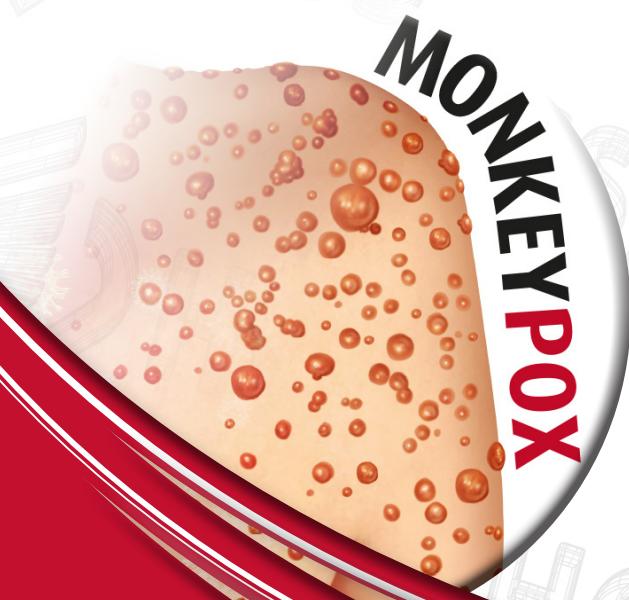




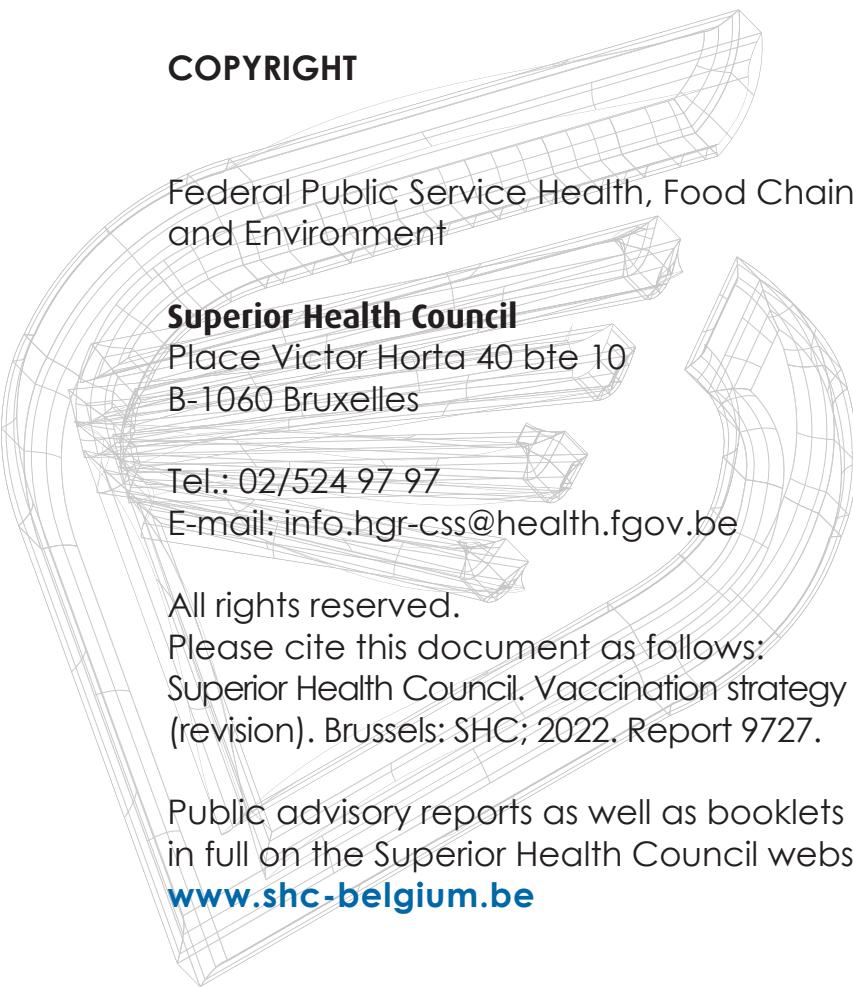
**Superior
Health Council**

VACCINATION STRATEGY AGAINST MONKEYPOX (REVISION)

**SEPTEMBER 2022
SHC № 9727**



.be



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and Environment

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ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9727

Vaccination strategy against Monkeypox – August 2022 (revision SHC 9720)

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 05 September 2022
This version was validated by the Board on 07 September 2022¹

I INTRODUCTION AND ISSUE

Monkeypox (MPX) is an infectious disease caused by the human monkeypox virus (hMPXv). This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family and is related to the virus which caused smallpox (eradicated in 1980). MPX is a zoonotic disease and human MPX cases have been reported since 1970, with rising frequency in recent years. From early May 2022 through 02 September 2022, a total of 52.997 cases of MPX were identified in a large amount of countries and areas in the World Health Organization (WHO). 29.338 cases are reported from the WHO Region of the Americas and 22.921 in the European Region ([WHO Health Emergency Dashboard](#)).

Based on case reports submitted by countries in the European Region, circulation has been ongoing since as early as March 2022 (WHO ER, 26/08/2022). WHO considers MPX as a Public Health Emergency of International Concern (PHEIC) since 23/07/2022.

As of September 05, 2022, a total of 726 confirmed cases of MPX have been reported by regional governments/administrations in Belgium. These include 384 cases in Flanders, 258 cases in Brussels and 84 cases in Wallonia (Sciensano, 05/09/2022).

For information only² : more global information on “real time” evolution of the epidemiology worldwide and in Belgium can be found here:

[WHO Health Emergency Dashboard](#)
<https://monkeypoxreport.ecdc.europa.eu/>
<https://ourworldindata.org/monkeypox>
<https://www.monkeypoxmeter.com/>
<https://www.sciensano.be/fr/sujets-sante/variole-du-singe-monkeypox/chiffres>

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.

² Epidemiology data will be rapidly be out-of-date.

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, transmission, preparedness and surveillance measures. These living documents (last update from 23/08/2022 and 30/08/2022) served as a scientific basis for this report:

[Variole du singe \(monkeypox\) | sciensano.be](https://www.sciensano.be/en/monkeypox)

Based on the scientific evidence from the cases reported in the current outbreak, **the likelihood of MPX spreading further in networks of people with multiple sexual partners in the EU/EEA is considered very high** and the likelihood of spreading among **the broader population is assessed as very low.**

The impact of the disease remains low for the majority of cases. The overall risk is therefore assessed as moderate for people having multiple sexual partners (including some groups of Gay, Bisexual and other Men-who-have-Sex-with-Men - GBMSM) and low for the broader population (ECDC, 08/07/2022 ; RAG, 29/07/2022).

Imvanex® is the only one vaccine authorised by the European Medicines Agency (EMA) for use against MPX disease in the EU. Imvanex® has been authorised to protect adults from MPX disease in the EU since 22 July 2022. It is also authorised to protect people against diseases caused by the vaccinia virus. These new indications were added to Imvanex®'s existing authorisation against smallpox, which has been in place in the EU since 2013.

