UK Health Security Agency

Recommendations for the use of pre and post exposure vaccination during a monkeypox incident

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Contents

Background

Monkeypox is a rare disease that is caused by infection with monkeypox virus, a DNA virus. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, it has emerged as the most important orthopoxvirus. Monkeypox occurs sporadically in central and western parts of Africa's tropical rainforest.

As monkeypox is related to the virus causing smallpox, vaccines designed for smallpox will likely provide a degree of cross-protection. Previous data from Africa suggests that previous vaccines against smallpox may be up to 85% effective in preventing monkeypox infection. In recognition of this protection, there is extant policy in the Green Book (Immunisation Against Infectious Diseases) (1) which recommends that:

"workers in laboratories where pox viruses (such as monkeypox or genetically modified vaccinia) are handled, and others whose work involves an identifiable risk of exposure to pox virus, should be advised of the possible risk and smallpox vaccination should be considered. Detailed guidance for laboratory staff has been prepared (Advisory Committee on Dangerous Pathogens and the Advisory Committee on Genetic Modification, 1990)".

Historically, first and second generation smallpox vaccines have been used for population-level and targeted occupational health-related immunisation programmes in the UK. These vaccines are reactogenic and associated with risks of other serious adverse events. The newer third generation smallpox vaccines have a much-improved side effect profile compared with first and second generation smallpox vaccines.

The modified vaccinia Ankara (MVA-BN) (Imvanex) vaccine, a third generation smallpox vaccine has been licensed by European Medicines Agency (2) in 2013 for the prevention of smallpox. In September 2019, the Food and Drug Administration (FDA) in the US approved MVA-BN (JYNNEOS) for the prevention of monkeypox as well as smallpox. Although not specifically licensed for the prevention of monkeypox in Europe, this vaccine has been used in the UK in response to previous incidents.

This document summarises the available data on MVA-BN (Imvanex) including from previous experience of use of this vaccine in contacts of monkeypox cases in the UK and details the current advice of an expert working group (see Appendix 1 for details) on the use of this vaccine for pre- and post-exposure use in England.

MVA-BN (Imvanex)

MVA-BN (Imvanex) is a third generation live modified vaccinia Ankara vaccine, manufactured by Bavarian Nordic (3). The virus used in the vaccine is attenuated through multiple passages in chicken embryo fibroblast cells, leading to a substantial loss of its genome. Many of the known

immune evasion and virulence factors are not encoded. 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 (4).

MVA-BN was approved for use in the European Union (EU) in 2013, for active immunisation against smallpox in adults. Currently, no other third generation smallpox vaccine is approved for use in the EU. Whilst the manufacturer has not sought an indication for monkeypox in the EU, MVA-BN is marketed as JYNNEOS in the USA and received FDA approval for prevention of small pox and monkeypox in September 2019 (5).

Efficacy

While MVA-BN efficacy studies were aimed at understanding its protective efficacy against smallpox, many of the licensing studies have been conducted using challenge with monkeypox virus.

In a macaque model, 2 doses of MVA-BN have been shown to induce 100% protection against a lethal challenge of aerosolised monkeypox (6) A separate study in cynomolgus macaques demonstrated no significant difference between the levels of neutralising antibody in animals vaccinated with ACAM2000 (a second-generation smallpox vaccine) and those vaccinated with 2 doses of MVA-BM (7).

Preclinical studies and phase I/II clinical trials of MVA-BN have suggested that 2 doses of vaccine are immunogenic generating antibody levels considered protective against smallpox, and by extrapolation, monkeypox as well. In a 2019 phase 3 efficacy trial published in the New England Journal of Medicine, 440 participants were randomly assigned to receive 2 doses of MVA followed by one dose of the established replicating-vaccinia vaccine ACAM2000 (the MVA group) or to receive one dose of ACAM2000 (the ACAM2000-only group). MVA vaccination induced a detectable response by week 2, with neutralising antibodies peaking at week 6 (GMTs 153.5). This compares with a lower peak GMT in the ACAM2000 group at week 4 (79.3). At day 14, the GMTs induced by a single MVA vaccination (16.2) was equal to that induced by ACAM2000 (16.2), and the percentages of participants with seroconversion were similar (90.8% and 91.8%, respectively) (8).

Previous MVA vaccination has also been shown to prevent formation of a full major cutaneous reaction in the majority of participants (77.0%) after subsequent ACAM2000 vaccination, as compared with a rate of full major cutaneous reaction of 92.5% after ACAM2000 alone. The maximum lesion area of the major cutaneous reaction was significantly reduced when ACAM2000 vaccination was preceded by MVA vaccination. These results are consistent with the findings observed in persons revaccinated with traditional smallpox vaccines, who were considered to be protected against smallpox on the basis of attenuation of the major cutaneous reaction (8).

There is very limited evidence on whether the vaccine can prevent or modify disease when given post-exposure. As the full course comprises 2 doses, post exposure vaccination is unlikely to completely prevent disease, but as some immunological response to the first dose can be detected within the first 2 weeks, rapid vaccination may modify disease severity for cases with longer incubation periods (2).

Antibody persistence and boosting

There are limited data on long-term immunogenicity. At 2 years after priming vaccination with 2 doses of MVA-BN in vaccinia naïve individuals, GMT for neutralisation antibodies had fallen to 1.3 and seropositivity had declined to 5.4%. This compares with a GMT of 22 and seropositivity of 77% observed in healthy vaccinia naïve individuals after the primary course. Two small clinical studies have demonstrated that MVA-BN is able to rapidly boost pre-existing immunological memory, induced by either licensed smallpox vaccines a long time ago or 2 years after MVA-BN. Following an MVA-BN boost 2 years after 2 doses of MVA-BN, GMT for neutralising antibodies at day 0 (pre-boost), 7 and 14 were one, 54 and 125, respectively and seropositivity was 5.4%, 92% and 99%, respectively. Two years after the booster dose, antibody levels persist for longer, with neutralising antibody GMT of 10.3 and seropositivity of 68.6% in previously vaccinated individuals (2, 6).

