

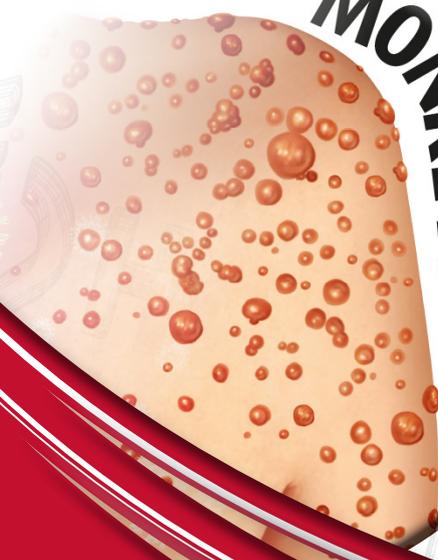


**Superior
Health Council**

VACCINATION STRATEGY AGAINST MONKEYPOX

**JUNE 2022
SHC No 9720**

**MONKEY
POX**



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Federal Public Service Health, Food Chain Safety
and Environment

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ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9720

Vaccination strategy against Monkeypox

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendation of vaccination strategy against Monkeypox in the context of the European multi-country outbreak in May 2022.

This version was validated by the NITAG on 01 June 2022
This version was validated by the Board on 01 June 2022¹

I INTRODUCTION AND ISSUE

The Superior Health Council (SHC) received an urgent request for advice on Monday 23 May 2022 from the Risk Management Group (RMG). The question is whether it is recommended (or not) to vaccinate people in the context of Monkeypox (MPX)' European multi-country outbreak in May 2022. If so, who and when and with which vaccine.

On 20 May 2022, the Risk Assessment Group (RAG) of Sciensano transferred to the Council a primary risk assessment "MONKEYPOX MULTI-COUNTRY OUTBREAK, MAY 2022" making a first synthesis of the available data on epidemiology, severity (self-limited disease), risk of spread in Belgium (low) and internationally (high), preparedness and surveillance measures and actions. This living document served as a scientific basis for this report:

[Monkeypox \(wiv-isp.be\)](https://www.wiv-isp.be)

On 23 May 2022, the European Centre for Disease Prevention and Control (ECDC) has published a rapid risk assessment available here:

<https://www.ecdc.europa.eu/en/publications-data/risk-assessment-monkeypox-multi-country-outbreak>

The SHC would like to emphasise some preventive measures **because the vaccine's availability is limited at this time**. The key messages from the ECDC and the RAG of Belgium are **strongly supported by the SHC to try to contain (at least in Europe) the cases that are currently occurring**. This is a realistic goal given the low transmission observed. However, this will not solve the long-term issue in countries where MPX is still endemic.

As of 25 May, a total of 118 confirmed MPX cases have been reported from 12 EU/EEA Member States (Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, The Netherlands, Portugal, Slovenia, Spain, Sweden - ECDC, 25/05/2022).

MPX can spread through **close, personal, often direct skin-to-skin contact** with MPX rash, sores or scabs, **through respiratory droplets** or **viral fluid** from a person with MPX and

¹ The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

through contact with objects, fabrics (clothing, bedding or towels), and surfaces that have been used by someone with MPX – formites (ECDC, 2021).

Transmission **through aerosols** (animal models, Zaucha et al., 2001) is unlikely, but warrant further study. Patients with complex exposures were more likely than patients with noninvasive exposures (aerosols) to have experienced pronounced signs of systemic illness (49.1% vs. 16.7%; $P = 0.41$) and to have been hospitalized during illness (68.8% vs. 10.3%; $P < 0.001$). Complex exposures were also associated with shorter incubation periods (9 days for complex exposures vs. 13 days for noninvasive exposures) and the absence of a distinct febrile prodrome. The findings of this study indicate that route of infection can influence MPX illness manifestations (Reynolds et al., 2006).

The predominance, in the current outbreak, of diagnosed human MPX cases **among men having sex with men (MSM)**, and the nature of the presenting lesions in some cases, suggest transmission occurred during intimate (close) contact and/or sexual intercourse. A cooperation with the German Armed Forces High Security Laboratory shows the first indications are that MPX could also be transmitted **through blood and semen** (not published yet in a peer-reviewed journal, German expert opinion, mass media communication).

Based on ECDC's epidemiological assessment, **the likelihood of MPX spreading in persons having multiple sexual partners in the EU/EEA is considered high and (very) low in the broader general population** (ECDC, RAG, 2021).

Although most cases in current outbreaks have presented with **mild disease symptoms**. Mainly in low incomes countries, MPX virus may cause severe disease in certain population groups (**young children, pregnant women, immunosuppressed persons**). However, the likelihood of cases with severe morbidity cannot be accurately estimated yet in high incomes countries. The overall risk is assessed as **moderate for persons having multiple sexual partners** (including some groups of MSM) and **low for the broader population** (particular attention must be taken in family and residential settings with close contact interactions). Treatment is mainly symptomatic and supportive, including prevention and treatment of secondary bacterial infections.

Smallpox vaccine can be considered **for post-exposure prophylaxis of close contacts at increased risk for severe disease**, however careful benefit/risk assessment should be performed for the exposed individual. Important information on the use of currently available smallpox vaccines is missing for groups at increased risk for severe disease.

In addition, **antivirals and human vaccinia immunoglobulin (accessibility in Belgium?) are potential treatment options for severe cases**.

EU/EEA countries should focus on prompt identification, management, contact tracing and reporting of new MPX cases. Countries should update their contact tracing mechanisms, their diagnostic capacity for orthopoxviruses and review the availability of smallpox vaccines, antivirals and personal protective equipment (PPE) for health professionals.

An interim case definition is proposed for case reporting. Guidance for the management of MPX cases and close contacts is also included.

Cases should remain **isolated, avoiding contact with immunosuppressed persons and pets, abstaining from sexual activity and close physical contact from the start of the symptoms until full healing of the skin lesions** (falling off of the crusts, which indicates the end of infectiousness). Most cases can remain at home with supportive care.

Close contacts of MPX cases should **self-monitor for the development of symptoms (appearance of skin lesions and/or fever) up to 21 days from the last exposure to a case.**

Healthcare workers should wear appropriate PPE (gloves, water-resistant gown, eye protection, FFP2 respirator, etc.) when screening suspected cases or caring for a MPX case. **Laboratory personnel** should also take appropriate precautions to avoid occupational exposure (PPE, hood, etc.).

Close contacts of a MPX case should be deferred from blood, organ or bone marrow donations for a minimum of 21 days from the last day of exposure.

Proactive risk communication and multiple community engagement activities should be carried out to increase awareness, provide updates and guidance to those at increased risk and the wider public. Risk communication messages should stress that MPX is spread through close contact between people, especially in the same household, potentially including the sexual route. **A balance should be kept between informing those most at risk but also communicating that the virus does not spread easily between people the risk to the broader population is (very) low** (particular attention must be taken in family and residential settings with close contact interactions).

There is a potential risk of **human-to-animal transmission in Europe**, therefore close intersectoral collaboration between human and veterinary public health authorities working from a 'One Health' perspective is needed to manage exposed pets and prevent the disease from being transmitted in wildlife. EFSA (European Food Safety Authority) is not aware to date of any reports on infections in animals (pets or wild animals) in the EU.

Several unknowns still exist regarding this outbreak and ECDC will continue to monitor developments closely and update the risk assessment as new data and information become available.

The issue of vaccination strategy from smallpox vaccines - ACAM2000® and MVA-BN® - Modified Vaccinia Ankara - Bavarian Nordic; Imvanex® (EU) - Imvamune® (CA) - Jynneos® (US) in the context of the European multi-country outbreak of Monkeypox in May 2022 was referred to the Belgian National Immunization Technical Advisory Group (NITAG).

II CONCLUSIONS AND RECOMMENDATIONS

1 CONCLUSIONS

1. The SHC would like to emphasise preventive measures because the vaccine's availability is limited at this time. The key messages from the ECDC and the RAG of Belgium are thus strongly supported by the SHC.

2. MPX is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. But, severe cases occur (mainly in low incomes countries) more commonly among **children, immunocompromised population (particularly persons with an active (low CD4 count) Human Immunodeficiency Virus – HIV; Ogoina et al., 2020) and pregnant women.** Particular attention is needed for Very- and High-Risk Contacts (V- and HRC, cf. 1.1 for definition) in connexion with these people. The targeted groups at higher risk should also include e.g. **sex workers and sexual and gender minorities (MSM, transgender, etc.).**

3. The case fatality ratio of MPX has historically ranged from 0 to 11% in the general population and has been higher among young children in low incomes countries. **In recent times, the case fatality ratio has been around 3 - 6%** (Central African 10.6% (95% CI: 8.4% – 13.3%) vs. West African 3.6% (95% CI: 1.7% – 6.8%; Bunge et al., 2021)). The West African clade (outbreaks in EU) appears to cause less severe disease compared to the Congo Basin clade. **The likelihood of cases with severe morbidity cannot be accurately estimated yet in high incomes countries.**

4. The overall risk is assessed as **moderate to high for persons having multiple sexual partners** (including some groups of MSM) and **(very) low for the broader population** (particular attention must be taken in family and residential settings with close contact interactions). Treatment is mainly symptomatic and supportive, including prevention and treatment of secondary bacterial infections.