Imvanex® is currently only authorised for subcutaneous injection (SC injection under the skin). However, data reviewed by the Emergency Task Force (ETF) suggest that a smaller dose (1/5) of the vaccine can trigger similar levels of antibodies when it is injected Intradermally (ID, just below the top layer of the skin) instead. This means that more people could be vaccinated. The EMA's ETF advice of 19/08/2022 aims to support national authorities who may decide to use Imvanex® as an ID injection. This would be a temporary measure to protect at-risk individuals while vaccine supplies remain limited (EMA, 19/08/2022).

For now, Post-Exposure Prophylaxis Vaccination (PEPV) is not considered by EMA as an indication of the vaccine.

In the United States, the vaccine is available under the brand name Jynneos®. EMA's ETF is recommending that Jynneos® can be used to prevent MPX, while supplies in the EU remain limited. This advice aims to support national authorities who may decide to import Jynneos® as a temporary measure.

More information on these vaccines can be found:

EMA – Imvanex®: <https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex>

FDA – Jynneos®: <https://www.fda.gov/vaccines-blood-biologics/jynneos>

On Monday 23 May 2022, the Superior Health Council (SHC) received an urgent request for advice from the Risk Management Group (RMG). The question is whether it is recommended (or not) to vaccinate people in the context of MPX' European multi-country outbreak in May 2022. If so, who and when and with which vaccine. For this revision and in the current context of a limited stock of vaccines in Belgium and worldwide, issues related to the increase of the

interval of 28 days between 2 doses as well as the ID administration of 1/5 of the dose will also be discussed.

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). This document is the second version of this advisory report.

II CONCLUSIONS AND RECOMMENDATIONS

1 CONCLUSIONS

Based on the level of scientific evidence from the cases reported in the current MPX outbreak and the scarce efficacy data of available vaccines on MPX, the SHC would like to emphasize the critical importance of non-pharmaceutical preventive measures. The fact that vaccine's availability is limited at this time reinforces the importance of these measures.

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 and in Americas) the cases that are currently occurring.

More Belgian guidelines for preventive measures are available here:

General information:

[Variole du singe \(monkeypox\) | sciensano.be](#)

Health Care Workers (HCW):

[info_hcw_nl.pdf \(sciensano.be\)](#)
[info_hcw_fr.pdf \(sciensano.be\)](#)

Patients:

[infofiche_voor_patienten_nl.pdf \(sciensano.be\)](#)
[infofiche_voor_patienten_fr.pdf \(sciensano.be\)](#)

1. The targeted groups at higher risk of infection are networks of people with **multiple sexual partners** (including some groups of GBMSM) and should also include for example **sex workers and sexual and gender minorities (transgender)**, etc.
2. MPX is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases are more commonly observed in the **immunocompromised population** (particularly persons with an active (low CD4 count) Human Immunodeficiency Virus - HIV). In low incomes countries, severe cases are also more commonly observed among **children and pregnant women** (Ogoina et al., 2020).

Therefore, particular attention is needed for immunocompromised people, pregnant women and children in connexion (as Very- and High-Risk Contacts - VHRC and HRC) with a confirmed case or in connexion with people with a higher risk of infection.

Actually, the number of infections in children remains very low. In Europe, 29 out of the 18 960 cases (7 female-22 male) were 0-17 years old (0,15%). And in the United States (based in info in the media), three cases were reported (in a minor, a toddler and an infant), out of 14.050 (0,02%).

3. Cases in the current outbreak present with a spectrum of symptoms and signs **that differs from that described in past outbreaks of MPX in endemic countries**. In addition, a small number of subclinical or even asymptomatic cases (De Baetselier et al., 2022 ; Patel et al., 2022) has been described. This finding should be verified and the public health relevance for transmission established. As regards the severity of the disease, in this outbreak cases have presented **with mild to moderate symptoms, with only a few hospitalizations reported**. Treatment is mainly **symptomatic and supportive**, including prevention and treatment of secondary bacterial infections (ECDC, RAG, July 2022).

4. In the context of the current outbreak, the WHO has reported **only 18 deaths on 52.015 cases worldwide**. 10 in the WHO African Region, 3 in Europe, 4 in Americas and 1 in the South-East Asia Region (02/09/2022).
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. MVA-BN® vaccines 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, Canada and EU.
7. **The vaccine effectiveness of 85%** of smallpox vaccines against hMPXv, 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). **These data were generated with first and second generation of the vaccine and can't be directly extrapolated to MVA-BN® vaccines.**
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. Third generation smallpox MVA-BN® vaccines have a better safety profile than older generations in the adult population. Nevertheless, ID injection shows a higher local reactogenicity compared to the standard dose and route. There was a relatively high percentage of subjects (20%) that failed to receive the second vaccination during a unique controlled clinical study (Frey et al., 2015).
10. In the absence of a formal opinion from the EMA on the safety of these vaccines for **immunosuppressed people, pregnant women and children**, MVA-BN® vaccines are considered as safe by the SHC.

If the physician assesses that the benefits outweigh the risks, the SHC supports vaccination of these patients on an individual basis. At this time, the Council does not see any major contraindications to their vaccination. But, an individual B/R balance must be done by the physician before vaccination for these groups.

- **Immunocompromised people**: the MVA-BN® vaccines cannot replicate in human cells and hence is less likely to cause side effects than conventional smallpox vaccines. MVA-BN® vaccines 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 (CHMP) 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).

- **Pregnant women:** the use of MVA-BN® vaccine during pregnancy and breast-feeding women is not well studied.

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).

- **Children:** the use of MVA-BN® vaccines for children is not well studied and MVA-BN® vaccines are not licensed for children.

Nevertheless, several paediatric studies of other vaccines using MVA as a vector (often at a considerably higher dose than used in Imvanex®) have been undertaken with a reassuring side effect profile. In a tuberculosis vaccine trial of approximately 1.500 infants, aged approximately 5 to 6 months, MVA85A (Tameris et al., 2013) at a dose of 1×10^8 Plaque-Forming Unit (PFU), this dose was very well tolerated. In a trial of 100 Gambian infants who received MVA85A (Ota et al., 2011) at a dose of 5×10^7 PFU and in a further study of 100 infants who received MVAmalaria (Afolabi et al., 2016) at a dose of $1\text{--}2 \times 10^8$ PFU, there was a tolerable safety profile. The adverse event profile with MVA-BN would be expected to be identical to the profile with these tuberculosis and malaria candidate vaccines and therefore provides some reassurance of its use in children (UKHSA, 2022).

Safety and efficacy of Jynneos® is currently not established in children, but data with similar vaccines including the MVA-based vaccines used in the vaccination campaigns in the 70's for smallpox are reassuring. If Jynneos is used in the paediatric population, the adult regimen should be considered and data collected to confirm a positive benefit/risk profile (EMA, 27/06/2022).

11. **In case of low vaccine supply, PEPV has been used for past imported outbreaks, but there are limited data on its efficacy.** Some of which are from animal challenge models (Nguyen et al., 2022) or more recent from human studies (Thy et al., 2022).

- a. In the UK outbreak in 2018, 3 cases were declared and 154 contacts were identified (including 147 HCWs). Among those contacts, 131 received PEPV (126 of whom were HCWs). 1 secondary case occurred in a vaccinated HCW who received PEPV 6 days after exposure.
- b. In a 2019 imported outbreak in the United Kingdom with a single case, 18 contacts were identified, 17 of whom (including some children) were vaccinated. There were no secondary cases. No clinically relevant post-vaccination adverse events were reported.