Following an MVA-BN boost in individuals who had received a live attenuated smallpox vaccine in the past, GMT neutralising antibodies and seropositivity were higher at baseline (day 0) at 22 and 77% and increased to 190 and 98% on day 14 (6).

Safety

Data from multiple clinical trials (9, 10, 11, 12, 13) show that MVA-BN has a favourable adverse event profile compared with first and second generation vaccines that have been studied in the pre- and post-eradication era (including the vaccines used to vaccinate groups of UK healthcare workers in 2003); this applies to common adverse events, such as local site reactions and influenza-like illness symptoms, as well as serious adverse events. The frequency of adverse events, particularly local site reactions, in smallpox vaccine-naïve individuals being vaccinated for the first time (with MVA-BN) does not appear to be significantly greater than the frequency of adverse events in revaccinees; this contrasts with the pattern observed with first and second generation vaccines (including those used in the UK). In the phase 3 clinical trial, there were fewer adverse events or adverse events of grade 3 or higher after both MVA vaccination periods in the MVA group than in the ACAM2000-only group (17 versus 64 participants with adverse events of grade 3 or higher, $P<0.001$) (8).

Use in children

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 Imvanex)

have been undertaken with a reassuring side effect profile. In a TB vaccine trial of approximately 1500 infants, aged approximately 5 to 6 months, MVA85A (14) at a dose of 1 x 10^8 pfu, this dose was very well tolerated. In a trial of 100 Gambian infants who received MVA85A (15) at a dose of 5 x 10^7pfu and in a further study of 100 infants who received MVA-malaria (16) at a dose of 1-2 x 10^8 pfu, there was a tolerable safety profile. 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.

Use in pregnancy

MVA-BN is not contraindicated in pregnancy. Although it has not formally been evaluated in pregnancy, animal studies (3 studies in female rats) identified no vaccine related fetal malformations. Use of MVA-BN in pregnant women is limited to fewer than 300 pregnancies without leading to any adverse events on pregnancy (6). 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 recommended for use in pregnancy, any theoretical risk needs to be weighed against the maternal risks of exposure to monkeypox in late pregnancy (such as risk of more severe disease from viral infections in third trimester) and any consequent fetal risks from maternal infection in early pregnancy.

Breast-feeding

MVA-BN is not contraindicated if breast-feeding. 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 monkeypox should therefore be offered vaccination, after discussion about the risks of monkeypox to themselves and to the breast-fed child.

Individuals with underlying medical conditions (including immunosuppression)

Individuals with atopic dermatitis are known to have developed more site-associated reactions and generalised symptoms following MVA-BN vaccination. A non-placebo controlled clinical trial found that erythema (61.2% versus 49.3%) and swelling at the injection site (52.2% versus 40.8%), headache (33.1% versus 24.8%), myalgia (31.8% versus 22.3%), chills (10.7% versus 3.8%), nausea (11.9% versus 6.8%), and fatigue (21.4% versus 14.4%) were all reported at a higher frequency in participants with atopic dermatitis than in healthy participants. In vaccinated clinical trial participants with atopic dermatitis, 7% experienced exacerbation of their condition during the course of the trials. Individuals in this group therefore need to have a risk assessment before being offered vaccination to balance the risk from exposure and the risk of side effects from vaccination (6).

The Committee for Medicinal Products for Human Use acknowledged that, compared with replication-competent smallpox vaccines, there would likely be a reduction in adverse reactions with MVA-BN, as this is largely replication-incompetent in humans. MVA-BN is therefore considered safe even in immunosuppressed individuals (17). Clinical trials on the use of MVA-BN including in immunocompromised individuals did not observe an increase in adverse events in this group (6). CDC recommends that MVA-BN can still be used in individuals who are severely immunosuppressed, for example those within 4 months of a haematopoietic stem-cell transplant (HSCT) and HIV-infected individuals with a CD4 count of less than 50 (18). However, specialist advice should be sought for these individuals prior to vaccination to ensure that the risk-benefit ratio remains in favour of vaccination at that time.

Table 1. Manufacturer recommendations for pre-exposure use of MVA-BN (6)

<table>
<tr><th></th><th>Individuals previously not vaccinated against smallpox</th><th>Individuals previously vaccinated against smallpox</th></tr>
<tr><td>General population (including people with atopic dermatitis)</td><td rowspan="2">0.5 ml subcutaneous injections
+
0.5 ml subcutaneous injections no less than 28 days later</td><td>0.5 ml subcutaneous injections</td></tr>
<tr><td>Immunocompromised population (including people with HIV)</td><td>0.5 ml subcutaneous injections
+
0.5 ml subcutaneous injections no less than 28 days later</td></tr>
</table>

Post-exposure prophylaxis for monkeypox (PEP)

The use of vaccination after an exposure to monkeypox may prevent or attenuate the infection. In the US, the Advisory Committee on Immunization Practices (ACIP) recommends that persons with an orthopoxvirus exposure should be evaluated by a health care provider and clinical management decisions, including post-exposure vaccination should be made on a case-by-case basis in consultation with public health authorities (19).