5. The incubation period (time from infection to symptoms) for MPX is usually 7–14 days but **can range from 5–21 days.** MPX is not considered contagious during its incubation period, but transmission 2 days (or more) before the start of the symptoms cannot be excluded and should be further studied (RAG, 2021).

6. No smallpox vaccine is authorised for use against MPX in the EU (of label use), but the 3rd generation smallpox vaccine Imvanex® has been authorised by EMA for the EU market against smallpox. MVA-BN® has shown protection in primate models challenged with lethal doses of MPX virus. Indication against MPX has thus been granted for MVA-BN® in the US and Canada. The smallpox vaccine can be used for **post-exposure prophylaxis (PEP)** of close contacts at increased risk for severe disease (cross-protection) and in a larger scale as pre-exposure prophylaxis or to control clusters.

7. **The vaccine effectiveness of 85%** of smallpox vaccines against MPX virus, reported by international agencies (WHO, GAVI, CDC, ECDC websites), is based on studies in the 1980s describing the protective effect of smallpox vaccine against MPX infection (Fine et al., 1988, MacCollum et al., 2009). **This data was generated with first and second generation of the vaccine and can't be directly extrapolated to MVA-BN® vaccine.**

8. The smallpox vaccine, if **administered within the first 4 days after exposure to a confirmed MPX case** can have protective effect (Fenner et al., 1988). CDC recommends that the vaccine be given within 4 days from the date of exposure in order to prevent onset of the disease. If given between 4 - 14 days after the date of exposure, vaccination may reduce the symptoms of disease, but may not prevent the disease.

<https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html>

9. Based on the safety profile and ease of administration, the SHC recommends to **use only the third generation smallpox vaccine MVA-BN®** (like Imvanex® - EU - cf. 3.1 for more details and EPAR) when indicated (see below).

- **Situations when PCR+ cases or Very- and High-Risk Contacts of a PCR+ case are in close connexion with** children, immunocompromised population (particularly persons with an active (low CD4 count) Human Immunodeficiency Virus – HIV) and pregnant or breast-feeding women are particularly at risk of severe disease. If vaccine supplies are insufficient in Belgium, these situations should be prioritised for PEP vaccination.
- **If an immunosuppressed individuals, a pregnant or breast-feeding women or a child are a Very- and High-Risk Contacts, they could be vaccinated after discussion with their physician.** The physician will assess whether the possible benefit in terms of preventing MPX would outweigh the potential risks of giving this vaccine (individual B/R balance must be done).

MVA-BN® is considered safe even in immunosuppressed individuals

The vaccinia virus in Imvanex® cannot replicate in human cells and hence is less likely to cause side effects than conventional smallpox vaccines. **Imvanex® would therefore be beneficial for people who cannot be given vaccines containing replicating viruses, such as patients with a weakened immune system.** The Committee for Medicinal Products for Human Use and CDC acknowledged that, compared with replication-competent smallpox vaccines, there would likely be a reduction in adverse reactions with MVA-BN®, as this is replication-incompetent in humans (UKHSA, 2021).

The use of MVA-BN® vaccine during pregnancy and breast-feeding women **should be avoided (EPAR – no sufficient data on safety and efficacy)**

However, the physician will assess whether the possible benefit in terms of preventing MPX would outweigh the potential risks of giving this vaccine. MPX is a risk in all trimesters of pregnancy. Any theoretical risk needs to be weighed against exposure to MPX. Fetal risks are present in all trimesters of pregnancy since the virus is transmitted from mother to infant through the placenta resulting in fetal death. Complications in pregnant women are mainly seen in the end of pregnancy. As it is a non-replicating vaccine, there is theoretically no reason for concerns in pregnancy and the adverse events profile would be expected to be similar to that in non-pregnant vaccinees (UKHSA, 2021).

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 MPX should therefore be offered vaccination, after discussion about the risks of MPX to themselves and to the breast-fed child (UKHSA, 2021).

For children who would be eligible, the 3rd generation vaccine MVA-BN® is not currently licensed (EPAR – no sufficient data on safety and efficacy).

The adverse event profile with MVA-BN® would be expected to be identical to the profile with tuberculosis and malaria candidate vaccines and therefore provides some reassurance of its use in children (UKHSA, 2021).

10. Tecovirimat SIGA® was recently approved by EMA for treatment of orthopoxviruses (including MPX), but it is not available in Belgium yet. Studies using a variety of animal species have shown that Tecovirimat is effective in treating orthopoxvirus-induced disease, but data on its effectiveness in treating human cases of MPX are not available. Human clinical trials indicated the drug was safe and tolerable with only minor side effects. Treatment with Tecovirimat could be considered for immunocompromised patients if available (Sciensano-RAG, 24/05/2022).

2 RECOMMENDATIONS

As a reminder, in 2015, the SHC advocated considering the value of vaccinating specific professional groups who might be exposed to the virus (pre-exposure prophylaxis). This consideration was to be done in consultation with the authorities responsible for the smallpox plan and with the relevant professional associations (SHC 9283, 2015).

<https://www.health.belgium.be/fr/lettre-9283-vaccination-antivariolique>

In view of the above conclusions and general considerations, the SHC recommends vaccination with Imvanex® vaccine (**2 doses at 28 days of interval; under the skin (S.C. - subcutaneous), preferably in the upper arm**; see 3.1 for more details) **preferably within 4 days** after exposure to a PCR confirmed MPX case.

Routine, mandatory smallpox vaccination has been suspended in Belgium since 1976 (SHC 9283, 2015). According to the epidemiological data and available Imvanex® vaccine supply, the SHC recommends that **only individuals who have not previously received a childhood smallpox vaccine are currently eligible for MPX vaccination** (Taub et al., 2018; Bartlett et al., 2003).

- In cases of immunodeficiency (of any origin), this recommendation does not apply even if pediatric smallpox vaccination has occurred as a child. Immunocompromised patients (e.g. HIV infected, patients under immunosuppressive therapy) who have been previously vaccinated against smallpox should receive two booster doses. The second booster vaccination should be given no less than 28 days after the first dose (EPAR).
- If we observe an increase of MPX in people already vaccinated in childhood and if we have sufficient vaccines, one booster dose could be considered in some particularly exposed or at risk groups like Health Care Workers (HCW).

The risk groups to be vaccinated are defined according to different scenario's, listed here below:

Scenario 1: in the coming month – very low vaccine supply

- Progressive cessation in Belgium of cases related to the Darklands festival and the Belgian Pride in Brussels;
 - Some positive cases imported via travel to Belgium;
 - Short transmission chains observed;
 - No massive increase of cases in neighbouring countries;
- Contact with medical doctor or an Emergency Department to allow diagnostic and contact tracing as much as possible;
- Classical measures of tracing, quarantine and isolation;
- **No systematic vaccination of VHRC and HRC** (exceptions can be made on an individual basis and on medical advice);
- Provide the opportunity for HCW and specific occupational groups (health care professionals investigating a possible case, etc.) **who have been exposed (as post-exposure prophylaxis) to the virus**, to have early access to the vaccine especially if they are in the following categories:
- HCW who had contact with MPX case (lesions or prolonged face-to-face contact) without appropriate PPE;
 - HCW or other persons who suffered a sharps injury or was exposed to MPX case body fluids or aerosol generating procedure without PPE;
 - Laboratory staff suffering exposure to occupational accident with virus-containing sample (splash, sharp or aerosol exposure etc) without PPE;

Scenario 2: within the next month – low to moderate vaccine supply

- Long and persistent chains of transmission linked to the Darklands festival and the Belgian Pride;
 - Appearance of several endogenous cases not linked to recent travel or to a known case or event with cases;
 - Separate clusters not easily linked via tracing;
 - Long transmission chains in Belgium and EU countries;
- **Post-exposure prophylaxis vaccination** of HCWs and specific occupational groups (health care professionals investigating a possible case, etc.) **who have been exposed to the virus**, to have early access to the vaccine especially if they are in the following categories:
- HCW (caregivers) of a MPX case and HCW who had contact with MPX case (lesions or prolonged face-to-face contact) without appropriate PPE;
 - HCW or other persons who suffered a sharps injury or was exposed to MPX case body fluids or aerosol generating procedure without PPE;
 - Laboratory staff suffering exposure to occupational accident with virus-containing sample (splash, sharp or aerosol exposure etc) without PPE;
 - Staff of the Sexually transmitted disease (STD) testing centers.

→ Systematic vaccination as **post-exposure prophylaxis (PEP)** of all:

- Very-high-risk contacts (VHRC)
 - Sexual partner(s);
 - Person(s) with prolonged skin to skin contact while the patient had a rash, sore or srabs.
- High-risk contacts (HRC)
 - Person(s) living in same household, or similar setting (e.g camping, overnight sleeping etc);
 - Person(s) sharing clothing, bedding, utensils etc, while the patient had a rash;
 - Co-passenger seated one -two seats distance around a case who was symptomatic, in airplane, bus or train ≥ 3 hours duration. This time period is set arbitrarily because there is no scientific evidence to guide the decision. It might be adapted if new information is available.

The SHC recommends that **the responsibility for moving from one scenario to another be given to the RAG (Sciensano)** who tracks case progress and tracing data in real time.

At this moment, the probability of further spread of MPX among the broader population in the coming months is assessed as very low leading to an overall low risk for the general population, therefore vaccination of a broader population is not recommended by the SHC (ECDC, 2022).