- c. In France, PEPV ring vaccination of two doses of MVA-BN®, 28 days apart, has been recommended since 29 May 2022 for people who have had physical skin-to-skin contact or have shared hygienic tools or textiles (such as toothbrushes or towels), or have had more than 3 hours of contact less than 2 meters apart, with a person with probable or confirmed symptomatic MPX. In one observational analysis, Thy and collaborators show that among the 276 vaccinated individuals, 12 (4%) had a confirmed MPX breakthrough infection with no severe infection. Ten out of 12 patients developed a MPX infection in the five days following vaccination and two had a breakthrough infection at 22 and 25 days. PEPV with a third-generation smallpox vaccine was well tolerated and effective against MPX but did not completely prevent breakthrough infections (Thy et al., 2022).
- d. **ECDC modelling results**: “The modelling suggests that PEPV vaccination of contacts would offer a marginally more efficient approach if there are both higher uptake levels and more effective tracing (as fewer vaccines would be needed for a relatively larger increase in the probability of outbreak control per vaccinated individual), while **the absolute probability of outbreak control with PEPV vaccination is still lower than with Primary Preventive Vaccination (PPV) vaccination**” (ECDC, 08/07/2022).

12. In case of more vaccine supply, **PPV** could be implemented in larger groups.

- a. **ECDC modelling results**: “Unless contact tracing can successfully identify a high proportion of infected contacts, mathematical modelling results indicate that **targeted PPV of individuals at high risk of exposure would be the most effective strategy to use vaccines to control the outbreak**. Therefore, prioritising groups of GBMSM at higher risk of exposure, as well as front-line staff with a risk for occupational exposure, should be considered in developing vaccination strategies. Modelling the efficient use of vaccines indicates that **PPV vaccination would be the most efficient strategy when there is less effective tracing**. In settings where higher vaccine uptake is expected, PEPV vaccination of close contacts of cases should also be considered, or even ring vaccination” (ECDC, 08/07/2022).

13. 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).

Recently, Webb and collaborators (2022) produce a systematic review of clinical guidelines for MPX. Treatment guidance was mostly limited to advice on antivirals. Seven guidelines advised cidofovir (7/14 - 50% - four specified for severe MPX only), 29% (4/14) tecovirimat, and 7% (1/14) brincidofovir (Webb et al., 2022).

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

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 as PPV**. In 2015, 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>

1) Routine, mandatory smallpox vaccination has been suspended in Belgium since 1976 (SHC 9283, 2015). According to the epidemiological data and available MVA-BN® 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).

- Confirmed cases of MPX should not be vaccinated.
- In cases of immunodeficiency (of any origin), this recommendation does not apply even if pediatric smallpox vaccination has occurred as a child. Immunocompromised patients 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 (cf. 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 (like some Health Care Workers - HCW) or groups at higher risk of severe disease, infection or transmission.

2) According to ECDC recommendations (08/07/2022) : At this point, **mass vaccination for MPX is not required nor recommended.**

3) Like recommended by international authorities, the SHC recommends PPV vaccination with a MVA-BN® vaccine.

- **with 2 doses at 28 days of interval** (FDA – EMA; Earl et al., 2007);
- **under the skin (S.C. – subcutaneous injection) in the upper arm;**
- **if vaccination is given as PEPV, then it should be given preferably within 4 days** (maximum 14 days) after exposure to a confirmed MPX case. If given between 4 - 14 days after the date of exposure, vaccination may reduce the symptoms of disease, but may not prevent the disease.

More practical information on these vaccines can be found:

EMA – Imvanex®: <https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex>

FDA – Jynneos®: <https://www.fda.gov/vaccines-blood-biologics/jynneos>

4) Transitional emergency measures due to the lack of vaccines in Belgium

If the RAG (Sciensano) and the Federal Public Service (FPS) Health consider that the Belgian epidemiological situation is not under control with the measures currently in place and that the supply of vaccines in Belgium is too limited, the Council **proposes two transitional emergency measures to temporarily increase the availability of doses in the short term.**

ATTENTION

- These transitional emergency measures apply only to immunocompetent individuals. The standard regimen recommended by the EMA should be used when in doubt or for clearly immunocompromised patients.
- These transitional emergency measures should end as soon as the Belgian epidemiological situation is under control or as soon as sufficient vaccines are available.
- These emergency measures are not (yet?) supported by robust scientific, immunological and clinical evidence in humans. The safety, the individual clinical impact and the effectiveness of these measures in terms of public health for the control of the outbreak in Belgium are not (yet?) validated on a large scale.
- These emergency measures are not subject to conventional authorization by the EMA. They must therefore be accompanied by a systematic and controlled system of informed consent from the person (complete and transparent medical information).
- If the person refuses these transitional measures, the Council strongly recommends limiting close contact and sexual activity to one fixed partner until the epidemiological situation improves or the Belgian and global availability of vaccines increases. Condoms (latex or polyurethane) may protect your anus (butthole), mouth, penis, or vagina from exposure to MPX. However, condoms alone may not prevent all exposures to MPX since the rash can occur on other parts of the body (CDC, 05/08/2022).
<https://www.cdc.gov/poxvirus/monkeypox/prevention/sexual-health.html>

Notes: These emergency measures, if applied in Belgium, should be subject to validated clinical protocols allowing the collection, at least at the Belgian level, of new scientific data concerning the safety and clinical effectiveness of these vaccine strategies against MPX. Registration of the vaccines administered in the existing tools should be made mandatory and a centralized national database would be recommended (to allow follow-up and research).

Priority 1: Transitional emergency measure concerning intradermal (ID) administration of 1/5 of the dose normally administered in SC

For non-immunocompromised persons, the SHC could support an emergency vaccination strategy with two ID administration of 1/5 of the normal SC dose at 28 days of interval.

This strategy is supported by the FDA since 09/08/2022 and the EMA since 19/08/2022.

<https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-authorizes-emergency-use-jynneos-vaccine-increase-vaccine-supply>

https://www.ema.europa.eu/en/documents/other/considerations-posology-use-vaccine-jynneos/imvanex-mva.bn-against-monkeypox_en.pdf

It is essential to recognize the importance of proper ID administration to ensure that immune responses will be comparable to those obtained with a standard SC dose. Therefore, it is recommended that ID administration of the reduced dose be performed by professionals experienced in the ID administration of vaccines.

The use of low volume syringes is recommended to maximize dose withdrawal.