If vaccination is to be used, the CDC advises that smallpox vaccine be given within 4 days from the date of exposure to prevent onset of the disease but should be offered up to 14 days post-exposure. Administration of vaccine within 14 days of exposure, may reduce the symptoms of disease, but may not prevent disease (20). The CDC recommendations are based on their use of ACAM2000, which is a second-generation smallpox vaccine, with a different side-effect profile to MVA-BN (Imvanex).

Experience of use of MVA-BN vaccine in previous incidents in the UK

In 2018 and 2019, several cases of imported monkey pox were reported in the UK and MVA-BN vaccine was offered as part of the incident response, including to children. In 2018, 3 cases of monkey pox were diagnosed in the UK, and MVA-BN vaccine was offered as post exposure vaccination to 17 community contacts (uptake of 5 out of 17; 29%). No onward transmission was identified from the first case. A total of 147 individuals at occupational risk (including healthcare workers and decontamination staff) were offered MVA-BN, (uptake of 126 out of 147; 85.8%), demonstrating high acceptability of vaccine. Following PEP, one case was identified in a healthcare worker who had received post exposure vaccine 6 to 7 days after initial exposure. In 2019, following another imported case, 17 of 18 category 2 and 3 contacts accepted post exposure vaccination. In these incidents, young children, including infants, have received post exposure vaccine with no known adverse events.

Recommendations

On the basis of the current available evidence, an UKHSA (previously PHE) convened expert working group has made the following recommendations for the use of the MVA-BN vaccine during an incident.

Whilst the priority is to ensure appropriate PPE is worn, MVA-BN may be offered to provide additional protection, depending on the nature and timing of exposure risk, as described below. Details of the risk exposure classifications referred to below can be found in the Contact Management SOP in the duty doctors' pack and in Appendix 6.

1. Pre-exposure vaccination for occupational exposure

The majority of those at risk of occupational monkeypox exposure in the UK are likely to be naïve to smallpox. In line with current policy in the 'Green Book: Immunisation against Infectious Disease' (1), naïve individuals at risk of exposure on the basis of an occupational health assessment, pre-exposure vaccination with 2 doses of MVA-BN with a minimum interval of 28 days is recommended. This would include those HCWs due to care for a patient with confirmed monkeypox and those individuals undertaking environmental decontamination, even if they will be wearing full PPE.

Although data on use of MVA-BN in immunosuppressed patients is reassuring and the vaccine is not contraindicated in this group, individuals who are known to be severely immunosuppressed should not routinely participate in the care of a patient with a high consequence infectious disease, such as confirmed monkeypox, and therefore these groups are unlikely to require pre-exposure vaccination.

The complete vaccine course with MVA-BN in immunocompetent individuals is 2 doses given at least 28 days apart. In the event of an incident, it is highly unlikely that there will be sufficient time to offer pre-exposure vaccination with 2 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 on assessment of ongoing risk of exposure.

For individuals with a history of receiving a single dose of a live smallpox vaccine, a single dose of MVA-BN is recommended.

If vaccine cannot be given before commencing work with potential exposure to monkeypox, post-exposure use of vaccine is likely to be advised (see below).

Table 2 summarises MVA-BN vaccine recommendations based on prior vaccine history.

2. Post-exposure vaccination

Individuals should be risk assessed and offered post-exposure vaccination with a single dose of MVA-BN according to the Contact Management Matrix and SOP, available in the duty doctors' pack and Appendix 6.

Vaccination should be administered as soon as possible (ideally within 4 days) after an identified exposure to prevent or attenuate infection but can be administered up to 14 days post-exposure which may still theoretically attenuate disease if it occurs towards the end of the range of incubation period. If exposure has been intermittent or continuous, post-exposure vaccination should be ideally given within 4 days of the last exposure.

As the vaccine might only attenuate rather than prevent disease in some cases, contacts who have been vaccinated require equivalent follow up to those contacts who remain unvaccinated.

For individuals with a history of receiving a single dose of a live smallpox vaccine, a single dose of MVA-BN is recommended.

For individuals who have received a single dose of MVA-BN previously (regardless of timing), completion of the primary course is recommended. There is no need to restart the course.

For individuals who have received a previous live smallpox vaccine and one MVA-BN vaccine, no further doses are recommended.

For individuals who have received 2 doses of MVA-BN within the last 2 years, no further doses are recommended.

For individuals who have received 2 doses of MVA-BN more than 2 years ago, a single booster dose of MVA-BN is recommended.

Table 2 summarises MVA-BN vaccine recommendations based on vaccine history. See page 13.

a) Community exposure

Individuals with a community exposure should be offered post-exposure vaccination if they are in risk categories 2 and 3. Individuals with a category 1B exposure may also be offered vaccination, whilst vaccination is not usually required for category 1A exposures. (Appendix 6).

b) Occupational exposure

Individuals with an occupational exposure (for example HCWs or those undertaking environmental decontamination) should be offered post-exposure vaccination if they are in risk

categories 2 and 3. Individuals with a category 1B exposure may also be offered vaccination, whilst vaccination is not usually required for category 1A (Appendix 6).

Completion of the course with a second dose at least 28 days later should be considered on assessment of a foreseeable future risk through work beyond the current episode.

3. Laboratory workers

Risk of exposure will be dependent on the nature of the setting. For example, whilst laboratory workers in containment level 3 labs (for example UKHSA Porton staff) who will handle samples from suspected cases may have already be vaccinated, those working in routine diagnostic laboratories are likely to be naïve. Laboratory workers who experience category 2 or 3 exposures (see Appendix 6) should be offered vaccination, following an occupational health assessment.