The SHC will adapt these preliminary recommendations according to the new epidemiological and clinical data available and stresses the importance of having (HAS, 20/05/2022):

- More precise data on the mode of human-to-human transmission for currently identified cases;
- Follow-up data on the epidemic ;
- Additional real-life data on the efficacy and safety of the 3rd generation smallpox vaccine, administered pre- and post-exposure to the MPX virus, on the prevention of severe forms and on the transmission of the disease;
- Data on the efficacy and safety of a booster dose in people who were vaccinated against smallpox in childhood.

Scenarios 3 and 4 are closer to mass vaccination. However, we do not have sufficient data to support such strategy now (Vaccine Effectiveness, safety, etc.) and sufficient vaccine. These preliminary reflexion for scenarios 3 and 4 are just for information and for anticipation duty. In case of an exponential increase in cases, strategies should be revised according to the epidemiology and availability of vaccines.

Scenario 3 (unlikely): in the coming months, there is an exponential increase in cases

→ Systematic vaccination of all risk groups with or without contact with a PCR+ case:

- HCW;
- Multiple sex partners and Sex workers;
- Sexual and gender minorities (MSM, transgender, etc.);
- Immunocompromised population (particularly persons with an active (low CD4 count) Human Immunodeficiency Virus – HIV **particularly persons with Human Immunodeficiency Virus - HIV**);
- Children (out of label use !; **with close B/R balance evaluation and risk of contacts evaluation**);
- Pregnant women (out of label use !; **with close B/R balance evaluation and risk of contacts evaluation**);

Scenario 4 (highly unlikely): in the coming months, there is an exponential increase in cases, hospitalizations and deaths

- Systematic vaccination of the entire Belgian population, starting with people who have never been vaccinated against smallpox and the groups most at risk of death and hospitalization, depending on the evolution of the epidemiological data and the available vaccine stocks.
- Only one booster dose if people have been vaccinated during childhood against smallpox before 1976.

III METHODOLOGY

After analysing the request, the Board and the Chair of the area Vaccination identified the necessary fields of expertise and decided to treat this urgent request by mail.

The issue of vaccination strategy from smallpox vaccines - ACAM2000® and MVA-BN® - Modified Vaccinia Ankara - Bavarian Nordic; Imvanex® (EU) - Imvamune® (CA) - Jynneos® (US) in the context of the European multi-country outbreak of Monkeypox in May 2022 was referred to the NITAG which included experts in vaccinology, geriatrics, general medicine, pediatrics, microbiology, infectiology and epidemiology. The experts provided a general and an ad hoc declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the available scientific literature published in both scientific journals (peer-reviewed), and reports from national (RAG-RMG, 24/05/2022) and international (ECDC, 23/05/2022; EMA-EPAR Imvanex®, 12/04/2022; FDA-ACAM2000®, 23/03/2019) organisations competent in this field as well as on the opinion of the experts.

Once the advisory report was endorsed by the NITAG by email and it was ultimately validated by the Board on 01/06/2022.

Keywords

Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Prevention	Preventie	Prévention	Verhütung
Vaccination	Vaccinatie	Vaccination	Impfung
Men having Sex with Men, MSM	Mannen die Seks hebben met Mannen, MSM	Hommes ayant des rapports Sexuels avec des Hommes, HSH	Männer, die Sexualverkehr mit Männern haben, MSM
Multiple sexual partners	Meerdere seksuele partners	Partenaires sexuels multiples	Mehrere Sexualpartner
High Risk Contacts, HRC	Contacten met hoog risico	Contacts à haut risque	Kontakte mit hohem Risiko
Smallpox	Pokken	Variole	Pocken
Monkeypox	Apenpokken	Variole du singe	Affenpocken

List of abbreviations used

AMM	<i>Autorisation de Mise sur le Marché</i> - Marketing Authorisation procedures
CMI	Cell-Mediated Immunity
ECDC	European Centre for Disease Prevention and Control - EU
EFSA	European Food Safety Authority - EU
EMA	European Medicines Agency - EU
FDA	Food and Drug Administration - US
GHSI	Global Health Security Initiative - G7+
HAS	Haute Autorité de Santé - FR
HCW	Health Care Worker
HCSP	<i>Haut Conseil de la santé publique</i> - FR
HIV	Human Immunodeficiency Virus
HRC	High Risk Contacts
LRC	Low Risk Contacts
MPX	Monkeypox
MSM	Men having Sex with Men
MVA-BN®	Modified Vaccinia Ankara - Bavarian Nordic; Imvanex®-Imvamune®-Jynneos®
NITAG	National Immunization Technical Advisory Group
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PPE	Personal Protective Equipment
RAG	Risk Assessment Group - BE
RMG	Risk Management Group - BE
SC	Subcutaneous injection
SEIR	Susceptible-latent-infectious-recovered models
SHC	Superior Health Council - BE
SNS	Strategic National Stockpile
STAKOB	Permanent working group of competence and treatment centers for diseases caused by highly pathogenic pathogens – DE
STD	Sexually transmitted disease
UKHSA	UK Health Security Agency - UK
VHRC	Very-high-risk contacts

IV ELABORATION AND ARGUMENTATION

1 Epidemiology- transmission and High Risk Contacts (HRC)

MPX is a zoonotic disease caused by an orthopoxvirus, and results in a smallpox-like disease in humans. Since MPX in humans was initially diagnosed in 1970 in the Democratic Republic of the Congo, it has spread to other regions of Africa (primarily West and Central), and cases outside Africa have emerged in recent years. A systematic review of peer-reviewed and grey literature on how MPX epidemiology has evolved, with particular emphasis on the number of confirmed, probable, and/or possible cases, age at presentation, mortality, and geographical spread has been recently published. The authors identified 48 peer-reviewed articles and 18 grey literature sources for data extraction. The number of human MPX cases has been on the rise since the 1970s, with the most dramatic increases occurring in the Democratic Republic of the Congo. **The median age at presentation has increased from 4 (1970s) to 21 years (2010–2019).** There was an overall case fatality rate of 8.7%, with a significant difference between clades - **Central African 10.6% (95% CI: 8.4%– 13.3%) vs. West African 3.6% (95% CI: 1.7%– 6.8%).** Since 2003, import- and travel-related spread outside of Africa has occasionally resulted in outbreaks. Interactions/activities with infected animals or individuals are risk behaviors associated with acquiring MPX. The review shows an escalation of MPX cases, especially in the highly endemic Democratic Republic of the Congo, a spread to other countries, and a growing median age from young children to young adults. **These findings may be related to the cessation of smallpox vaccination, which provided some cross-protection against MPX,** leading to increased human-to-human transmission. The appearance of outbreaks beyond Africa highlights the global relevance of the disease. Increased surveillance and detection of MPX cases are essential tools for understanding the continuously changing epidemiology of this resurging disease (Bunge et al., 2022).

MPX can spread through **close, personal, often direct skin-to-skin contact** with MPX rash, sores or scabs, **through respiratory droplets** or **viral fluid** from a person with MPX and **through contact with objects, fabrics (clothing, bedding or towels), and surfaces** that have been used by someone with MPX – fomites (ECDC, 2021).

Transmission **through aerosols** (animal models, Zaucha et al., 2001) is unlikely, but warrant further study. Patients with complex exposures were more likely than patients with noninvasive exposures (aerosols) to have experienced pronounced signs of systemic illness (49.1% vs. 16.7%; $P = 0.41$) and to have been hospitalized during illness (68.8% vs. 10.3%; $P < 0.001$). Complex exposures were also associated with shorter incubation periods (9 days for complex exposures vs. 13 days for noninvasive exposures) and the absence of a distinct febrile prodrome. The findings of this study indicate that route of infection can influence MPX illness manifestations (Reynolds et al., 2006).

1.1 High Risk Contacts (HRC) classification

Human-to-human transmission of MPX occurs through close contact with infectious material from skin lesions of an infected person, and also through respiratory droplets in prolonged face-to-face contact and through fomites.

The predominance, in the current outbreak, of diagnosed human MPX cases **among men having sex with men (MSM)**, and the nature of the presenting lesions in some cases, suggest transmission occurred during intimate (close) contact and/or sexual intercourse (ECDC, 23/05/2022).

A cooperation with the German Armed Forces High Security Laboratory shows the first indications are that MPX could also be transmitted **through blood and semen** (not published yet in a peer-reviewed journal, German expert opinion, mass media communication).

The following groups are defined as high risk contacts (HRC) by RAG, ECDC and RMG:

Very-high-risk contacts (VHRC)

- Sexual partner(s);
- Person(s) with prolonged skin to skin contact while the patient had a rash, sore or scabs.

High-risk contacts (HRC)

- Person(s) living in same household, or similar setting (e.g camping, overnight sleeping etc);
- Person(s) sharing clothing, bedding, utensils etc, while the patient had a rash;
- HCW (caregivers) of a MPX case and HCW who had contact with MPX case (lesions or prolonged face-to-face contact) without appropriate PPE;
- HCW or other persons who suffered a sharps injury or was exposed to MPX case body fluids or aerosol generating procedure without PPE;
- Laboratory staff suffering exposure to occupational accident with virus-containing sample (splash, sharp or aerosol exposure etc) without PPE;
- Staff of the Sexually transmitted disease (STD) testing centers.
- Co-passenger seated one -two seats distance around a case who was symptomatic, in airplane, bus or train ≥ 3 hours duration. This time period is set arbitrarily because there is no scientific evidence to guide the decision. It might be adapted if new information is available.