This ID approach also has some limitations due to the very limited safety data available (<200 people), the higher reactogenicity compared to the standard dose and route and the fact that there was a relatively high percentage of subjects (20%) that failed to receive the second vaccination during this unique controlled clinical study (Frey et al., 2015). This is well supported by others studies (Frey et al., 2021 ; Wilck et al., 2010)

Excerpts from the EMA document: "***Intradermal delivery of vaccines, allowing antigen sparing, is approved for several vaccines, notably BCG (tuberculosis vaccine), influenza and rabies vaccines. Intradermal delivery of a reduced dose of MVA-BN has been investigated in a phase 2 clinical trial (NCT 00914732 – Frey et al., 2015). Vaccinia-naïve healthy adults (18-38 years) with no prior history of smallpox vaccination were randomised to receive either 2 subcutaneous [SC] doses (0.5 mL, 108 TCID50/dose) in the deltoid area or 2 intradermal [ID] doses (0.1 mL, 2x107 TCID50/dose) in the volar area of the forearm with a 4-week interval. The vaccine administered in the trial can be regarded as similar to the currently marketed product even though the description of the nominal strength is different. The lower ID dose of IMVANEX, one fifth of the SC dose, was immunologically non-inferior to the standard SC dose.*** As the study was conducted in healthy subjects, questions remain whether the reduced ID dose will be immunologically non-inferior to the standard SC dose in specific groups such as immunocompromised individuals or in people with HIV. The exact level of protection and duration of protection afforded by the vaccine regimens are unknown. **No data on cellular immunity have been reported.** As shown with another MVA vaccine, **the ID route resulted in significantly higher local adverse reactions (i.e., erythema, induration) than the SC route.** Around 30% more subjects for ID vs. SC administration reported symptoms of local reactogenicity after the first dose and around 20% more subjects after the second dose. Moderate/severe erythema and induration occurred after any vaccination in almost all subjects with the ID route, with higher rates of severe reactions after the second dose (80% vs. 40%). Following any vaccination, the proportion of subjects with erythema or induration at the local injection site graded as severe (>30 mm) was 58.1% for the SC group and 94.8% for the ID group. In addition, the proportion of subjects who experienced local reactogenicity lasting at least 30 days, unexpected nodules and skin discolouration at the vaccination site was 25% and 67.0% for the SC group and ID group, respectively. However, SC and ID groups did not significantly differ in systemic reactogenicity. There was no significant difference in the proportion of subjects with moderate/severe systemic reactions among groups after vaccination. No vaccine-related serious adverse events were reported during the study. It is also important to note that the available data on ID administration **are based on 2 doses of vaccine**, which are deemed critical to achieve vaccine response and to maintain protection in the longer term. **There is no intradermal presentation authorised in the EU.** The EMA has neither information on the maximum number of 0.1 mL doses that can be effectively withdrawn from the authorised presentation nor information on vial stopper performance/integrity after repeated puncture since no feasibility study has been conducted on this. **However, the use of low-dead volume syringes is recommended to maximise dose withdrawal.** There is no information on storage conditions (e.g. time out of refrigeration) between multiple uses to support physico-chemical stability or stability from a microbiological perspective. **From a microbiological point of view, once opened, the product should be used immediately".**

Priority 2: Transitional Emergency Measure regarding the extension of the deadline

For non-immunocompromised individuals, the SHC could support a **two dose emergency strategy with a longer delay for the second dose**. As there are few data on the degree of protection and duration of effect after the first dose, **this extension of the 28-day interval between the two doses should be as limited as possible**. Depending on how the situation evolves in terms of vaccine supply, the second dose should be administered as soon as possible after the 28 days recommended by regulatory authorities.

This strategy is supported by extrapolation of some human immunological data and clinical evidence in animal models (Earl et al., 2008 ; Greenberg et al., 2016 ; Maclennan et al., 2019 ; Pittman et al., 2019 ; Osterholm et al., 2022). This strategy has also already partially implemented by some NITAGs for certain groups especially in case of PEPV vaccination.

On clinicatrials.gov the results of a phase 2 are interesting. It shows a rather strong anamnestic response to a booster dose 2 years after 1 or 2 doses. The data look re-assuring for longer term immunity after one dose.

[An Open-Label Phase II Study to Evaluate Immunogenicity and Safety of a Single IMVAMUNE Booster Vaccination Two Years After the Last IMVAMUNE Vaccination in Former POX-MVA-005 Vaccinees - Study Results - ClinicalTrials.gov](#)

However, some authors caution about this approach in view of the number and type of neutralising antibodies and thus their effectiveness in fully protecting the individual after a single dose (Townsend et al., 2013 ; Zaeck et al., 2022). In addition, this approach is not currently supported by the FDA and WHO. EMA has not commented on this topic.

*Excerpts from the FDA document: "This option was determined to be **inadvisable**, particularly because it might both be insufficiently protective while at the same time providing individuals with a false sense of reassurance that they were protected against monkeypox when the actual level of protection would be unknown and quite possibly inadequate".*

Excerpts from the WHO document: "The third-generation vaccine MVA-BN is characterized by its lower reactogenicity, and as a consequence the vaccine is differentiated from other products by its recommended schedule of two doses to be administered 4 weeks apart. While some authorities may consider offering PEP as a single dose, there is as yet little data on the relative effectiveness of this approach."

People who have already received the first SC dose with an extended delay for the second one **may be eligible to receive the second ID injection as soon as possible**
(cf. Priority 1).

The SHC therefore has a clear preference for priority 1 in this context.

5) For Belgium, the targeted risk groups vaccination program is defined as below by the SHC. Actually Belgium is in a situation (epidemiologically and vaccine supply) in which some prioritization of eligible risk groups for PPV is still needed according to RAG's advices.

<https://www.sciensano.be/fr/sujets-sante/variole-du-singe-monkeypox/avis-du-risk-assessment-group-rag>

→ **More systematic PPV vaccination of risk groups**

Prioritization of eligible risk groups for PPV is still needed according to RAG's advices

- Male and transgender sex workers;
- GBMSM at high risk of exposure or severe disease;
 - HIV-positive patient
 - Pre-Exposure Prophylaxis (PrEP) user
 - Patient with different sexually transmitted infection (STIs) episodes
 - Immunocompromized patient
 - Etc.

According to new epidemiology data and more vaccine supply in the future, this could be extended for example to

- All (male and female) multiple sex partners and sex workers (Petersen et al., 2022);
- All (male and female) immunocompromised patients;
- All front-line staff and HCWs with a risk for occupational exposure (SHC 9283, 2015);
- Male and transgender sex workers and GBDSM at high risk of exposure or severe disease who have already been vaccinated against smallpox in childhood (one booster);
- All sexual and gender minorities;
- Etc.

→ **PEPV vaccination of some VHRC and HRC included unprotected HCWs**

cf. point 3.4. and RAG definition of VHRC and HRC

- 1) All VHRC, within 4 days of exposure, to prevent infection; for persons in this group at risk of severe disease (people with immune disorders, pregnant women and children), vaccine may be considered up to 14 days after exposure, to reduce the severity of any infection;
- 2) The HRC (including unprotected health care workers) at risk of a serious course of possible infection (people with immune disorders, pregnant women), preferably within 4 days of exposure, up to a maximum of 14 days after.

Note: In the absence of a formal opinion from the EMA on the safety of these vaccines for immunosuppressed people, pregnant women and children, **MVA-BN® vaccines are considered as safe by the SHC**. If the physician assesses that the benefits outweigh the risks, the SHC supports vaccination of these patients on an individual basis. At this time, the Council does not see any major contraindications to their vaccination. An individual B/R balance **must be done by the physician before vaccination**.

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, with a longer interval, ID, etc. 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;
- Etc.

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 Belgian National Immunization Technical Advisory Group (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), preprint article and reports from national (RAG-RMG) and international (WHO; ECDC; CDC; EMA; FDA; others NITAGs) 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 SHC on 07/09/2022.

