monkeypox virus. https://www.ema.europa.eu/en/documents/public-statement/possible-use-vaccine-jynneos-against-infection-monkeypox-virus_en.pdf.
2. European Medicines Agency (2022). EMA recommends approval of Imvanex for the prevention of monkeypox disease. <https://www.ema.europa.eu/en/news/ema-recommends-approval-imvanex-prevention-monkeypox-disease>.
3. World Health Organization (2022). WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern. <https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern>.
4. Federal Drug Administration (2022). Monkeypox Update: FDA Authorizes Emergency Use of JYNNEOS Vaccine to Increase Vaccine Supply. <https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-authorizes-emergency-use-jynneos-vaccine-increase-vaccine-supply>.
5. European Medicines Agency (2022). Considerations on posology for the use of the vaccine Jynneos/ Imvanex (MVA-BN) against monkeypox. https://www.ema.europa.eu/en/documents/other/considerations-posology-use-vaccine-jynneos/imvanex-mva-bn-against-monkeypox_en.pdf.
6. 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(5):749-58. DOI: [10.1093/infdis/jis753](https://doi.org/10.1093/infdis/jis753).
7. Overton ET, Stapleton J, Frank I, et al (2015). Safety and Immunogenicity of Modified Vaccinia Ankara-Bavarian Nordic Smallpox Vaccine in Vaccinia-Naive and Experienced Human Immunodeficiency Virus-Infected Individuals: An Open-Label, Controlled Clinical Phase II Trial. *Open Forum Infect Dis*;2(2):ofv040. DOI: [10.1093/ofid/ofv040](https://doi.org/10.1093/ofid/ofv040).

8. Wilck MB, Seaman MS, Baden LR, et al (2010). Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. *J Infect Dis* ;201(9):1361-70. [DOI: 10.1086/651561](https://doi.org/10.1086/651561).
9. Frey SE, Wald A, Edupuganti S, et al (2015). Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. *Vaccine*;33(39):5225-34. [DOI: 10.1016/j.vaccine.2015.06.075](https://doi.org/10.1016/j.vaccine.2015.06.075).
10. World Health Organization (2018). Rabies vaccines: WHO position paper – April 2018. *Weekly epidemiological record*;16(201-220):93 <https://www.who.int/publications/i/item/who-wer9316>
11. Egunsola O, Clement F, Taplin J, et al (2021). Immunogenicity and Safety of Reduced-Dose Intradermal vs Intramuscular Influenza Vaccines: A Systematic Review and Meta-analysis. *JAMA Netw Open*;4(2):e2035693. [DOI: 10.1001/jamanetworkopen.2020.35693](https://doi.org/10.1001/jamanetworkopen.2020.35693).
12. Centers for Disease Control and Prevention (2022). JYNNEOS Vaccine <https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html>
13. Centers for Disease Control and Prevention (2022). JYNNEOS Smallpox and Monkeypox Vaccine Standing Orders for Administering Vaccine Intradermally: ALTERNATIVE DOSING REGIMEN <https://www.cdc.gov/poxvirus/monkeypox/files/interim-considerations/monkeypox-jynneos-standing-orders-alt-dose.pdf>.
14. Melbourne Vaccination Education Centre (2022). Intradermal vaccination. <https://mvec.mcri.edu.au/references/intradermal-vaccination/>.
15. European Medicines Agency (2022). Imvanex Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/imvanex-epar-product-information_en.pdf.
16. Centers for Disease Control and Prevention (2022). How to administer a JYNNEOS vaccine intradermally. <https://www.youtube.com/watch?v=TLv1mR6mECQ>

ACKNOWLEDGEMENTS

NIAC would like to thank all the individuals and organisations who provided data, time, advice and information in support of this work.