Low-risk contacts (LRC)

All other contacts (including social interactions, work colleagues, persons sharing fitness equipment, etc.) are considered low risk contacts.

Healthcare-associated transmission of monkeypox has been observed on multiple occasions in areas where the disease is endemic. Data collected by the US CDC from an ongoing CDC-supported program of enhanced surveillance in the Tshuapa Province of the Democratic Republic of the Congo, where the annual incidence of human monkeypox is estimated to be 3.5-5/10,000, **suggests that there is approximately one healthcare worker infection for every 100 confirmed monkeypox cases**. Herein, we describe a study that commenced in February 2017, the intent of which is to evaluate the effectiveness, immunogenicity, and safety of a third-generation smallpox vaccine, MVA-BN® (IMVANEX®, IMVAMUNE®), in healthcare personnel at risk of MPX virus infection. The authors describe procedures for documenting exposures to MPX virus infection in study participants, and outline lessons learned that may be of relevance for studies of other investigational medical countermeasures in hard to reach, under-resourced populations (Petersen et al., 2019).

1.2 ECDC 23/05/2022

As of 25 May, a total of 118 confirmed MPX cases have been reported from 12 EU/EEA Member States (Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, The Netherlands, Portugal, Slovenia, Spain, Sweden - ECDC, 25/05/2022).

<https://www.ecdc.europa.eu/en/news-events/epidemiological-update-monkeypox-multi-country-outbreak>

Table 1. Number of confirmed cases by country, EU/EEA, as of 25 May 2022

	Confirmed cases
Austria	1
Belgium	4
Czech Republic	1
Denmark	1
France	5
Germany	5
Italy	5
The Netherlands	6
Portugal	37
Slovenia	1
Spain	51
Sweden	1
Total	118

On 7 May 2022, the United Kingdom reported an imported case of MPX in a person travelling from Nigeria. The case reported developing a rash-like illness on 29 April 2022 and travelled from Lagos to London on 3-4 May. The diagnosis was confirmed by monkeypox virus PCR (Polymerase Chain Reaction) on a vesicular swab on 6 May by the UK Health Security Agency (UKHSA) Rare and Imported Pathogens Laboratory. On 13 May 2022, the UK reported two further cases of MPX who are part of the same family and not linked to the single imported case from Nigeria which was notified on 7 May. The cases were confirmed by PCR testing on vesicle swabs. A third family member had previously developed a rash but recovered fully. None of the individuals in this cluster had travelled or had contact with anyone with a relevant travel history.

On 15 May 2022, the UK reported four additional cases of MPX, confirmed by PCR. None of these cases have known epidemiological links to the imported case from Nigeria (notified on 7 May) or to the family cluster (notified on 13 May). The four cases were MSM and presented with a vesicular rash-like illness. They were identified through attendance at genitourinary medicine clinics. The cases are being managed in high risk infectious diseases units in the UK.

On 18 May 2022, two additional cases (also MSM) were reported, one in London and one in the South-East of England.

On 20 May 2022, 11 additional cases were reported by the UKHSA, and bring the total number of MPX cases confirmed in England to 20. All cases reported in the UK have been confirmed as caused by the MPX virus West African clade.

Starting from the 18 May, multiple EU/EEA Member States reported additional suspected or confirmed cases:

- On 18 May, Portugal reported 14 cases of MPX virus confirmed by real-time PCR in the Lisbon and Tagus River Valley Region. All cases were men with a clinical presentation of rash (some ulcerative), fever, myalgia and asthenia. None of the cases needed hospitalisation. On 20 May, nine additional confirmed cases were reported, bringing the total number of confirmed cases to 23. In two cases, the west African clade was identified.
- On 19 May, Spain reported seven confirmed and 23 suspected cases of MPX, all among men. On 20 May, 16 additional confirmed cases were reported. On 22 May, seven more cases were confirmed, with 39 new suspected cases under investigation.
- On 19 May, Belgium reported a confirmed case in a man with travel history to Lisbon, Portugal. His partner developed similar symptoms and was confirmed on the 20 May. As of 22 May, a total of four confirmed cases had been reported.
- On 19 May, Germany confirmed its first case in a man with travel history to Spain and Portugal. On 20 May, two more confirmed cases were reported.
- On 20 May, France reported its first confirmed case in a man with no travel history, with three additional cases under investigation.
- On 20 May, Italy reported one confirmed case of MPX in a man who required hospitalisation and had travel history to Spain. On 21 May, two further confirmed cases were reported.
- On 18 May, Sweden reported a confirmed case in a man.
- On 20 May, the Netherlands reported one confirmed case, a man with travel history to Belgium.
- On 22 May, Austria reported its first confirmed case.

Etc.

<https://www.ecdc.europa.eu/en/publications-data/risk-assessment-monkeypox-multi-country-outbreak>

1.3 Sciensano - RAG 24/05/2022

This living document served as a scientific basis for this report: [Monkeypox \(wiv-isp.be\)](https://www.wiv-isp.be/monkeypox)

On the 19/5, a first confirmed case of MPX has been reported in Belgium, in a man, HIV positive, presenting with fever and papules on 10/05. He had unprotected sex with several men in Lisbon between 6 and 8 May. The regular partner of the man also developed symptoms on 19/5 (flu-like illness and cutaneous lesions), test results are pending. Since the index case had multiple unprotected (unidentifiable) sexual contacts at a Gay festival (Darklands, 6,000 participants) 2 days before presenting symptoms and due to international links between MSM communities, more cases can be expected in the coming days/weeks.

On 20/05, a third case was identified in Leuven, in a MSM who also attended the Darklands festival and presented at the emergency ward with cutaneous lesions on 19/5. More suspected cases are under investigation. The likelihood for further spread in Belgium outside the MSM community is estimated to be low because of the moderate transmissibility of the virus. However, infections among close contacts could occur.

On 24/05, a total of 6 confirmed cases have been reported and 1 probable (no PCR test performed yet). All cases are in MSM up to now. The first case reported could genomically be linked to the outbreak in Portugal, with further spread to his partner. All the other cases identified could be linked to one single event. More cases can still be expected.

The likelihood for further spread in Belgium outside the MSM community is estimated to be low because of the moderate transmissibility of the virus. However, infections among close contacts could occur.

Data will be regularly updated in the coming weeks !

Since cases have been reported in at least 5 countries (EU countries and UK) among MSM and in the context of the highly interconnected sexual networks among MSM, together with the start of the MSM events season with large number of participants (including the Belgian Pride the weekend of 21/05 in Brussels), it can be expected that there will be cases reported in other countries.

The likelihood for further (inter)national spread is high
(probably more in the MSM group)

2 Monkeypox: signs and symptoms

2.1 WHO fact sheet, 19/05/2022

<https://www.who.int/news-room/fact-sheets/detail/monkeypox>

The incubation period (interval from infection to onset of symptoms) of MPX is usually from 6 to 13 days but **can range from 5 to 21 days**.

The infection can be divided into two periods:

1. The invasion period (lasts between 0 - 5 days) characterized by fever, intense headache, lymphadenopathy (swelling of the lymph nodes), back pain, myalgia (muscle aches) and intense asthenia (lack of energy). **Lymphadenopathy is a distinctive feature of MPX** compared to other diseases that may initially appear similar (chickenpox, measles, smallpox).

2. The skin eruption usually begins within 1 - 3 days of appearance of fever. The rash tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face (in 95% of cases), and palms of the hands and soles of the feet (in 75% of cases). Also affected are oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%), as well as the cornea. The rash evolves sequentially from macules (lesions with a flat base) to papules (slightly raised firm lesions), vesicles (lesions filled with clear fluid), pustules (lesions filled with yellowish fluid), and crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off.

MPX is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases occur **more commonly among children (in low incomes countries)** and are related to the extent of virus exposure, patient health status and nature of complications. **Underlying immune deficiencies** may lead to worse outcomes. Although vaccination against smallpox was protective in the past, today **persons younger than 40 to 50 years of age** (depending on the country) may be more susceptible to MPX due to cessation of smallpox vaccination campaigns globally after eradication of the disease. Complications of MPX can include secondary infections, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision. The extent to which asymptomatic infection may occur is unknown.

The case fatality ratio of MPX has historically ranged from 0 to 11% in the general population and has been higher among young children in low incomes countries. **In recent times, the case fatality ratio has been around 3 - 6%** (Central African 10.6% (95% CI: 8.4% – 13.3%) vs. West African 3.6% (95% CI: 1.7% – 6.8%; Bunge et al., 2021)). The West African clade (outbreaks in EU) appears to cause less severe disease compared to the Congo Basin clade. **The likelihood of cases with severe morbidity cannot be accurately estimated yet in high incomes countries.**

2.2 Sciensano - RAG 24/05/2022

This living document served as a scientific basis for this report: [Monkeypox \(wiv-isp.be\)](https://www.wiv-isp.be)

Typical or classical human MPX often begins with a combination of fever > 38°5 C, headache, chills, asthenia, localized or generalized, lymph node swelling, back pain and muscle aches. Commonly, within one to three days after onset of fever, the patient develops a rash, which tends to first appear on the face and then spreads to other parts of the body, including hands and feet. The cutaneous lesions often first present as macules, evolving successively to papules, vesicles, pustules, crusts and scabs. The number of lesions may range from a few to thousands. Cutaneous lesions generally all appear at the same stage which is a hallmark characteristic of smallpox and MPX, and distinguishes them from chickenpox.