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

ANSES	<i>Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail</i> - FR
CDC	Centers for Disease Control and Prevention - US
CHMP	Committee for Medicinal Products for Human Use – EMA/EU
ECDC	European Centre for Disease Prevention and Control - EU
EFSA	European Food Safety Authority - EU
EMA	European Medicines Agency - EU
ETF	Emergency Task Force – EMA/EU
FDA	Food and Drug Administration - US
FPS	Federal Public Service
GAVI	GAVI, the vaccine Alliance - World

GHSI	Global Health Security Initiative - G7+
HAS	Haute Autorité de Santé - FR
HERA	European Health Emergency preparedness and Response Authority
HCW	Health Care Worker
HCSP	<i>Haut Conseil de la santé publique</i> - FR
HIV	Human Immunodeficiency Virus
hMPXV	human monkeypox virus
HRC	High Risk Contacts
ICU	Intensive Care Unit
ID	Intradermal injection
LRG	Low Risk Contacts
MPX	Monkeypox
GBMSM	Gay, Bisexual and other men-who-have-sex-with-men
MVA-BN®	Modified Vaccinia Ankara - Bavarian Nordic; Imvanex®-Imvamune®-Jynneos®
NITAG	National Immunization Technical Advisory Group
PCR	Polymerase Chain Reaction
PEPV	Post-Exposure Prophylaxis Vaccination
PFU	Plaque-Forming Unit
PHEIC	Public Health Emergency of International Concern
PPE	Personal Protective Equipment
PPV	Primary Preventive Vaccination
PrEP	Pre-Exposure Prophylaxis (ViH)
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
STP	Strategic Stockpiles
STI	Sexually transmitted infection
EU/EEA	European Union / European Economic Area
UKHSA	UK Health Security Agency - UK
VE	Vaccine Effectiveness
VHRC	Very-high-risk contacts
WHO	World Health Organization - World

IV ELABORATION AND ARGUMENTATION

1 Introduction and transmission

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 scrabs, **through respiratory droplets** or **viral fluid** from a person with MPX and **through contact with objects, fabrics (clothing, bedding or towels), and surfaces** (Atkinson et al., 2022 ; Gould et al., 2022) that have been used by someone with MPX-fomites (ECDC, 2021).

The predominance, in the current outbreak, of diagnosed human MPX cases **among GBMSM**, 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). Peiró-Mestres and collaborators (2022) tested 147 clinical samples collected at different time points from 12 patients by real-time Polymerase Chain Reaction (PCR). MPX DNA was detected in saliva from all cases, sometimes with high viral loads. Other samples were frequently positive: rectal swab (11/12 cases), nasopharyngeal swab (10/12 cases), semen (7/9 cases), urine (9/12 cases) and faeces (8/12 cases). These results improve knowledge on virus shedding and the possible role of bodily fluids in disease transmission (Peiró-Mestres et al., 2022).

Transmission **through aerosols** (animal models, Gould et al., 2022 ; Zaucha et al., 2001) is unlikely, but warrants 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).

To date, transmission of the virus **by ingestion of contaminated food** has not been proven. Based on the available data, the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* (ANSES) nevertheless indicates that the risk of transmission of the Monkeypox virus to humans through food cannot be excluded (ANSES, 24 June 2022).

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. In the available scientific literature, data on the **susceptibility of pets** to MPX are very limited or even absent. At this point in time, lagomorphs, such as rabbits or hares, are receptive and susceptible under experimental conditions, especially rabbits. These are the most represented animals among the new pets. Sciuridae, including squirrels and prairie dogs, seem to constitute a receptive and sensitive family, possibly the most at risk of contamination by humans. Pet rodents, such as brown rats, mice, guinea pigs or hamsters, seem to be not very receptive to the virus in adulthood but could be for the youngest animals. Data are lacking for ferrets and dogs. Concerning cats, only one serological study exists with negative results (ANSES, 10 June 2022).

Recently, Seang and collaborators (2022) show the first evidence of human-to-dog transmission of hMPXv. Given the dog's skin and mucosal lesions as well as the positive hMPXv PCR results from anal and oral swabs, they hypothesise a real canine disease, not a simple carriage of the virus by close contact with humans or airborne transmission (or both). Their findings should prompt debate on the need to isolate pets from MPX virus-positive individuals and call for further investigation on secondary transmissions via pets (Seang et al., 2022).

2 Clinical presentation

MPX is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases are more commonly observed in the **immunocompromised population** (particularly persons with an active (low CD4 count) HIV). In low incomes countries, severe cases are also more commonly observed among **children and pregnant women** (Ogoina et al., 2020).

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).

Cases in the current outbreak present with a spectrum of symptoms and signs that differs from that described in past outbreaks of MPX in endemic countries.

Among cases for which age and/or gender is known, the largest proportion of cases were between 31 and 40 years old (7.602/18.917 – 40%) and male (16.065/16.241 – 98.9%). Among cases with known HIV status, 38% (2.749/7.322) were HIV-positive. Among cases that reported symptoms, the majority presented with a rash (8.937/11.587 – 77.1%) and systemic symptoms such as fever, fatigue, muscle pain, chills or headache (7.495/11.587 - 65%). **505 cases were hospitalized (5.8%), of which 179 cases required clinical care. Three cases were admitted to an intensive care unit (ICU), among whom one for reasons unrelated to monkeypox infection.**

The outbreak in the Region is being driven by close skin-to-skin contact **occurring predominantly during sexual activity**. Some (57) cases were reported to be HCWs, however **no occupational exposure has been reported**. The current assessment is that **occupationally acquired infections are rare in the presence of standard and transmission-based precautions** and could be mitigated with implementation of appropriate infection prevention and control procedures during sample collection from skin lesions (WHO, 26/08/2022).

In UK, patients presented with mucocutaneous lesions, most commonly on the genitals (n=111 participants, 56.3%) or in the perianal area (n=82, 41.6%). 170 (86.3%) participants reported systemic illness. The most common systemic symptoms were fever (n=122, 61.9%), lymphadenopathy (114, 57.9%), and myalgia (n=62, 31.5%). 102/166 (61.5%) developed systemic features before the onset of mucocutaneous manifestations and 64 (38.5%) after (n=4 unknown). 27 (13.7%) presented exclusively with mucocutaneous manifestations without systemic features. 71 (36.0%) reported rectal pain, 33 (16.8%) sore throat, and 31 (15.7%) penile oedema. 27 (13.7%) had oral lesions and 9 (4.6%) had tonsillar signs. 70/195 (35.9%) participants had concomitant HIV infection. 56 (31.5%) of those screened for sexually transmitted infections had a concomitant sexually transmitted infection. Overall, 20 (10.2%) participants were admitted to hospital for the management of symptoms, most commonly **rectal pain and penile swelling** (Patel et al., 2022).

