13a Monkeypox/Smallpox (variola)

NOTIFIABLE

Key changes

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13a.1.1 Introduction

Monkeypox is a zoonotic disease caused by an orthopoxvirus that results in a smallpox-like disease in humans. The Orthopoxvirus genus also includes variola virus (which causes smallpox), vaccinia virus (used in the smallpox vaccine), and cowpox virus. There are two strains of monkeypox, the Central African and West African strain.

Monkeypox was first recognised in 1958 when two outbreaks of a pox-like disease occurred in monkeys kept for research. The first human case was recorded in 1970 in the Democratic Republic of the Congo (DRC), and since then the infection has been reported in a number of central and western African countries. Most cases are reported from the DRC and Nigeria.

Prior to 2022, cases were rarely reported outside Africa and those that were generally related to international travel. In 2003, monkeypox was recorded in the US when an outbreak occurred in humans and pet prairie dogs following importation of rodents from Africa. The human infections followed contact with an infected pet and all patients recovered.

On 7 May 2022, monkeypox was identified in the UK in a person with recent travel to Nigeria. Since then, hundreds of cases have been reported in non-endemic countries without a history of travel to Africa.

On 23 July 2022, WHO declared the global monkeypox outbreak a Public Health Emergency of International Concern, with the vast majority of cases in the European Region.

13a.1.2 Epidemiology

Monkeypox is indigenous to the rainforests of Central and West Africa. The number of human monkeypox cases has been increasing since the 1970s, with the most dramatic increases occurring in the DRC. This is possibly due to the cessation of smallpox vaccination with subsequent waning of immunity and other factors including deforestation, disruption of animal habitats, increase in population mobility and possible genetic evolution of the virus.

There are two clades (strains) of monkeypox,the Central African and West African strains. A recent systematic review reported a case fatality rate of 10.6% for the Central African strain and 3.6% for the West African strain in a Nigerian population. The West African lineage is generally associated with milder disease and is responsible for the 2022 outbreak.

Prior to the present international outbreak the disease was more common in males with a median age of 21 years. Those infected included traders, students, artisans, healthcare professionals, farmers, hunters and transport workers. Eating inadequately cooked meat and other products of infected animals is a possible risk factor.

The natural reservoir of monkeypox has not yet been identified, though rodents are the most likely hosts.

Up to 18 October 2022, 25,177 cases have been identified from 45 countries throughout the WHO European Region. Almost all were male (24,576/24,977 - 98%) and 39% were aged between 31-40 years. Of the 10,802 male cases with known sexual orientation, 96% self identified as men who have sex with men. Among cases with known HIV status, 38% (3,787/10,064) were HIV positive. Less than 10% (6%) were hospitalised and five cases were admitted to ICU, four of whom died of monkeypox. Five cases of occupational exposure have been reported.

In Ireland, 200 cases have been reported and all but two are male with a median age of 35 years. Sexual orientation is known for 182, all but one of whom self-identified as gay, bisexual or other men who have sex with men (gbMSM). Eighteen cases (10%) have been hospitalised; 11 for clinical care related to monkeypox infection, two for isolation purposes only and information on the reason for admission for the other five is awaited. The epidemiological picture to date in Ireland is similar to that seen in other countries, where cases are primarily in gbMSM.

Transmission

Transmission can occur through contact with the virus from an animal human or other source, e.g., preparation or ingestion of bush meat or contact with bedding contaminated with the virus. The virus enters the body through broken skin, respiratory tract, or mucous membranes (eyes, nose, mouth, anus or vagina). It usually takes close physical contact with a symptomatic individual for transmission to occur.

Airborne transmission is thought to occur primarily through large respiratory droplets that generally cannot travel more than one to two metres. Close household or sexual contact poses the greatest risk of person-to-person spread, particularly direct contact with lesions. Transmission can also occur from mother to fetus. The risk of spread within the community is very low.

Incubation period
The incubation period is 6-13 days (range 5–21 days).

13a.1.3 Effects
Initial symptoms include fever (38.5-40.5°C), severe headache, lymph node enlargement, back pain, myalgia and intense weakness. The rash appears within 1 to 10 days of development of fever, usually beginning on the face and then spreading to other parts of the body. The lesions seen in monkeypox are similar to those of chickenpox. Symptoms generally last for 2–4 weeks.