Based on clinical information for the cases in the UK and in Portugal, and particularly in sexually active people, the clinical presentation seems atypical, with cutaneous lesions more predominant in the genital area (perianal), and not all at the same stage. More ulcerations have also been reported, possibly because of the place of the lesions. For most people, MPX is a self-limited disease, typically lasting two to four weeks and resulting in complete recovery, but in some cases, MPX can be more severe, requiring hospitalization. Illness severity is influenced by the route of infection. Onset of perianal or genital lesions in the absence of subjective fever has been reported by CDC. <https://www.cdc.gov/poxvirus/monkeypox/response/2022/index.html>

The West African clade appears to cause less severe disease compared to the Congo Basin clade. In Africa, the case-fatality rate of MPX ranges from 1% to 10%.

The case fatality ratio of MPX has historically ranged from 0 to 11% in the general population and has been higher among young children in low incomes countries. **In recent times, the case fatality ratio has been around 3 - 6%** (Central African 10.6% (95% CI: 8.4% – 13.3%) vs. West African 3.6% (95% CI: 1.7% – 6.8%; Bunge et al., 2021)). **The West African clade (outbreaks in EU) appears to cause less severe disease compared to the Congo Basin clade (could be even lower in high incomes countries?).**

In low incomes countries, severe cases occur more commonly among **children** and **immunocompromised population, particularly persons with HIV**, and are related to the extent of virus exposure, patient health status and severity of complications. <https://www.who.int/emergencies/disease-outbreak-news/item/monkeypox-democratic-republic-of-the-congo>

Particular attention is needed for HRC in contact with **young children, pregnant women** and **immunocompromised persons**. The targeted groups at higher risk should also include e.g. **sex workers** and **transgender**.

In a retrospective review of hospital records of 40 human MPX cases from Nigeria, the majority developed fever and self-limiting vesiculopustular skin eruptions. Five deaths were reported. Compared to human immunodeficiency virus (HIV)–negative cases, HIV type 1–coinfected cases had more prolonged illness, larger lesions, and higher rates of both secondary bacterial skin infections and genital ulcers. There were 9 HIV type 1 (HIV-1)/MPX-coinfected patients, including 4 with newly diagnosed HIV-1 infection and 5 patients previously on antiretroviral therapy. Three of these 5 cases had apparently failed first-line antiretroviral therapy and their CD4 cell counts at hospitalization were 101, 354, and 357 cells/μL, respectively. The case with a CD4 count of 357 cells/μL had a viral load of 4.798 copies/mL. Three of the 4 newly diagnosed HIV cases had CD4 counts of 20, 55, and 300 cells/μL. CD4 cell counts and HIV viral loads were not available for other patients at the time of this report (Ogoina et al., 2020).

3 Vaccination against Smallpox and Monkeypox

3.1 Smallpox vaccination (data mainly for first and second generation vaccines : DryVax® and ACAM2000®)

When administered prior to exposure to smallpox virus, vaccinia vaccine has historically had an efficacy in the range of 90.7%–96.7%. Vaccination within the first few days (perhaps as late as 4 days) after exposure to smallpox virus may prevent or significantly ameliorate subsequent illness (Fenner et al., 1988).

Neutralizing antibodies and evidence of cell-mediated immunity (CMI) may persist for ≥ 30 years after primary (first-time) vaccination, **but it is not known what serologic markers correlate with protection against infection**. Prior to smallpox eradication, immunity to smallpox in countries where it was endemic resulted from the combined effects of vaccination and exposure to variola virus that led only to subclinical disease (variola sine eruptione). Data from countries where smallpox virus was introduced after a prolonged absence does show that having been vaccinated many years before is at least partially protective against a fatal outcome. Among patients who were infected with smallpox after it had been imported into Europe, ~52% of those who had never been vaccinated died, whereas only 11.1% of those vaccinated >20 years previously died. **Best estimates are that an increased level of protection against smallpox persists for at least 3 years after primary vaccination and that substantial but waning immunity may persist for ≥ 10 years** (Bartlett et al., 2003).

In another study, Taub and collaborators (2018) show that vaccinated participants maintained antivaccinia IgG and neutralizing antibody titers above 3 natural logs **essentially indefinitely**. The absolute titer of antivaccinia antibody was only slightly higher after multiple vaccinations. In 97% of the participants, no decrease in vaccinia-specific antibody titers was noted with age over a follow-up period of up to 88 years. Moreover, Baltimore Longitudinal Study of Aging participants who survived active smallpox infections in their youth retained antivaccinia antibody titers that were similar to the levels detected in vaccinated subjects. These data suggest that **multiple or recent vaccinations are not essential to maintain vaccinia-specific antibody responses in human subjects. Scarce vaccine supplies should be applied first to individuals who have not previously been vaccinated.**

Compared with other currently available vaccines in the United States, the smallpox vaccine has a higher rate of local reactions (95%), systemic reactions (20%–40%), and serious or life-threatening reactions (15–50 reactions per million persons vaccinated). The CDC recently published an extensive review of adverse events associated with smallpox vaccinations, which includes guidance for their management (CDC, 2003).

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5204a1.htm>

Frequency of adverse events due to smallpox vaccination in 1968 (CDC).

Class of event, event	No. of events per million vaccinees			
	National survey [24]		Ten-state survey [25]	
	All primary ^a vaccinees	Vaccinees ≥1 year old	All primary ^a vaccinees	Vaccinees ≥1 year old
Serious but not life-threatening reactions				
Inadvertent inoculation	25.4	27.1	529.2	532.0
Generalized vaccinia	23.4	17.7	241.5	222.8
Erythema multiforme	NA	NA	164.6	131.3
Total	48.8		935.3	
Life-threatening reactions				
Postvaccinial encephalitis	2.9	2.4	12.3	8.6
Progressive vaccinia (vaccinia necrosum)	0.9	1.0	1.5	1.7
Eczema vaccinatum	10.4	10.6	38.5	41.5
Total	14.2		52.3	
Death	1.1	0.6	1.5	NR

NOTE. Table reproduced, with slight modifications, from Centers for Disease Control and Prevention Web site (<http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp>). Data are from [24–26]. NR, none reported.

^a I.e., first-time vaccinees.

Contraindications to Smallpox Vaccination (CDC)

In the event of confirmed, imminent, or likely exposure to the smallpox virus, there are no absolute contraindications to vaccinia vaccination. However, in the current circumstances, given the potential for serious adverse reactions to the vaccine, there are number of risk groups for which vaccination is contraindicated. According to CDC recommendations, the following conditions and therapies are contraindications for smallpox vaccination at this time.

1. Pregnancy or intended pregnancy within 4 weeks after vaccination
2. Immunodeficiency
 - a. HIV infection (at any stage or CD4 count)
 - b. Congenital or acquired immunodeficiency disorder
 - c. Organ, marrow, or stem cell transplantation
 - d. Generalized malignancy
 - e. Leukemia
 - f. Lymphoma
 - g. Agammaglobulinemia
 - h. Autoimmune diseases
3. Immunosuppressive therapy
 - a. Long-term corticosteroid therapy (≥20 mg/day of prednisone [or equivalent dose of other steroids, including topical and inhaled steroids] for ≥14 days)
 - b. Radiotherapy
 - c. Antimetabolite therapy

- d. Alkylating agent therapy
- e. Chemotherapy
- f. Therapy with immunomodulatory medications for patients with organ transplants or autoimmune diseases: for example, corticosteroids, azathioprine, mycophenolate mofetil, cyclosporin, tacrolimus, and etanercept
- 4. Eczema/atopic dermatitis (active disease or prior history)
- 5. Skin diseases (active) or lesions
 - a. Burns
 - b. Wounds
 - c. Contact dermatitis
 - d. Recent surgical incisions
 - e. Chickenpox
 - f. Shingles
 - g. Herpes
 - h. Psoriasis
 - i. Darier disease
 - j. Severe acne
- 6. Conjunctival or corneal diseases; florid inflammation or pruritic lesions of the eye
- 7. Allergy to a component of DryVax (polymyxin B, streptomycin, chlortetracycline, neomycin, or phenol)
- 8. Contact: close contact with a person with any of the conditions listed here (i.e., household contact)

Some health care institutions and public health agencies have also chosen to exclude persons who have not been previously vaccinated, because of the higher risk of serious adverse events, and/or persons living with children <1 year of age, because of the higher risk of contact vaccinia.

3.2 Monkeypox vaccination

There is no vaccine available specifically for vaccination against MPX. However, the smallpox vaccine can be used for **post-exposure prophylaxis (PEP)** of close contacts at increased risk for severe disease (cross-protection) and in a larger scale as (pre-exposure prophylaxis) preventive measure. JYNNEOS® (only available in US) is a vaccine indicated for prevention of smallpox **and MPX disease** in adults 18 years of age and older determined to be at high risk for smallpox or MPX infection.