Completion of the course with a second dose at least 28 days later should be considered on assessment of a foreseeable risk through work.

4. Individuals with underlying conditions

Individuals with skin conditions such as atopic dermatitis, should have an individual risk assessment carried out. Specialist advice should be sought prior to vaccination for individuals who are severely immunosuppressed (for example those within 12 months of HSCT, HIV-infected individuals with a CD4 count of less than 100) to balance the risks from an exposure, protection afforded by vaccination, and potential side effects from the vaccine.

5. Prioritisation of vaccine stock during an incident

When supplies are limited, vaccine should be prioritised according to whether it is for pre or post exposure use, the risk and timing of exposure and the ability to benefit. Vaccine should be prioritised for post exposure use in the order of risk exposure as summarised in Appendix 6.

Amongst the contacts being offered post exposure vaccination, those whose last exposure is within 4 days, should be prioritised over those exposed 4 to 14 days previously. This is because post exposure vaccination is likely to be most effective when given as soon as possible.
Once post exposure vaccination has been completed and if sufficient supplies allow, vaccine should then be offered to individuals completing their second or booster dose as part of a pre-exposure vaccine course.

6. Completing the primary vaccine course

The licensed primary course of MVA-BN comprises 2 doses, given at least 28 days apart.

If there is a foreseeable risk of subsequent occupational exposure to monkeypox, HCWs, laboratory workers, and individuals undertaking environmental decontamination in exposure categories 1B, 2 and 3, who have received one dose of MVA-BN either as pre- or post-exposure prophylaxis, should be offered a second dose at least 28 days after the first to complete the manufacturer-recommended schedule. This should be undertaken regardless of whether the incident is ongoing.

For those staff at occupational risk who have received a single dose of MVA-BN or a different smallpox vaccine at any time in the past, only one further dose of MVA-BN is required to complete the recommended schedule, with a minimum interval of 28 days between doses.

There is no requirement to restart the 2-dose schedule.

Individuals who received a single dose of vaccine as a result of community exposure, (regardless of exposure category), do not need to be offered a second dose as they do not have a foreseeable risk of further exposure to monkeypox and will be past the incubation period from the exposure that warranted post exposure vaccination.

Table 2 summarises the advice for the completion of MVA-BN course, see page 13.

7. Reinforcing (booster) doses

There are limited data to determine the need and timing of a booster dose after a 2-dose primary course of MVA-BN for those at ongoing occupational risk of monkeypox. Studies have demonstrated a rapid boosting response following a single booster in individuals who have completed a primary schedule, demonstrating ongoing memory and persistence of antibodies to 24 months.

Given the evidence of immunological memory from 2 priming doses and the incubation period of monkeypox, it is likely that adequately primed individuals will make a good response to natural exposure that will protect or reduce the severity of any breakthrough infection. As the response to a booster is good and leads to better persistence, however, a single booster dose at 2 years may be considered for pre exposure use in individuals who have received 2 doses of MVA-BN and are at ongoing high risk of occupational exposure or for post exposure use amongst contacts who have had a significant exposure (category 2 or 3). The data do not support giving a booster dose of MVA-BN in those who have had one dose of MVA-BN and a different smallpox live vaccine in the past. Table 2 summarises MVA-BN reinforcing dose (booster) recommendations based on prior smallpox vaccine history.

Long term immunogenicity studies are in progress. If a booster dose is considered necessary, then a single dose of 0.5 ml should be administered.

Table 2. Recommendation of MVA-BN vaccination and booster doses based on vaccine history for those at occupational foreseeable risk of exposure

	Immediate advice	Follow up at 28 days	Follow up at 2 years
No previous vaccine	first dose	second dose	boost
Previous live vaccine (not MVA-BN)	first dose	none	none
Previous single dose of MVA-BN	second dose	none	boost
Previous complete course of MVA-BN less than 2 years ago	none	none	boost
Previous complete course of MVA-BN 2 or more years ago	boost	none	none

See section 5 on prioritisation if supplies are limited.

8. Vaccine prescribing and administration

The vaccine is licensed in Europe for use against smallpox, so, as well as having the data to support safety and efficacy in accordance with the license, the vaccine will have been manufactured to a high standard and have undergone independent batch testing before release. As the vaccine does not have a marketing authorisation for protection against monkeypox in Europe, however, use for this indication would be considered ‘off-label’. Off-label use of vaccines and other medicines can be undertaken on the basis of additional evidence or expert opinion. In this instance, there is no alternative UK licensed vaccine for the management of monkeypox and the US FDA approval of MVA-BN for the management of monkeypox indicates that there is a sufficient rationale for using the medicine for this indication.

Furthermore, animal studies have demonstrated that vaccination with MVA-BN protected non-human primates from severe disease associated with a lethal challenge of monkeypox virus. Healthcare workers can therefore be reassured that prescribing and administering MVA-BN for monkeypox in accordance with these guidelines would be in line with best practice.

Where expert guidance practice supports the use of a medicine outside the terms of its licence, it is not always necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients or carers require or which they may see as relevant – a patient information leaflet is available for this purpose. The vaccine should be given by sub-cutaneous injection in a dose of 0.5ml.