The disease is more severe in young children, pregnant women, older persons and those with severe immunocompromise especially if related to HIV.

For further information refer to HPSC guidance.
https://www.hpsc.ie/a-z/zoonotic/monkeypox/guidance/

13a.2 Smallpox
13a.2.1 Introduction
Smallpox is a highly infectious systemic illness caused by the variola virus, a species of Orthopoxvirus. Humans are the only reservoir. There are two strains of the smallpox virus, each with a different clinical course. Variola minor has a case fatality rate of less than 1%; Variola major has a case fatality rate among unvaccinated populations ranging from 15% to 45% or higher. Following a global vaccination campaign led by the WHO, the last naturally occurring case of smallpox was in 1977. It is the only disease to have been eradicated.

13a.2.2 Epidemiology
Smallpox was first described over 3,000 years ago in Egypt. Based on available data, the disease was endemic in a number of European countries from the mid-18th century. In the 20th century alone an estimated 300 million people died of the disease. The last known case of naturally occurring smallpox occurred in Somalia in 1977. In December 1979, the WHO declared that smallpox had been eradicated.

Transmission
Smallpox is spread by respiratory droplets or by direct or indirect contact with the virus shed from skin lesions. Airborne spread is thought to be less frequent, but transmission over significant distances has been documented, including transmission through a hospital stairwell. The virus is stable in dried form for months and has been transmitted by fomites such as bed linen.

Infectivity
Smallpox is infectious from the development of the rash to the disappearance of all scabs - approximately three weeks. Infectivity is highest early in the clinical disease.

13a.2.3 Effects

The incubation period is typically 10 to 14 days (range 7 to 19 days). Prodromal symptoms include sudden onset of high fever, malaise, headache, fatigue and occasional abdominal pain and vomiting. After two to four days the fever subsides and a rash first appears on the face and extremities (centrifugal), including the palms and soles, and subsequently on the trunk. The lesions progress at the same pace through the phases of macules, papules, vesicles, pustules and crusted scabs. The crusted scabs fall off three to four weeks after the appearance of the rash, leaving pitted scars. The patient remains febrile throughout the evolution of the rash and customarily experiences considerable pain as the pustules grow and expand.

In 5% to 10% of patients, more rapidly progressive, malignant disease develops, which is almost always fatal within 5 to 7 days. In such patients, the lesions are so densely confluent that the skin looks like crinkled rubber; some patients exhibit bleeding into the skin and intestinal tract. Such cases are difficult to diagnose, but they are exceedingly infectious.

Death rates vary depending on the virulence of the circulating strain and the vulnerability of the population it attacks. The case fatality rate is higher in pregnant women and in young children.

During the first 2 to 3 days of rash, the lesions may be confused with varicella (chickenpox). However, all smallpox lesions develop at the same pace and appear identical; they are mainly on the face and extremities (centrifugal) and to a lesser extent on the trunk. Chickenpox lesions develop in crops. With chickenpox, papules, vesicles, pustules and scabs may be seen simultaneously on adjacent areas of skin; they appear mainly on the trunk (centripetal), and almost never on the palms or soles.

13a.3 Monkeypox/smallpox vaccine

Two monkeypox vaccines are distributed in the EU, both containing Smallpox Modified Vaccinia Ankara –Bavarian Nordic (MVA-BN). Imvanex is authorised by the EMA, and Jynneos by the FDA.

Licensed indications

1. Imvanex: active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults.

2. Jynneos: prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection.

   Jynneos is considered as a suitable vaccine against monkeypox by the EMA Emergency Task Force together with the CHMP Biologics Working Party and the European Directorate for the Quality of Medicines & HealthCare.

The vaccine contains a non-replicating form of vaccinia virus that does not cause disease in humans as it cannot replicate in human cells.

Vaccine efficacy and effectiveness
The efficacy or effectiveness of the vaccine against smallpox has not been studied.

Efficacy in animals: Non-human primate studies have demonstrated that vaccination with the vaccine induced a comparable immune response and protective efficacy to traditional smallpox vaccines. A significant reduction in both mortality and morbidity compared to non-vaccinated controls was demonstrated.