<https://www.fda.gov/vaccines-blood-biologics/jynneos>

The vaccine effectiveness of 85% of smallpox vaccines against MPX virus, reported by international agencies (WHO, GAVI, CDC, ECDC websites), is based on studies in the 1980s describing the protective effect of smallpox vaccine against MPX infection (Fine et al., 1988, MacCollum et al., 2009). **This data was generated with first and second generation of the vaccine and can't be directly extrapolated to MVA-BN® vaccine.**

The smallpox vaccine, if **administered within the first 4 days after exposure to a confirmed MPX case** can have protective effect (Fenner et al., 1988). CDC recommends that the vaccine be given within 4 days from the date of exposure in order to prevent onset of the disease. If given between 4 - 14 days after the date of exposure, vaccination may reduce the symptoms of disease, but may not prevent the disease.

<https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html>

3.3 ACAM2000® (FDA, 23/03/2018 – second generation vaccine)

FDA licensed Smallpox (Vaccinia) Vaccine, Live, with the proprietary name ACAM2000®, for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

The vaccine is manufactured by Sanofi Pasteur Biologics Co. The approval and availability of **this second-generation smallpox vaccine** in the Strategic National Stockpile (SNS) enhances the emergency preparedness of the United States against the use of smallpox as a dangerous biological weapon.

Currently, designated U.S. military personnel receive the vaccine. In addition, laboratory researchers working on certain pox viruses are also be eligible to receive the vaccine. The vaccine is not recommended for use by the general population, as there is no smallpox disease in the world.

⇒ Link to FDA: <https://www.fda.gov/vaccines-blood-biologics/vaccines/acam2000-smallpox-vaccine-questions-and-answers>

The vaccine is made from a virus called **vaccinia, which is a "pox"-type virus related to smallpox but causes milder disease**. ACAM2000® cannot cause smallpox; it does not contain the smallpox virus, but rather **the "live" vaccinia virus - not dead virus like many other vaccines**. **For this reason, attentively caring for the vaccination site is important to prevent the virus from spreading from the vaccination site to other parts of the body, or to other people.**

ACAM2000® is administered differently than the typical "shot" associated with most vaccinations. **A two-pronged stainless steel (or bifurcated) needle is dipped into the vaccine solution and the skin is pricked several times in the upper arm with a droplet of the vaccine**. The virus begins growing at the injection site causing a localized infection or "pock" to form. A red, itchy sore spot at the site of the vaccination within 3-4 days is an indicator that the vaccination was successful; that is, there is "a take." A blister develops at the vaccination site and then dries up forming a scab that falls off in the third week, leaving a small scar. The vaccine stimulates a person's immune system to develop antibodies and cells in the blood and elsewhere that can then help the body fight off a real smallpox infection if exposure to smallpox ever occurs.

ACAM2000® also was found to be acceptable as a booster in those previously vaccinated for smallpox.

The vaccine may cause **myocarditis and pericarditis**, which are inflammation and swelling of the heart and surrounding tissues and can be very serious. Based on clinical studies, myocarditis and/or pericarditis occur in 1 in 175 adults who get the vaccine for the first time.

In the ACAM2000® clinical trial experience, seven individuals of the 2,983 ACAM2000® first-time recipients and three individuals of the 868 Dryvax® first-time recipients were suspected to have myocarditis/pericarditis. There were no cases in those subjects who had been vaccinated previously.

Serious health problems, including those that are life-threatening, can also occur in unvaccinated people who are accidentally infected by someone who has recently received the vaccine. In particular, unvaccinated people who are pregnant, or have problems with their heart or immune system, or have skin problems like eczema, dermatitis, psoriasis, and have close contact with a vaccine recipient are at an increased risk for serious problems

if they become infected with the vaccine virus, either by being vaccinated, or by being in close contact with a person who was vaccinated.

It is very important for the ACAM2000® recipient to properly care for the vaccination site to prevent the virus in the vaccine from spreading and infecting another part of the body and other people.

A healthcare provider may decide not to give ACAM2000® if a person has a weakened immune system (e.g., leukemia, HIV, AIDS, transplant recipients, people with cancer that has spread, and those undergoing treatment with medicines that suppress the immune system such as steroids, prednisone, and cancer drugs). In addition, healthcare providers may decide not to vaccinate individuals with skin conditions such as eczema, dermatitis or psoriasis who are at increased risk of complications.

These types of serious adverse events are similar to those that occurred in the past with other smallpox vaccines.

More commonly observed side effects include: itching, sore arm, fever, headache, body ache, mild rash and fatigue.

Severe Immune Deficiency

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. **Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000®.** These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation.

Pregnancy

ACAM2000® has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and fetal death. **If ACAM2000® is administered during pregnancy, the vaccinee should be apprised of the potential hazard to the foetus.** Pregnant women who are close contacts of vaccinees may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

The evolution of the normal local reaction to primary smallpox vaccination (Bartlett et al., 2003).

Day(s) after vaccination	Event and/or lesion
0	Vaccination
3–4	Papule
5–6	Vesicle with or without erythema
8–9	Pustule
≥12	Crust forms and becomes a scab
17–21	Scab detaches and leaves a scar

NOTE. Data are from [19].

3.4 IMVANEX® (EMA-EPAR, 12/04/2022 – third generation vaccine)

The **3rd generation smallpox vaccine** Imvanex® (Modified Vaccine Ankara-MVA) has been authorised by EMA for the EU market against smallpox (EMA, 2022).

⇒ Link to EPAR: [Imvanex | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/EPAR/imvanex/imvanex.htm)

Imvanex® is a vaccine used to protect against smallpox in adults. It contains a **live modified form** of the vaccinia virus (**a non-replicative virus**) called 'vaccinia Ankara', which is related to the smallpox virus.

Imvanex® is given by injection **under the skin (S.C. - subcutaneous), preferably in the upper arm**. People who have not been previously vaccinated against smallpox should receive two 0.5 ml doses, with the second dose given at least 28 days after the first.

If a booster dose is necessary for those who have been vaccinated against smallpox in the past, a single 0.5 ml dose should be given except for patients with a weakened immune system (the body's natural defences) who should receive two booster doses, with the second dose given at least 28 days after the first.

It is not yet known how long the protection will last.

The most common side effects with Imvanex® (**which may affect more than 1 in 10 people**) are headache, nausea, myalgia (muscle pain), tiredness and injection site reactions (pain, redness, swelling, hardening and itching). Imvanex must not be used in patients who are hypersensitive (allergic) **to the active substance or any of the substances found at trace levels, such as chicken protein, benzonase and gentamicin**.

Immunocompromised

The vaccinia virus in Imvanex® **cannot replicate in human cells** and hence is less likely to cause side effects than conventional smallpox vaccines. **Imvanex® would therefore be beneficial for people who cannot be given vaccines containing replicating viruses, such as patients with a weakened immune system**.

Data have been generated in Human Immunodeficiency Virus (HIV) infected individuals with CD4 counts ≥ 100 cells/ μ l and ≤ 750 cells/ μ l. Lower immune response data have been observed in HIV infected individuals compared to healthy individuals. There are no data on the immune response to Imvanex® in other immunosuppressed individuals.

Pregnancy and breast-feeding

The use of this vaccine during pregnancy and breast-feeding **is not recommended**. However, the physician will assess whether the possible benefit in terms of preventing smallpox would outweigh the potential risks of giving this vaccine.

More specific references on Imvanex®

Clinical Review Memo

<https://www.fda.gov/media/131078/download> (pp 5-6, 196)

Phase 3 Clinical Trial

<https://clinicaltrials.gov/ct2/show/NCT01913353>

https://www.nejm.org/doi/10.1056/NEJMoa1817307?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed

Animal study, e.g.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2072046/pdf/nihms30252.pdf>

1) 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® (Modified Vaccinia Ankara - Bavarian Nordic, Imvanex®) 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.

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.** Clinical trials on the use of MVA-BN® including in immunocompromised individuals did not observe an increase in adverse events in this group. 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 and HIV-infected individuals with a CD4 count of less than 50. 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.

2) 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. **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 MPX 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.

3) 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 MPX should therefore be offered vaccination, after discussion about the risks of MPX to themselves and to the breast-fed child.

4) Children

The adverse event profile with MVA-BN® would be expected to be identical to the profile with tuberculosis and malaria candidate vaccines and therefore provides **some reassurance of its use in children.**

Bartlett et al. (2003) **provide clinicians with answers to some of the most important and frequently asked questions related to smallpox vaccination.** Information that has direct bearing on this issue is broad in scope, complex, and multidisciplinary, and this article is offered as an attempt to distil this information into a single accessible resource. The information is **organized as questions and answers and grouped in the following major sections:** Purpose and Approach of the US Smallpox Vaccination Program, Description of the Current Vaccine and Vaccine Supply, Efficacy and Duration of Immunity Following Vaccination, Vaccine Administration, Vaccine Safety and Adverse Reactions, Contraindications to Smallpox Vaccination, Treatment of Vaccine-Related Complications, Liability Issues Related to Smallpox Vaccination, and The Recent Israeli Smallpox Vaccination Series. <https://doi.org/10.1086/374792>

Both vaccines are available (or can be purchased) in Belgium.

The vaccine Imvanex® could be ordered by the FOD/SPF (contacts: Tinatin Shubladze and Stephane Martin: tish@bavarian-nordic.com; stma@bavarian-nordic.com). Contacts have been taken with the company, and coordination at European level of the availability of the vaccine is ongoing.