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Appendices

1. Expert group membership
2. Smallpox immunisation consent form
3. Smallpox immunisation consent form (under 16s)
4. Imvanex vaccination: patient information leaflet
5. Smallpox immunisation record form
6. Monkeypox contact tracing classification and vaccination matrix

Appendix 1. Membership of the 2020 expert group

* Dr Mary Ramsay – Director of Public Health Programmes, including Immunisation, UKHSA; Honorary professor, London School of Hygiene and Tropical Medicine

* Professor Andrew Pollard – Chair of Joint Committee on Vaccination and Immunisation; Professor of Paediatric Infection and Immunity, University of Oxford

* Professor Thomas Evans, Chair of Advisory Committee on Dangerous Pathogens; Professor of Molecular Microbiology, University of Glasgow

Dr Michael Jacobs - Consultant and Honorary Associate Professor of Infectious Diseases, Royal Free Hospital

* Dr Gayatri Amirthalingam - Consultant Medical Epidemiologist and interim Deputy Director, Immunisation and Vaccine Preventable Diseases Division, UKHSA

Abhishek Katiyar - Senior Specialist Pharmacist, Royal Free Hospital

* Dr Sema Mandal - Consultant Medical Epidemiologist, Immunisation and Vaccine Preventable Diseases Division, UKHSA

* Members who reviewed 2022 update

Appendix 2. Smallpox immunisation consent form

Patient's name:	Date of birth (dd/mm/yy):
Patient's NHS number:	
Patient's address:	
Patient's GP:	
Organisation or department administering vaccine:	
Patient previously vaccinated with Imvanex® or other smallpox vaccine:	Yes ☐ No ☐
If yes, name of vaccine if not Imvanex®:	If yes, date of first dose (dd/mm/yy):
Organisation or department which administered first dose:	

[insert name of organisation] is offering Imvanex® (Modified Vaccinia Ankara - Bavarian Nordic; MVA-BN) to individuals who have recently been exposed to monkeypox virus.

Imvanex® is authorised by the European Medicines Agency for active immunisation against smallpox in adults. Although the vaccine is not licensed specifically for the prevention of monkeypox infection, it has been approved for this indication in the USA and has been used for this purpose in previous incidents in the UK. Monkeypox virus is closely related to the virus that causes smallpox, and smallpox vaccines are expected to protect people from getting monkeypox; however, the precise level and length of protection that Imvanex® provides against monkeypox is unknown. The recommended schedule for primary vaccination is 2 doses of Imvanex® given no less than 28 days apart.

It is believed that people can be infected with the monkeypox virus by 3 routes: by contact with an infected animal, by direct contact with an infected person, or by contact with material that has been contaminated by the monkeypox virus. The virus does not spread easily between humans. However, as a precautionary measure and after careful assessment, this vaccine is being offered to those individuals who may be at risk of developing monkeypox infection. It may not always be clear if someone has been exposed to monkeypox. In such situations, vaccination may be offered if contact with the virus cannot be ruled out.

A single dose of Imvanex® vaccine (injection) is being advised following a confirmed or suspected exposure to monkeypox. Although vaccination is thought to provide the greatest protection when given as soon as possible following contact, the vaccine may still be offered up to 14 days after the date of exposure.

Current stocks of Imvanex® (as of 11 May 2022) have an expiry date of September 2022.

For those at foreseeable occupational risk of monkeypox exposure, a second dose of Imvanex® is being offered at least 28 days after the first dose to complete the recommended schedule. Flu-like symptoms (refer to the separate information sheet) are a common side-effect of vaccination; however, serious side-effects are rarely observed. Any adverse reaction or illness following vaccination may require further medical assessment and if concerned, you should call your UKHSA contact point (if under follow-up) or clinic where you were vaccinated.

Please read the list of contraindications below and tell the person who is to administer the vaccine if any of these apply to you, prior to vaccination.

If you consent to the vaccination, please complete:

a) Have you had any allergies to immunisation in the past?
   Yes or no
b) Have you had any allergies to eggs or egg products (including chicken or feathers) in the past?
   Yes or no
c) Do you have any serious allergies?
   Yes or no

If yes, please specify

_____

d) Do you currently have a raised temperature or feel feverish?
   Yes or no
e) Do you have atopic dermatitis?
   Yes or no
f) Do you have a condition or are you receiving treatment that weakens the immune system?
   Yes or no
g) Are you pregnant?
   Yes or no

If you have answered yes to any of the above, please show this to the health professional before receiving the vaccine.

I have had the opportunity to read the information provided in this consent form and the information provided in the separate patient information leaflet.
I consent to be immunised with Imvanex® vaccine by [insert name of NHS organisation]

Patient's name:_____

Patient's signature:_____

Date (dd/mm/yy):_____

Appendix 3. Smallpox immunisation consent and record form for individuals under 16 years of age

Patient's name:	Date of birth:
Patient's NHS number: Patient's address: Patient's GP:	
Organisation or department administering vaccine:	

If you are not the person receiving the vaccine, please tick your relationship to them:	
	Mother
	Father
	Legal guardian
	Other (state relationship):

[Insert name of organisation] is offering Imvanex® (Modified Vaccinia Ankara - Bavarian Nordic; MVA-BN) to individuals who have recently been exposed to monkeypox virus.

Imvanex® is authorised by the European Medicines Agency for active immunisation against smallpox in adults. Although the vaccine is not licensed specifically for the prevention of monkeypox infection, it has been approved for this indication in the USA and has been used for this purpose in previous incidents in the UK. Monkeypox virus is closely related to the virus that causes smallpox, and smallpox vaccines are expected to protect people from getting monkeypox; however, the precise level and length of protection that Imvanex® provides against monkeypox is unknown. The recommended schedule for primary vaccination is 2 doses of Imvanex® given no less than 28 days after the first dose.