Immunogenicity
Clinical studies of seroconversion rates (ELISA GMT) included vaccinia-naïve healthy individuals as well as individuals with HIV infection and atopic dermatitis who received two doses of Imvanex four weeks apart. Conversion rates ranged from 96 to 99% two weeks after the second dose. Rates were lower in those with HIV. Limited data on immunogenicity at 24 months showed seropositivity had fallen to 23%.

Previous smallpox vaccines have been shown to be 85% effective in preventing monkeypox in close contacts. Data show high immunogenicity in humans compared to another smallpox vaccine. Vaccination after monkeypox exposure may help prevent the disease or make it less severe.

Vaccine storage
The exact level and duration of protection against monkeypox are unknown with either subcutaneous or intradermal administration.

The vaccine should be stored in a freezer at -20°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C. After thawing, the vaccine should be used immediately or if previously stored at -20°C +/-5°C, the vaccine can be stored for up to eight weeks at +2°C to +8°C prior to use. Once thawed, the vaccine cannot be refrozen.

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.

Dose, route and schedule

1. Unvaccinated:

The dose is 0.5ml subcutaneously (SC) in the deltoid area. The course is two doses no less than 28 days apart.

While vaccine supplies remain limited, monkeypox vaccine may be administered **intradermally (ID)** in the volar (palmar) side of the forearm **for those aged 18 years and older**. If the volar (palmar) side of the forearm is not an option (e.g., scarring or patient preference), the vaccine may be administered ID into the deltoid area. Two 0.1ml doses no less than 28 days apart are required.

Available data regarding ID administration are based on two doses of vaccine no less than 28 days apart so it is important that the vaccine course is completed.

ID administration 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.

Directions for intradermal administration

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 (palmar) side of the forearm or in the deltoid area.
- 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 or in the deltoid area.
- 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. 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 still has erythema or induration at the site of the first ID dose may have the second ID dose in the other forearm or in the deltoid area.

It may be helpful to view the CDC video 'How to administer a JYNNEOS vaccine intradermally'

2. *Previous smallpox vaccination*
The course is one 0.5ml dose SC in the deltoid area or 0.1ml ID in the volar (palmar) side of the forearm or in the deltoid area.

Those who are immunocompromised require two doses no less than 28 days apart **regardless of whether they have had previous smallpox vaccination**.

A person is fully immunised two weeks after the completion of a course.

13a.4 Recommendations

13a.4.1 Pre exposure prophylaxis for healthcare workers (including domestic staff etc.)

All healthcare workers (including e.,g., domestic and some laboratory staff) should follow recommended infection protection control (IPC) measures. Where possible, healthcare workers (including domestic staff etc.) who are immunocompromised or pregnant should not directly care for suspected or confirmed monkeypox cases.

While the priority is to ensure appropriate IPC measures are followed, the vaccine may provide additional protection depending on the nature and timing

of exposure risk. Designated healthcare and laboratory staff (including domestic staff etc.) who will be involved in the management of monkeypox cases or their samples should be offered vaccination.

13a.4.2 Pre exposure prophylaxis for those at high risk of infection

Those at high risk of infection should follow recommended IPC measures.

Pre-exposure prophylactic (PrEP) vaccination should be offered to those at high risk of infection e.g., gay, bisexual, men who have sex with men (gbMSM) and others at high risk of unprotected exposure. They could be identified from attendance at sexual health clinics with a recent history of multiple partners, attending commercial venues expressly for engaging in public sex (sex on premises venues) or using a proxy marker such as bacterial sexually transmitted infection in the past year. These are risk factors similar to those used to assess eligibility for HIV PrEP and should be applied regardless of HIV status.

The vaccine course should be administered to high risk individuals as soon as practicable.

13a.4.3 Post exposure prophylaxis

High and intermediate risk contacts within four days of last exposure to a laboratory confirmed case should be offered one dose of the vaccine. This may include healthcare workers (including domestic staff, etc.) caring for the case, and other contacts who have not previously been vaccinated.

The vaccine can prevent the onset of symptoms if given within four days of last exposure. If given within five to 14 days after the date of last exposure, it may reduce the symptoms but may not prevent the disease.

If there is a likelihood of ongoing exposure, those who have not had smallpox vaccination require a second dose given 28 days after the first.

13a.4.4 Prioritisation

If vaccine supplies permit, pre and post exposure prophylaxis should be offered as above.