The Belgian Army has a stock of ACAM 2000®, that can be requested by the FOD/SPF Public Health.

Based on the safety profile and ease of administration, the SHC recommends the only use of a third generation smallpox vaccine MVA-BN® (like Imvanex® - EU).

4 Drugs

Tecovirimat SIGA® was recently approved by EMA for treatment of orthopoxviruses (including MPX), but it is not available in Belgium yet. Studies using a variety of animal species have shown that Tecovirimat is effective in treating orthopoxvirus-induced disease, but data on its effectiveness in treating human cases of MPX are not available. Human clinical trials indicated the drug was safe and tolerable with only minor side effects. Treatment with Tecovirimat could be considered for immunocompromised hospitalized patients if available (Sciensano-RAG, 24/05/2022).

Based on similar data, FDA approved a second drug for smallpox: brincidofovir.

- Note that: In France, the *Haute Autorité de Santé* (HAS) also indicates that "the proposed vaccine strategy is part of a more global management strategy including the availability of antiviral treatments not evaluated by the HAS but having a Marketing Authorization (MA) in the indication of MPX, in particular for eligible children, for whom the 3rd generation vaccine does not benefit from MA today (HAS, 20/05/2022)".

- Note that: In France, new guidelines has just been published (HCSP, 25/05/2022) <https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1212>

“ *Le Haut Conseil de la santé publique (HCSP) recommande **en priorité de mettre en place un traitement de support adapté si nécessaire** (traitement d’une fièvre mal tolérée, d’une encéphalite, d’un sepsis, d’une surinfection cutanée ou respiratoire bactérienne).*

Concernant les différentes thérapeutiques disponibles (antiviraux, immunoglobulines spécifiques) contre le MPXV et la doctrine de recours à ces dernières, et selon expertise au cas par cas, le HCSP recommande :

- *de ne pas traiter systématiquement tous les cas confirmés avec un antiviral ou des immunoglobulines ;*
- *de discuter de façon collégiale (infectiologue référent, praticien prenant en charge le patient et le cas échéant l’ANSM et le CNR) l’opportunité d’un traitement spécifique pour les populations cibles (immunodéprimés dont les personnes vivant avec le VIH, femmes enceintes, sujets jeunes) ;*
- *de hiérarchiser les thérapeutiques spécifiques si leur indication est jugée nécessaire :*
 - *Utiliser le tecovirimat en première intention, du fait de sa disponibilité par voie orale et sa tolérance.*
 - *Utiliser le brincidofovir en deuxième intention, sous réserve de disponibilité (avantages : voie orale, meilleure tolérance que le cidofovir).*
 - *Utiliser le cidofovir en troisième intention, en raison de ses inconvénients : voie injectable, forte toxicité rénale et hématologique ainsi qu’un potentiel effet carcinogène, tératogène et reprotoxique. Ce produit est actuellement disponible en accès compassionnel.*
 - *Réserver les immunoglobulines humaines anti-vaccin pour des populations particulières, lorsque les antiviraux ne peuvent pas être utilisés : femmes enceintes, jeunes enfants avec poids de moins de 13 kg ».*

- Note that: In Germany, « Administration of human vaccinia immunoglobulin may also be considered as PEP after high-risk exposure in persons with expected impaired vaccine response. Administration may also be considered for children (STAKOB, 05/2022)”. At present, the SHC does not know whether these immunoglobulins are available and easily accessible in Belgium. Human Vaccine Immunoglobulins - Emergent Biosolutions Laboratory - are extracted from human plasma of selected healthy donors who have high levels of antibodies to the vaccinia virus. They were granted marketing authorization in the United States only in 2005.

https://www.symbiopharma.com/pipeline_e/04.html

<https://www.emergentbiosolutions.com/wp-content/uploads/2022/01/VIGIV-Canada-Monograph-French.pdf>

5 Other NITAGs recommendations

21/05/2022 - UKHSA

<https://www.gov.uk/government/publications/monkeypox-vaccination>

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

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: <ul style="list-style-type: none"> 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

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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.

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20/05/2022 – HAS

https://www.has-sante.fr/jcms/p_3340378/fr/avis-n2022-0034/sespev-du-20-mai-2022-du-college-de-la-haute-autorite-de-sante-relatif-a-la-vaccination-contre-monkeypox

La HAS recommande la mise en œuvre d'une stratégie vaccinale réactive en post-exposition avec le vaccin Imvanex® (autour d'un cas confirmé), dit de troisième génération (au vu de son profil de tolérance, meilleur que celui des vaccins de 1ère et 2ème génération et de son efficacité), administré idéalement dans les 4 jours après le contact à risque et au maximum 14 jours plus tard avec un schéma à deux doses (ou trois doses chez les sujets immunodéprimés), espacées de 28 jours, pour les personnes adultes contacts à risque élevé de variole du singe tels que définis par Santé publique France, incluant les professionnels de santé exposés sans mesure de protection individuelle.

23/05/2022 – STAKOB - RKI

<https://www.rki.de/DE/Content/InfAZ/A/Affenpocken/Affenpocken.html>

... At the current stage of the outbreak, **it is not possible to make a firm statement about the value of vaccination**. An offer of vaccination to the particularly exposed population should be evaluated at a later date when availability has improved. **Experts believe that the 1st and 2nd generation smallpox vaccines should not be used** in MPX infections due to their unfavorable side effect profile. Currently, the vaccine Imvanex® is not available in Germany, the procurement is currently under review at national and European level ...

... There are currently no approved therapeutics available for post-exposure prophylaxis in MPX. Imvanex® is also approved for MPX prophylaxis in the United States (JYNNEOS®) and Canada (Imvamune®). Data on the use of Imvanex® vaccination as postexposure prophylaxis are lacking to date. The approval of Imvanex® in Europe by the EMA so far refers only to smallpox infection. **Nevertheless, according to expert opinion, the early use of Imvanex® is considered to be effective against MPX ...**

... Based on the current state of knowledge, STAKOB (permanent working group of competence and treatment centers for diseases caused by highly pathogenic pathogens) recommends **post-exposure prophylaxis with Imvanex® only for HRC**. Guidance on the use of Imvanex® e.g. for exposure to MPX is being developed by the STIKO. Currently, the vaccine Imvanex® is not available in DE ...

... Administration of human vaccinia immunoglobulin may also be considered as PEP after high-risk exposure in persons with expected impaired vaccine response. Administration may also be considered for children ...

24/05/2022 – RIVM

<https://www.rivm.nl/en/monkeypox>

The current smallpox vaccine can be used during the first few days of a possible infection (post-exposure prophylaxis). The vaccine can also be used preventively in people who are at greater risk of infection.

25/05/2022 - Latvian NITAG

- As postexposure (should be done within 4 days after the contact) prophylaxis vaccination with Imvanex® vaccine **may be offered to close contacts**, incl. HCW, lab staff. High risk patients which are being defined as close contact, should be advised by specialist to outweigh risk/benefit balance on MPX infection and vaccine.

- Preexposure **could be considered in Lab staff** working directly with the MPX testing.

- 1 or 2 doses depending on previous smallpox vaccination, immunosuppression and continuous exposure.

NITAG Latvia Chair, Dace Zavadzka (personal communication)

6 Future

Smallpox has emerged as the most threatening bio-terrorism agent; as the first- and second-generation smallpox vaccines have been controversial and have caused severe adverse reactions, new demands for safe smallpox vaccines have been raised and some attenuated smallpox vaccines have been developed. Lim and collaborators (2021) have developed a **cell culture-based highly attenuated third-generation smallpox vaccine candidate KVAC103 strain** by 103 serial passages of the Lancy-Vaxina strain derived from the Lister in Vero cells. Several clones were selected, taking into consideration their shape, size, and growth rate in mammalian cells. The clones were then inoculated intracerebrally in suckling mice to test for neurovirulence by observing survival. Protective immune responses in adult mice were examined by measuring the levels of neutralization antibodies and IFN- γ expression. Among several clones, clone 7 was considered the best alternative candidate because there was no mortality in suckling mice against a lethal challenge. In addition, enhanced neutralizing antibodies and T-cell mediated IFN- γ production were observed in clone 7-immunized mice. Clone 7 was named “KVAC103” and was used for the skin toxicity test and full-genome analysis. KVAC103-inoculated rabbits showed reduced skin lesions compared to those inoculated with the Lister strain, Lancy-Vaxina. A whole genome analysis of KVAC103 revealed two major deleted regions that might contribute to the reduced virulence of KVAC103 compared to the Lister strain. Phylogenetic inference supported the close relationship with the Lister strain. Collectively, our data demonstrate that KVAC103 holds promise for use as a third-generation smallpox vaccine strain due to its enhanced safety and efficacy (Lim et al., 2021).

Costantino and collaborators (2020) constructed **three modified susceptible-latent-infectious-recovered (SEIR) models to simulate targeted, ring and mass vaccination in response to a smallpox outbreak in Sydney, Australia**. They used age-specific distributions of susceptibility, infectivity, contact rates, and tested outputs under different assumptions. The number of doses needed of second- and third-generation vaccines are estimated, along with the total number of deaths at the end of the epidemic. **They found a faster response is the key and ring vaccination of traced contacts is the most effective strategy and requires a smaller number of doses**. However if public health authorities are unable to trace a high proportion of contacts, mass vaccination with at least 125.000 doses delivered per day is required. This study informs a better preparedness and response planning for vaccination in a case of a smallpox outbreak in a setting such as Sydney.