It is believed that people can be infected with the monkeypox virus by 3 routes: by contact with an infected animal, by direct contact with an infected person, or by contact with material that has been contaminated by the monkeypox virus. The virus does not spread easily between humans. However, as a precautionary measure and after careful assessment, this vaccine is being offered to those individuals who may be at risk of developing monkeypox infection. It may

not always be clear if someone has been exposed to monkeypox; in such situations, vaccination may be offered if contact with the virus cannot be ruled out.

A single dose of Imvanex® vaccine (injection) is being advised following a confirmed or suspected exposure to monkeypox. Although vaccination is thought to provide the greatest protection when given as soon as possible following contact, the vaccine may still be offered up to 14 days after the date of exposure.

Current stocks of Imvanex® (as of 11 May 2022) have an expiry date of September 2022.

For those at foreseeable occupational risk of monkeypox exposure, a second dose of Imvanex® is being offered at least 28 days after the first dose to complete the recommended schedule. Flu-like symptoms (refer to the separate information sheet) are a common side-effect of vaccination; however, serious side-effects are rarely observed. Any adverse reaction or illness following vaccination may require further medical assessment and, if concerned, you should call your UKHSA contact point (if under follow-up) or clinic where you were vaccinated.
Please read the list of contraindications below and tell the person who is to administer the vaccine if any of these apply to your child, prior to vaccination.

If you consent to the vaccination, please complete:

a) Has your child had any allergies to immunisation in the past?
   Yes or no
b) Has your child had any allergies to eggs or egg products (including chicken or feathers) in the past?
   Yes or no
c) Does your child have any serious allergies?
   Yes or no

If yes, please specify _____

d) Does your child currently have a raised temperature or feel feverish?
   Yes or no
e) Does your child have atopic dermatitis?
   Yes or no
f) Does your child have a condition or are you receiving treatment that weakens the immune system?
   Yes or no
g) Is the person receiving the vaccine pregnant?
   Yes or no

If you have answered yes to any of the above, please show this to the health professional before receiving the vaccine.

I have had the opportunity to read the information provided in this consent form and the information provided in the separate patient information leaflet.

I consent to be immunised with Imvanex® vaccine by [Insert name of NHS organisation]

Patient's name:_____

Patient's signature:_____

Date (dd/mm/yy):_____

I have had the opportunity to read the information provided in this consent form and the information provided in the separate information leaflet.

I consent for the child named above to be immunised with Imvanex vaccine by [Insert name of NHS organisation]

Parent or guardian's name:_____

Parent or guardian's signature:_____

Date (dd/mm/yy):_____

Date:	Type:	Maker:	Batch No.	Expiry:	Site:	Dose:	Route:	Given by:
		Bavarian Nordic				0.5 ml	s/c	

Vaccinator name [please print]:

_____

Appendix 4. Imvanex vaccination: patient information leaflet

IMVANEX suspension for injection

Smallpox vaccine (Live Modified Vaccinia Virus Ankara)

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you. Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor or nurse.

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

What IMVANEX is and what it is used for

MVA-BN (Imvanex) is a modified vaccinia Ankara vaccine, manufactured by Bavarian Nordic. It was initially developed to use for the prevention of smallpox. When a person is given the vaccine, the immune system (the body's natural defence system) will produce its own protection in the form of antibodies against the smallpox virus. IMVANEX does not contain smallpox virus and cannot spread or cause smallpox.

As monkeypox is cause by a virus similar to the one that causes smallpox, vaccines designed for smallpox are considered effective in preventing or reducing the severity of the monkeypox. Whilst this vaccine is not currently licensed for specific use against monkeypox in Europe, in September 2019, the vaccine received approval for use in the prevention of monkeypox from the US Food and Drug Administration. As this medicine (Imvanex) has been authorised by the European Medicines Agency for use as pre- and post-exposure prophylaxis for smallpox, the vaccine has been manufactured to a high standard and has undergone independent batch testing before release. the UK Health Security Agency (UKHSA) and the Joint Committee on Vaccination and Immunisation (JCVI) recommends its use in response to cases of monkeypox.

UKHSA recommends that Imvanex is offered to:

1. Persons who already have had a significant contact with a patient with confirmed monkeypox (post exposure). Post exposure vaccination with a single dose of vaccine should be offered as soon as possible after a significant contact to maximise the benefit from the vaccine.
2. Healthcare workers who are currently caring for and who are due to start caring for a patient with confirmed monkeypox (pre exposure). A single dose of vaccine should be offered as soon as possible to provide some immediate benefit, and should offer some longer term protection if the patient remains in care. A second dose after 4 weeks will be offered if the healthcare worker is at continued risk.

Although there is good evidence that a full course of vaccine should protect against monkeypox, the level and duration of protection from a single dose given after or around the time of exposure to the infection is less clear. The vaccine is offered because it has a good safety profile and may help to modify or reduce the symptoms of disease if given within 2 weeks of exposure.

Can you use IMVANEX for post exposure in children

When deciding whether it is appropriate to use smallpox vaccination to reduce the risk of a child developing monkeypox after exposure, it is important to consider both the risk of catching the disease and the risk of a child getting severe monkeypox.

The risk of catching the disease will depend on the level of physical contact with the case, or (if not touching) the closeness and duration of time spent near the case or in the rooms where a case has been.

The severity of disease appears to depend on which part of Africa the monkeypox virus originates from. The overall risk of dying is more than one in 9 for those who were identified as having caught monkeypox in Central Africa, compared to around one in 25 for those in West Africa. The true risk of dying if you catch monkeypox is probably much lower than has been reported because many milder cases are not diagnosed.