Characteristics of cases - international

UK Technical report 30/08/2022

Metric	Count	Denominator (excluding cases with missing responses)	Percentage (%)
Gay, bisexual, or men who have sex with men	857	886	96.7%
History of STI in the last year	481	899	53.5%
4 to 9 sexual partners in the last 3 months	312	904	34.5%
10+ sexual partners in last 3 months	267	904	29.5%
Living with HIV	228	867	26.3%
Ever used PrEP (among HIV negative)	490	624	78.5%



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In Belgium, among the cases for which the sex is known (n=703, 99%), there are 699 **males**, 2 females and 2 persons who identify themselves differently. The vast majority of them are **between 16 and 71 years old**. **One case was reported in a child under the age of three**. Information on symptoms is known for 621 individuals (88%). Almost all patients (96%) had **skin lesions**, which were mainly in the anal-genital region (n = 404, 64%). About 58% had **general symptoms such as fever, general malaise, 33% lymph node swelling**, etc.

Thirty-two of the 585 people (5%) for whom information is known were **hospitalised, 24 because of treatment (two of them had an underlying immune disorder)**, 3 because home isolation was not possible, and 5 for which the reason was unknown. **To date, one death has been reported in a person with underlying health problems**.

Based on the current data on presumed transmission (n = 528), it appears that the virus is mainly transmitted **through sexual contact** (92%). Of all cases, 145 (22%) could identify a specific contact with another confirmed case.

Most of the people for whom information was available (507/604, 84%) had an idea of the presumed place or context where the infection was transmitted. **Sexual contact in a private setting was most often mentioned** (272/507, 54%). About one in six (n = 77, 15%) had attended a large domestic or foreign event where sexual contact had taken place. Sex saunas or other places that facilitate sexual contact were identified by 111 men (22%). Attendance at a party, in a household, or other non-sexual activity was reported by 35 people (7%). In the latter context, transmission may have occurred from person to person, through very close but non-sexual contact. **While initially the infection was mainly reported through sexual contact at large events, recently more cases related to sexual contact in the private sphere are reported.**

It should be noted that the collection and interpretation of this data is limited by the fact that it is very sensitive information (Sciensano, 30/08/2022).

In addition, a small number of subclinical or even asymptomatic cases (De Baetselier et al., 2022 ; Patel et al., 2022 ; Ferré et al., 2022) has been described. This finding should be verified and the public health relevance for transmission established. As regards the severity of the disease, in this outbreak cases have presented **with mild to moderate symptoms, with only a few hospitalizations reported**. Treatment is mainly **symptomatic** and **supportive**, including prevention and treatment of secondary bacterial infections (ECDC, RAG, July 2022).

In the context of the current outbreak, the WHO has reported **only 18 deaths on 52.015 cases worldwide**. 10 in the WHO African Region, 3 in Europe, 4 in Americas and 1 in the South-East Asia Region (02/09/2022).

3 Epidemiology, mathematical models and High Risk Contacts (HRC) definition

From early May 2022 through 02 September 2022, a total of 52.997 cases of MPX were identified in a large amount of countries and areas in the World Health Organization (WHO). 29.338 cases are reported from the WHO Region of the Americas and 22.921 in the European Region ([WHO Health Emergency Dashboard](#)).

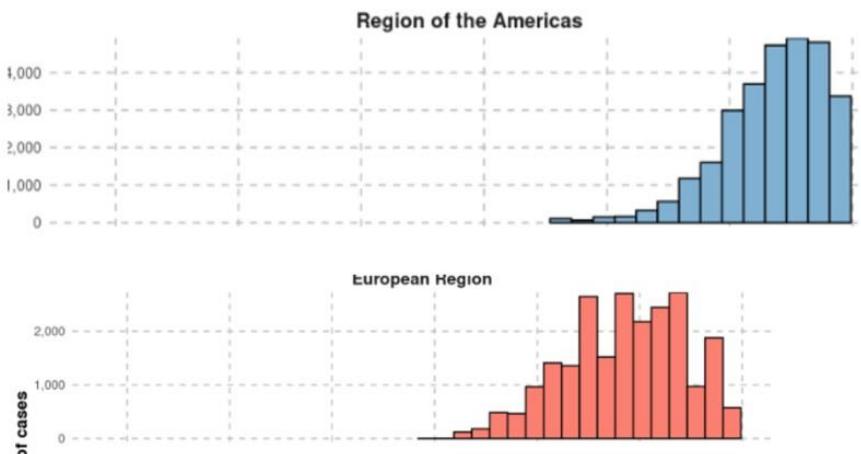
For information only³ : more global information on “real time” evolution of the epidemiology worldwide and in Belgium can be found here :

[WHO Health Emergency Dashboard](#)
<https://monkeypoxreport.ecdc.europa.eu/>
<https://ourworldindata.org/monkeypox>
<https://www.monkeypoxmeter.com/>
<https://www.sciensano.be/fr/sujets-sante/variole-du-singe-monkeypox/chiffres>

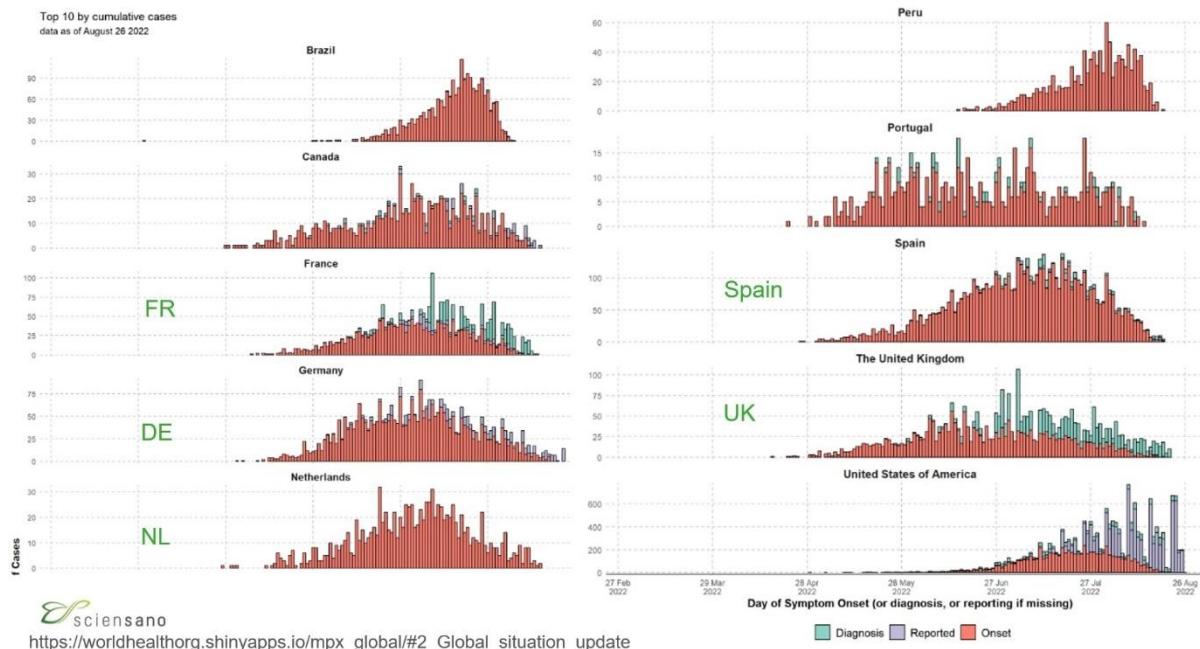
3.1 Europe

In Europe as well as in the US, there is now a decrease in the number of new cases, but a delay in diagnosis and notification cannot be excluded.