G7+ - Global Health Security Initiative (GHSI) Workshop “Best Practices in Vaccine Production for Smallpox and other Potential Pathogens“: https://cdn.who.int/media/docs/default-source/documents/health-topics/smallpox/bestpractices-smallpox-paul-ehrllich-institute9edbb432-b6ad-46da-9708-b458b3b4eb7a.pdf?sfvrsn=fdc398ff_1&download=true

V REFERENCES

- Bartlett J., Luciana Borio, Lew Radonovich, Julie Samia Mair, Tara O'Toole, Michael Mair, Neil Halsey, Robert Grow, Thomas V. Inglesby, Donald A. Henderson, Thomas V. Inglesby, Tara O'Toole, Smallpox Vaccination in 2003: Key Information for Clinicians, *Clinical Infectious Diseases*, Volume 36, Issue 7, 1 April 2003, Pages 883–902, <https://doi.org/10.1086/374792>
- Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, et al. (2022). The changing epidemiology of human monkeypox—A potential threat? A systematic review. *PLOS Neglected Tropical Diseases* 16(2): e0010141. <https://doi.org/10.1371/journal.pntd.0010141>
- CDC - Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions: guidelines for clinicians, *MMWR Recomm Rep*, 2003, vol. 52 RR4 (pg. 1-29).
- Costantino B.M.V., Jai Narain, Abrar Ahmad Chughtai, Arpita Das, C Raina MacIntyre. (2020) Modelling the impact of a smallpox attack in India and influence of disease control measures. *BMJ Open* 10:12, pages e038480.
- CSS - Conseil Supérieur de la Santé. Demande d'avis concernant la prolongation de la suspension de l'obligation de la vaccination antivariolique. Bruxelles: CSS; 2015. Avis n° 9283. <https://www.health.belgium.be/fr/lettre-9283-vaccination-antivariolique>
- ECDC - European Centre for Disease Prevention and Control. Monkeypox multi-country outbreak – 23 May 2022. ECDC: Stockholm; 2022. <https://www.ecdc.europa.eu/sites/default/files/documents/risk-assessment-monkeypox-multi-country-outbreak.pdf>
- EMA - European Medicines Agency. Imvanex Smallpox vaccine (Live Modified Vaccinia Virus Ankara). Amsterdam: EMA; 2022. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex>
- Fenner, Frank, Henderson, Donald A, Arita, Isao, Jezek, Zdenek, Ladnyi, Ivan Danilovich. et al. (1988). Smallpox and its eradication. World Health Organization. <https://apps.who.int/iris/handle/10665/39485>.
- HAS – Haute Autorité de Santé. Avis n° 2022.0034/SESPEV du 20 mai 2022 du collège de la Haute Autorité de santé relatif à la vaccination contre Monkeypox. 20/05/2022. https://www.has-sante.fr/jcms/p_3340378/fr/avis-n2022-0034/sespev-du-20-mai-2022-du-college-de-la-haute-autorite-de-sante-relatif-a-la-vaccination-contre-monkeypox
- HCSP – Haut Conseil de la santé publique. Haut Conseil de la santé publique. AVIS relatif à la conduite à tenir autour d'un cas suspect, probable ou confirmé d'infection à Monkeypox virus. 24 mai 2022. <https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1212>
- Lim H., Hyun Ju In, You-Jin Kim, Sundong Jang, Yun Ha Lee, Su Hwan Kim, Sun Hwa Lee, Jun Hyuk Park, Hyo Jin Yang, Jung-Sik Yoo, Sang-Won Lee, Mi Young Kim, Gyung Tae Chung, Sang Gu Yeo. Development of an attenuated smallpox vaccine candidate: The KVAC103 strain. *Vaccine*, Volume 39, Issue 36, 2021. ISSN 0264-410X, <https://doi.org/10.1016/j.vaccine.2021.06.060>.
- McCollum AM, Damon IK. Human monkeypox. *Clinical Infectious Diseases*. 2014;58(2):260–267. Available at: <https://academic.oup.com/cid/article/58/2/260/335791>
- Ogoina D, Iroezindu M, James HI, Oladokun R, Yinka-Ogunleye A, Wakama P, Oti-Odibi B, Usman LM, Obazee E, Aruna O, Ihekweazu C. Clinical Course and Outcome of Human Monkeypox in Nigeria. *Clin Infect Dis*. 2020 Nov 5;71(8):e210-e214. doi: 10.1093/cid/ciaa143. PMID: 32052029.
- PEM FINE, Z JEZEK, B GRAB, H DIXON, The Transmission Potential of Monkeypox Virus in Human Populations, *International Journal of Epidemiology*,

Volume 17, Issue 3, September 1988, Pages 643–650, <https://doi.org/10.1093/ije/17.3.643>

- Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Muyembe Tamfum JJ, Nguete B, Hughes CM, Monroe BP, Reynolds MG. Vaccinating against monkeypox in the Democratic Republic of the Congo. *Antiviral Res.* 2019 Feb;162:171-177. doi: 10.1016/j.antiviral.2018.11.004. Epub 2018 Nov 14. PMID: 30445121; PMCID: PMC6438175.
- Reynolds MG, Yorita KL, Kuehnert MJ, Davidson WB, Huhn GD, Holman RC, Damon IK. Clinical manifestations of human monkeypox influenced by route of infection. *J Infect Dis.* 2006 Sep 15;194(6):773-80. doi: 10.1086/505880. Epub 2006 Aug 8. PMID: 16941343.
- STAKOB. Hinweise zur Therapie der Affenpocken, Stand 05/2022. Veröffentlicht unter: www.rki.de/stakob-stellungnahmen
- Taub DD, Ershler WB, Janowski M, Artz A, Key ML, McKelvey J, Muller D, Moss B, Ferrucci L, Duffey PL, Longo DL. Immunity from smallpox vaccine persists for decades: a longitudinal study. *Am J Med.* 2008 Dec;121(12):1058-64. doi: 10.1016/j.amjmed.2008.08.019. PMID: 19028201; PMCID: PMC2610468.
- UKHSA – UK Health Security Agency. Recommendations for the use of pre and post exposure vaccination during a monkeypox incident. Updated May 2022 v6.7. <https://www.gov.uk/government/publications/monkeypox-vaccination>
- WHO – World Health Organisation. Fact sheet Monkeypox: [Monkeypox \(who.int\)](https://www.who.int)
- Zaucha GM, Jahrling PB, Geisbert TW, Swearengen JR, Hensley L. The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (*Macaca fascicularis*). *Lab Invest.* 2001 Dec;81(12):1581-600. doi: 10.1038/labinvest.3780373. PMID: 11742030.

VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: [About us](#).

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: [conflicts of interest](#)).

The following experts endorsed this advisory report by email on 01 June 2022. The NITAG was chaired by **Yves VAN LAETHEM**; the scientific secretary was Fabrice Péters and Veerle Mertens.

BOIY Tine	Pediatrics	UZA
BLUMENTAL Sophie	Pediatric Infectious Disease	HUDERF
CALLENS Steven	Infectiology, Internal medicine	UZ Gent
CARILLO SANTISTEVE Paloma	General medicine, vaccination	ONE
CHATZIS Olga	Pediatrics, Vaccinology	UCL
CORNELISSEN Laura	Epidemiology, Obstetrics, Gynaecology	Sciensano
DE LOOF Geert	General medicine	BCFI
DOGNE Jean- Michel	Pharmacovigilance	UNamur, EMA
FLAMAING Johan	Geriatry	UZ Leuven
FRERE Julie	Pediatrics, Infectiology	CHU Liège
LEROUX-Roels Isabel	Vaccinology, Infection Prevention, Microbiology	UZ Gent
MAERTENS Kirsten	Vaccinology	UAntwerpen
MANIEWSKI Ula	Infectiology, tropical infectious diseases, vaccinology	ITG
PELEMAN Renaat	Infectiology, Vaccinology	UZ Gent
ROBERFROID Dominique	Epidemiology	KCE, UNamur
ROSSI Camelia	Infectiology, internal medicine	CHU Ambroise Paré
SWENNEN Béatrice	Epidemiology, Vaccinology	ULB
TILMANNE Anne	Pediatrics, Infectiology	CHU TIVOLI
TUERLINCKX David	Pediatrics, Vaccinology	CHU UCL Namur
VAN DAMME Pierre	Epidemiology, Vaccinology	UAntwerpen
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine, HIV	CHU Saint-Pierre, ULB
VERHAEGEN Jan	Microbiology, Bacteriology	UZ Leuven
WAETERLOOS Geneviève	Quality of vaccines and blood products	Sciensano

The following experts or administrations were heard but did not take part in endorsing the advisory report.

DAEMS Joël	Directorate Drugs	RIZIV-INAMI
LERNOUT Tinne	Epidemiology of infectious diseases	Sciensano-RAG
MALI Stephanie		AFMPS-FAGG
THEETEN Heidi	Vaccinology	VAZG
VANDEN DRIESSCHE Koen	Pediatrics	UZA
WUILLAUME Françoise	Vaccine vigilance	AFMPS-FAGG

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.

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