In children there is less data available. However, a large study of over 100 adult and child cases in Nigeria found that those who died were mostly adults, and/or were those who were HIV-positive, had a secondary skin infection or were very young (under 1 year old). This suggest that the risk to older children is low. However, there is also some evidence from Central Africa that children of all ages are at higher risk of more severe disease and death than adults when infected with monkeypox. Therefore, we cannot be very certain about the risk to children and we must assume the risk of severe disease is at least as high as in adults.

The vaccine has been not been used widely in children but vaccine based on the same virus have been used in large studies in babies and seem to work very well and have an acceptable

safety record. The vaccine has been given safely to children, including at least one infant, in the UK after previous cases.

What you need to know before you receive IMVANEX

You must not receive IMVANEX:

If you have previously had a sudden life-threatening allergic reaction to any ingredient of Imvanex (these are listed in section 6) including those present in the vaccine in very small amounts (or chicken protein, benzonase or gentamicin).

Warnings and precautions

If you are ill with a high temperature you will need to be assessed by your doctor to determine if you may be displaying early signs of monkeypox. If it is assessed that your illness is not related to monkeypox, you may still be offered the vaccine. The presence of a minor infection, such as a cold, should not require postponement of the vaccination, but talk to your doctor or nurse first.

You can be given this vaccine whether or not you have received smallpox vaccination in the past. Tell your doctor or nurse before you receive IMVANEX:

- if you have atopic dermatitis (see section 4)
- if you have HIV infection or any other condition or treatment leading to a weakened immune system

IMVANEX may not fully protect all people who are vaccinated.

Pregnancy and breast-feeding

If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, talk to your doctor. The virus in the vaccine does not grow well in the human body and so cannot spread to an unborn child or through breast milk. Although the vaccine is not routinely recommended in pregnancy, your doctor will discuss with you about the benefits in terms of preventing monkeypox which is likely to outweigh the any theoretical risks of giving you this vaccine.

Other medicines or vaccines and IMVANEX

Tell your doctor or nurse if you are taking or have recently taken any other medicines or if you have recently received any other vaccine.

Driving and using machines

There is no information on the effect of IMVANEX on your ability to drive or use machines. However, it is possible that if you experience any of the side effects listed in section 4, then some of these may affect your ability to drive or use machines (for example dizziness).

IMVANEX and sodium

This medicinal product contains less than 1mmol sodium (23 mg) per dose and is therefore essentially 'sodium-free'.

How IMVANEX is given

The vaccine will be injected under the skin, preferably into the upper arm, by your doctor or a nurse.

Side effects of IMVANEX

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Very common (may affect more than one in 10 people):

- headache
- aching muscles
- feeling sick
- tiredness
- pain, redness, swelling, hardness or itching at the injection site

Common (may affect up to one in 10 people):

- chills
- fever
- joint pain, pain in extremities
- loss of appetite
- discolouration, lump or bruising at the injection site

Uncommon (may affect up to one in 100 people):

- nose and throat infection, upper respiratory tract infection
- swollen lymph nodes
- abnormal sleep
- dizziness, abnormal skin sensations

- muscle stiffness, back pain, neck pain
- sore throat, runny nose, cough
- diarrhoea, vomiting, abdominal pain, dry mouth
- rash, itch, skin inflammation, skin discolouration
- warmth, bleeding, irritation, scaling, inflammation, abnormal skin sensation, reaction
- underarm swelling, flushing, chest pain, pain in the armpit
- bruising

Rare (may affect up to one in 1,000 people):

- sinus infection
- pink eye
- hives (nettle rash)
- skin bruising
- sweating
- night sweats
- lump in skin
- muscle cramps
- muscle pain
- muscle weakness
- swelling of the ankles, feet or fingers
- swelling of the face, mouth and throat
- faster heart beat
- spinning sensation (vertigo)
- migraine
- nerve disorder causing weakness, tingling or numbness, drowsiness
- rash, numbness, dryness, movement impairment, blisters at injection site
- weakness
- feeling unwell
- influenza-like illness

Other side effects

If you already have atopic dermatitis, you may experience more intense local skin reactions (such as redness, swelling and itching) and other general symptoms (such as headache, muscle pain, feeling sick or tired), as well as a flare-up or worsening of your skin condition. The most common side effects reported were at the site of injection. Most of them were mild to moderate in nature and resolved without any treatment within 7 days.

If you get any of the following side effects, tell your designated medical contact point.

Serious side effects

Contact a doctor immediately, or go immediately to the emergency department of your nearest hospital if you experience any of the following symptoms:

- difficulty in breathing
- dizziness
- swelling of the face and neck

These symptoms may be a sign of a serious allergic reaction.

Reporting of side effects

If you get any side effects, talk to your designated medical contact point. This includes any other symptoms not listed in this leaflet.

What IMVANEX contains

One dose (0.5 ml) contains modified Vaccinia Ankara – Bavarian Nordic Live virus, in chick-embryo cells.

Other ingredients are: trometamol, sodium chloride, and water for injections. It also contains residues of gentamicin and benzonase.

This leaflet was revised by UKHSA on 8 May 2022. Detailed information on this medicine is available on the European Medicines Agency website.

Appendix 5. Smallpox immunisation record form

Imvanex (Modified Vaccinia Ankara - Bavarian Nordic; MVA-BN)

Patient's name:	Date of birth:
Patient's NHS number:	
Patients address:	
Patient's GP:	
Organisation or department administering vaccine:	
Patient previously vaccinated with a smallpox vaccine:	Yes ☐ No ☐
If yes, name of vaccine if not Imvanex®:	If yes, date of first dose:
Organisation or department which administered first dose:	

Patient consent (see accompanying form)								
Consent form signed by patient: (please tick) Yes ☐ No☐								
Date:								
Date:	Type:	Maker:	Batch No.	Expiry:	Site:	Dose:	Route:	Given by:
		Bavarian Nordic				0.5 ml	s/c	

Vaccinator name (please print):

_____

As with any vaccine, adverse events may be observed in some individuals following Imvanex® vaccination. Imvanex® is a 'black triangle' medicinal product and the clinical organisation administering Imvanex® vaccine should assess and report clinical signs and symptoms that are reported following vaccination and which may represent vaccine-associated adverse events; this includes submitting a report via the MHRA Yellow Card Scheme, when indicated.