MPX worldwide



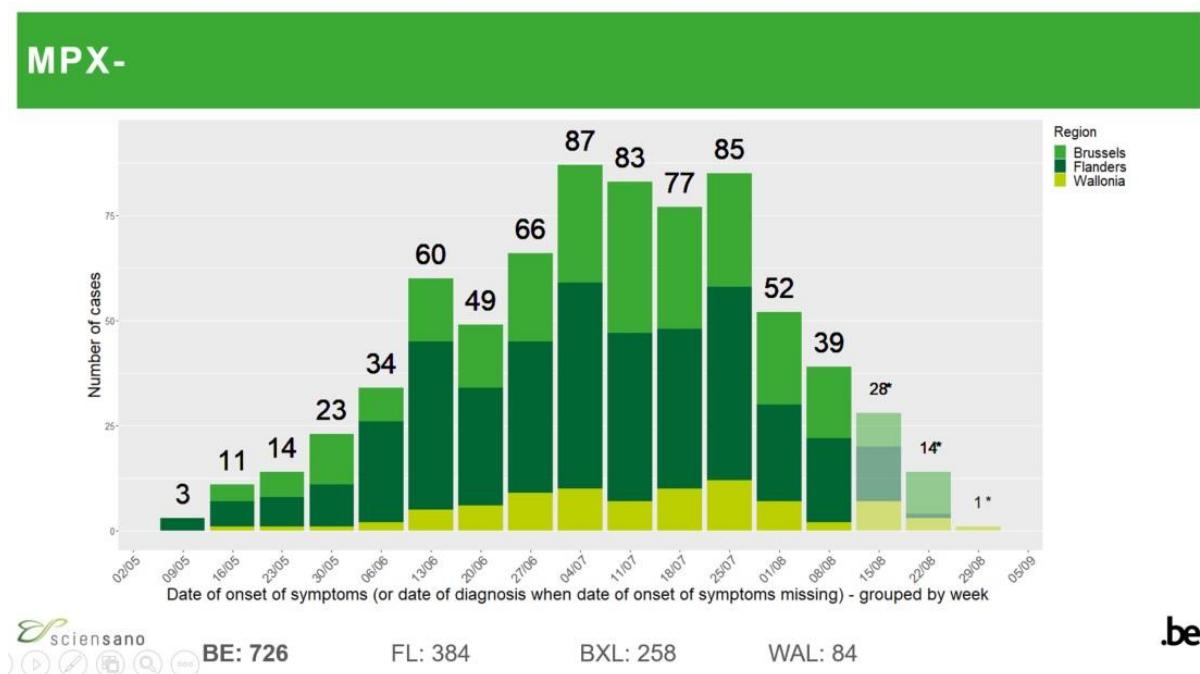
³ Epidemiology data will be rapidly be out-of-date.



3.2 Belgium (Sciensano 30/08/2022)

As of September 05, 2022, a total of 726 confirmed cases of MPX have been reported by regional governments/administrations in Belgium. These include 384 cases in Flanders, 258 cases in Brussels and 84 cases in Wallonia (Sciensano, 30/08/2022).

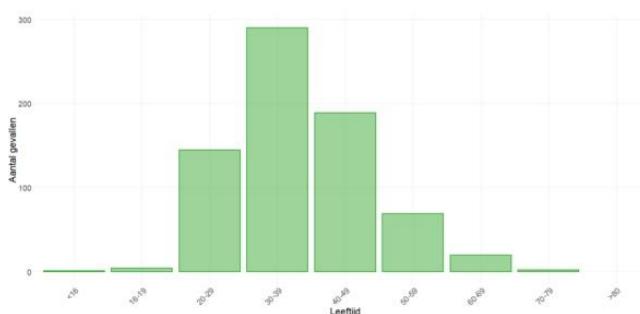
Like in Europe, the number of new infections seems to slow down, but the decreasing trend still needs to be confirmed the coming weeks



The majority of cases are observed in men (99%) and 2 women and 2 transgender persons. The age is distributed as follows (Median 37 years; IQR 30-43):

Demographics

- Men 99%
- Age:



- Mainly gbMSM: 94% (585/622)
Hetero: 6%



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In addition, 67% of cases are HIV+ in Belgium compared to about 50% in the rest of Europe.

HIV status & PrEP use

- HIV Status (n = 476 (67%))

HIV+	171
HIV-	335
PrEP	166
no PrEP	152
Unk	16



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3.3 Mathematical models (ECDC and UK)

Model-based, stochastic simulations of MPX outbreaks have been developed by ECDC in collaboration with the European Health Emergency preparedness and Response Authority (HERA) to include vaccination as a response option. These simulations can be interpreted as an MPX outbreak starting in any given country or setting. Simulations accounted for uncertainties in parameters related to the current outbreak. They investigated the potential impact of MPX outbreak response strategies for achieving outbreak control, particularly of vaccination strategies used PPV and PEPV. The model built on a previously published branching process model, which was substantially adapted to the current MPX situation.

According ECDC report, modelling **the efficient use of vaccines indicates that PPV vaccination would be the most efficient strategy when there is less effective tracing**. The modelling also suggests that **PEPV vaccination of contacts would offer a marginally more efficient approach** if there are both higher uptake levels and more effective tracing (as fewer vaccines would be needed for a relatively larger increase in the probability of outbreak control per vaccinated individual), while the absolute probability of outbreak control with PEPV is still lower than with PPV. In settings where higher vaccine uptake is expected, PEPV vaccination of close contacts of cases should also be considered, or even ring vaccination. Among these, contacts with a high risk of developing severe disease, like children, pregnant women, and immunocompromised individuals, should be prioritized (ECDC, 08/07/2022).

In case of low vaccine supply, **PEPV** has been used for past imported outbreaks, **but there are limited data on its efficacy**. Some of which are from animal challenge models (Nguyen et al., 2022) or more recent from human studies (Thy et al., 2022).

- a. In the UK outbreak in 2018, 3 cases were declared and 154 contacts were identified (including 147 HCWs). Among those contacts, 131 received PEPV (126 of whom were HCWs). 1 secondary case occurred in a vaccinated HCW who received PEPV 6 days after exposure.
- b. In a 2019 imported outbreak in the United Kingdom with a single case, 18 contacts were identified, 17 of whom (including some children) were vaccinated. There were no secondary cases. No clinically relevant post-vaccination adverse events were reported.
- c. In France, PEPV ring vaccination of two doses of MVA-BN®, 28 days apart, has been recommended since 29 May 2022 for people who have had physical skin-to-skin contact or have shared hygienic tools or textiles (such as toothbrushes or towels), or have had more than 3 hours of contact less than 2 meters apart, with a person with probable or confirmed symptomatic MPX. In one observational analysis, Thy and collaborators show that among the 276 vaccinated individuals, 12 (4%) had a confirmed MPX breakthrough infection with no severe infection. Ten out of 12 patients developed a MPX infection in the five days following vaccination and two had a breakthrough infection at 22 and 25 days. PEPV with a third-generation smallpox vaccine was well tolerated and effective against MPX but did not completely prevent breakthrough infections (Thy et al., 2022).

In case of more vaccine supply, **PPV** could be implemented in larger groups.

In UK, models seems to show a progressive decrease of cases in the future. Nowcast growth rate and incidence of MPX cases in England. 7a shows estimates by specimen date and 7b shows estimates by report date.