In the event of limited vaccine supplies, priority should be given to the groups in the following order:

i. High risk contacts within 4 days of last exposure
ii. Intermediate risk contacts within 4 days of last exposure
iii. High and intermediate risk contacts from 5 to 14 days of last exposure
iv. Pre-exposure prophylaxis following individual risk assessment

13a.4.5 Prior to vaccination

Vaccine recipients should be given comprehensive information about the disease, the risks of contracting it, and the benefits and risks of the vaccine. They should be informed that they may develop adverse reactions similar to the prodromal symptoms of monkeypox infection during the first 48 hours after vaccination.

Contraindications

Anaphylaxis to any of the vaccine constituents (these include benzonase, chicken protein, ciprofloxacin, gentamicin and trometamol).

Intradermal administration is not recommended for those with a history of keloid scar formation. They should receive subcutaneous vaccination.

Precautions

Acute severe febrile illness - defer until recovery **unless the risks of deferral outweigh the low risks of vaccination**.

No interval is required between a COVID-19 or an influenza vaccine and a monkeypox vaccine. The vaccines should be given in different arms.

There should be an interval of four weeks between monkeypox/smallpox vaccine and a subsequent COVID-19 vaccine because of the unknown risk of myocarditis.

Immunocompromised

The vaccine can be administered subcutaneously or intradermally in those with immunocompromise aged 18 years and older, although the immune response may be lower than in those who are immunocompetent.

Pregnancy

There are limited data on the use of the vaccine in pregnancy. However, animal studies do not indicate harmful effects regarding reproductive toxicity. There is no theoretical reason for concerns in pregnancy and the adverse events profile is expected to be similar to that in non-pregnant vaccinees.

Consideration may be given to using the vaccine, a non replicating vaccine, in pregnancy for those at increased risk following individual benefit risk assessment.

Breastfeeding

Consideration may be given to using the vaccine, a non replicating vaccine, for those at increased risk who are breastfeeding following individual benefit risk assessment.

Children

The vaccine is not authorised for use in those under 18 years of age and safety and effectiveness have not been established. Based on clinical trials of vaccines using similar platforms, adverse events are expected to be similar to those in adults. As monkeypox may cause severe disease in children, the vaccine may be considered for use in children at increased risk following an individual risk assessment.

Adverse reactions

Subcutaneous (SC) administration

Local	*Very common*: injection site erythema, induration, pain, pruritus and swelling
	Common: injection site discolouration, haematoma, nodule, warmth
	Uncommon: injection site haemorrhage, irritation
	Rare: injection site anaesthesia, dryness, exfoliation, inflammation, movement impairment, paraesthesia, peripheral oedema, rash, vesicles
General	*Very common*: fatigue, headache, myalgia and nausea
	Common: appetite disorder, arthralgia, fever, pain in extremity, pyrexia, rigors/chills
	Uncommon: chest pain, cough, dermatitis, diarrhoea, dizziness, flushing, hepatic enzyme increased, lymphadenopathy, malaise, mean platelet volume decreased, musculoskeletal stiffness, nasopharyngitis, paraesthesia, pharyngolaryngeal pain, pruritus, rash, rhinitis, sleep disorder, troponin increased, underarm swelling, upper respiratory tract infection, vomiting, white blood cell count decreased
	Rare: asthenia, angioedema, axillary pain, back pain, conjunctivitis, contusion, dry mouth, ecchymosis, influenza, influenza like illness, hyperhidrosis, migraine, muscle spasms, muscular weakness, musculoskeletal pain, neck pain, night sweats, oropharyngeal pain, peripheral sensory neuropathy, sinusitis, skin discolouration, somnolence, subcutaneous nodule, tachycardia, vertigo, white blood cell count increased.

Similar rates of side effects are seen after either dose.

Those with atopic dermatitis may have higher rates of local and general adverse reactions following vaccination. In clinical trials of those with atopic dermatitis, 7% experienced exacerbation of their condition after vaccination.

Intradermal (ID) administration
A 2015 clinical study of the Jynneos vaccine evaluated the safety of a two-dose series of 0.1ml given ID compared to 0.5ml given SC.

The proportion of those with erythema, induration or itching 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 six or more months.

Pain at the injection site was less commonly reported and systemic reactions were similar to those after SC administration.

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