Appendix 6. Monkeypox contact tracing classification and vaccination matrix

Exposure risk category	Description	Risk	Surveillance	Recommendation for PEP	Example scenarios	Information sheets
3 Unprotected direct contact or high risk environmental contact	Direct exposure of broken skin or mucous membranes to symptomatic monkeypox case (once symptomatic), their body fluids or potentially infectious material (including on clothing or bedding) without wearing appropriate PPE[1] This includes: • inhalation of droplets or dust from cleaning contaminated rooms • mucosal exposure to splashes • penetrating sharps injury from contaminated device or through contaminated gloves • people who normally share a residence (either on a permanent or part time basis) with a person who has been diagnosed with monkeypox, and who have spent at least 1 night in the residence during the period when the case is infectious	High	Active monitoring Provide information and number for contact Daily communication with contact for 21 days after last exposure Self-isolation for 21 days, including exclusion from work No travel permitted Avoid contact with immunosuppressed people[2], pregnant women, and children aged under 12 where possible.	Offer MVA-BN vaccine (Imvanex®), ideally within 4 days (up to a max. 14 days)	Body fluid in contact with eyes, nose, or mouth Penetrating sharps injury from used needle Contact in room during aerosol-generating procedure without appropriate respiratory PPE[1] Changing a patient's bedding without appropriate PPE[1] Sexual contact Household contact	See active follow up category 3 information sheet See monkeypox isolation for symptomatic contacts sheet
2 Unprotected exposure to infectious materials including droplet or airborne potential route	Not category 3 but: Intact skin-only contact with a symptomatic monkeypox case, their body fluids or potentially infectious material or contaminated fomite **or** Passengers seated directly next to case on plane **or** No direct contact but within one metre of symptomatic monkeypox case without wearing appropriate PPE[1]	Medium	Active monitoring Provide information and number to contact Daily communication with contact for 21 days after last exposure Avoid contact with immunosuppressed people[2], pregnant women, and children aged under 12 where possible. Exclude from work for 21 days if work involves contact with immunosuppressed people[2], pregnant women or children aged under 12 (not	Offer PEP with MVA-BN vaccine (Imvanex®), ideally within 4 days (up to a max. 14 days)	Clinical examination of patient before diagnosis without appropriate PPE[1] Entering patient's room without wearing appropriate PPE[1] and within 1 metre of case Driver and passengers in shared car or taxi with case, or sitting next to case on plane Subsequent patients in consulting room after a confirmed case was seen and prior to room cleaning	See active follow up category 2 information sheet If symptoms develop see monkeypox isolation for symptomatic contacts sheet

Exposure risk category	Description	Risk	Surveillance	Recommendation for PEP	Example scenarios	Information sheets
			limited to healthcare workers) Discuss travel on a case by case basis if asymptomatic			
1-B Protected physical or droplet exposure	Not category 3 or 2 but: Contact with confirmed monkeypox case or environment contaminated with monkeypox while wearing appropriate PPE[1] (with no known breaches)	Low	Passive monitoring Provide information sheet and number to contact Can continue with routine activities and travel as long as asymptomatic	Offer PEP with MVA-BN vaccine (Imvanex®)[3], ideally within 4 days (up to a max. 14 days)	Healthcare staff working in HCID specialist unit wearing appropriate PPE[1] Person undertaking decontamination of rooms where a confirmed case has stayed while wearing PPE[1]	See passive follow up information sheet
1-A No physical contact, unlikely droplet exposure	Not category 3, 2 or 1B but: Community contact between 1 and 3 metres of a symptomatic case **or** Healthcare worker (HCW) involved in care of monkeypox case who is not wearing appropriate PPE[1] for contact between 1 and 3 metres and has had no direct contact with contaminated objects **or** Passengers seated within 3 rows from case on plane	Low	Passive monitoring Provide information sheet and number to contact Can continue with routine activities and travel as long as asymptomatic	PEP not usually required.	Staff entering patient room without PPE[1] AND a. without direct contact with patient or their body fluids **and** b. maintaining a distance of more than 1 metre from patient Passengers who have been seated within 3 rows, but not directly next to, a case on plane	See passive follow up information sheet
0 No contact	Not category 3,2 or 1A or 1B: No known contact with symptomatic monkeypox case in last 21 days **or** Passengers seated more than 3 rows away from case on plane **or** Laboratory staff operating to UK standards handling specimens relating to a monkeypox case	None	None	PEP not required	Passengers seated away from case on plane (i.e. more than 3 rows away) Staff handling specimens in a UK laboratory to UK standards	See general information sheet

Notes

1. Full PPE includes as a minimum: FFP3 respirator, long sleeved gown, gloves and eye protection as per the National infection prevention and control manual for England (page 57).
2. Severely immunosuppressed patients, as per Green Book definition.
3. If MVA-BN vaccine (Imvanex) supplies are limited, follow prioritisation advice.
4. Data on median incubation periods for monkeypox is limited and may be influenced by factors including type of exposure. This guidance may be subject to revision as further data is accrued.

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation heath secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

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