<https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-7>

Figure 7a

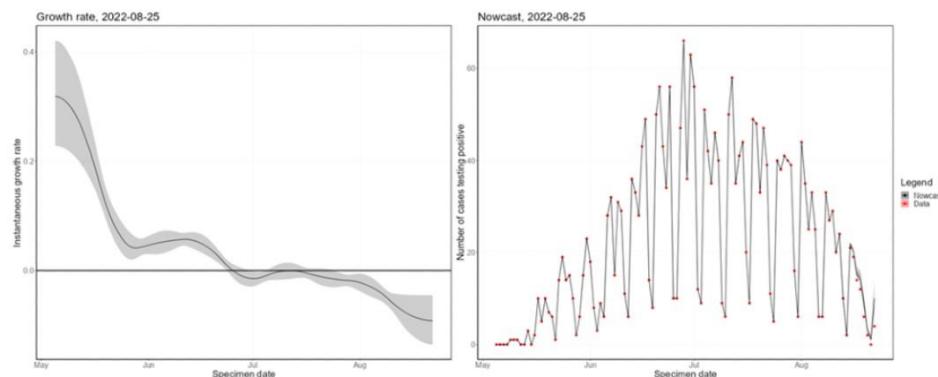
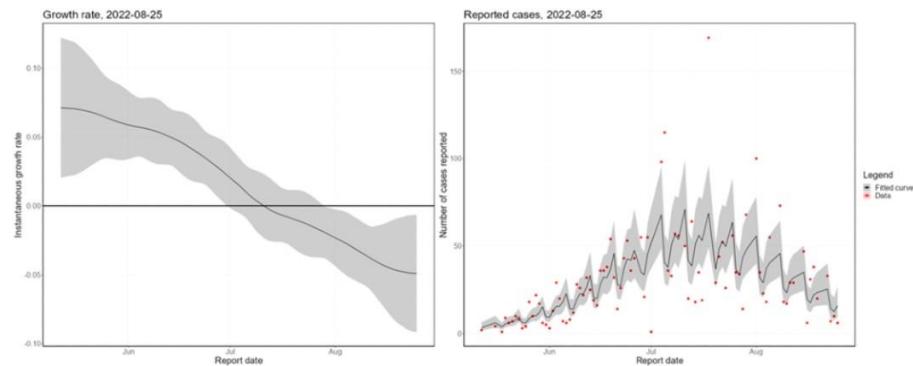


Figure 7b



Based on the scientific evidence from the cases reported in the current outbreak, **the likelihood of MPX spreading further in networks of people with multiple sexual partners in the EU/EEA is considered very high** and the likelihood of spreading among **the broader population** is assessed as **very low**. **The impact of the disease remains low for the majority of cases**. The overall risk is therefore assessed as **moderate** for people having multiple sexual partners (including some groups of Gay, Bisexual and other Men-who-have-Sex-with-Men - GBMSM) and **low** for the broader population (ECDC, 08/07/2022 ; RAG, 29/07/2022).

3.4 High Risk Contacts (HRC) classification

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)

- Household contacts;
- Sharing of clothing, bedding, kitchen utensils, etc. while having lesions;
- Unprofessional caregivers, while having lesions;
- Professional caregivers who were in close contact without Personal Protective Equipment (PPE), including staff of the Sexually transmitted disease (STD) testing centers;
- Professional caregivers exposed to contagious materials (sharp injury, body fluids, aerosols);
- Lab staff exposed to contagious specimen;
- Close and prolonged (>=3h) fellow passengers in bus, train or plane. 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 MPX has been observed on multiple occasions in areas where the disease is endemic. The US CDC collected data 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 MPX is estimated to be 3.5-5/10 000. These data suggest that there is approximately **one HCW infection for every 100 confirmed MPX cases.**

A study commenced in February 2017, with the intention to evaluate the effectiveness, immunogenicity, and safety of a third-generation smallpox vaccine, MVA-BN®, in HCW 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).

4 Vaccination against Smallpox and Monkeypox

Vaccines against smallpox are inferred to be effective in preventing or minimizing the severity of MPX based on available immunogenicity data from clinical studies and efficacy data from animal challenge studies. Some countries have maintained strategic stockpiles (STP) of first-generation smallpox vaccines. These old vaccines against smallpox **are not recommended for MPX, as they do not meet current safety and manufacturing standards.**

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. 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.

Imvanex® is the only one vaccine authorised by the EMA for use against MPX disease in the EU. Imvanex® has been authorised to protect adults from MPX disease in the EU since 22 July 2022. It is also authorised to protect people against diseases caused by the vaccinia virus. These new indications were added to Imvanex®'s existing authorisation against smallpox, which has been in place in the EU since 2013.

Imvanex® is currently only authorised for SC injection (under the skin). However, data reviewed by the EMA suggest that a smaller dose (1/5) of the vaccine can trigger similar levels of antibodies when it is injected ID (just below the top layer of the skin) instead. This means that more people could be vaccinated. The EMA's EMA advice of 19/08/2022 aims to support national authorities who may decide to use Imvanex® as an ID injection. This would be a temporary measure to protect at-risk individuals while vaccine supplies remain limited (EMA, 19/08/2022).

For now, Post-Exposure Prophylaxis Vaccination (PEPV) is not considered by EMA as an indication of the vaccine.

In the United States, the vaccine is available under the brand name Jynneos®. EMA's EMA advice is recommending that Jynneos® can be used to prevent MPX, while supplies in the EU remain limited. This advice aims to support national authorities who may decide to import Jynneos® as a temporary measure.

More information on these vaccines can be found:

EMA – Imvanex®: <https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex>

FDA – Jynneos®: <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>

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.**

Third generation smallpox MVA-BN® vaccines have a better safety profile than older generations in the adult population. Nevertheless, ID injection shows a higher local reactogenicity compared to the standard dose and route. There was a relatively high percentage of subjects (20%) that failed to receive the second vaccination during a unique controlled clinical study (Frey et al., 2015).

In the absence of a formal opinion from the EMA on the safety of these vaccines for **immunosuppressed people, pregnant women and children**, MVA-BN® vaccines are considered as safe by the SHC. If the physician assesses that the benefits outweigh the risks, the SHC supports vaccination of these patients on an individual basis. At this time, the Council does not see any major contraindications to their vaccination. But, an individual B/R balance must be done by the physician before vaccination for these groups.

- **Immunocompromised people**: the MVA-BN® vaccines cannot replicate in human cells and hence is less likely to cause side effects than conventional smallpox vaccines. MVA-BN® vaccines 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 (CHMP) 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).
- **Pregnant women**: the use of MVA-BN® vaccine during pregnancy and breast-feeding women is not well studied.

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).

- **Children**: the use of MVA-BN® vaccines for children is not well studied and MVA-BN® vaccines are not licensed for children.

Nevertheless, several paediatric studies of other vaccines using MVA as a vector (often at a considerably higher dose than used in Imvanex®) have been undertaken with a reassuring side effect profile. In a tuberculosis vaccine trial of approximately 1.500 infants, aged approximately 5 to 6 months, MVA85A (Tameris et al., 2013) at a dose of 1×10^8 Plaque-Forming Unit (PFU), this dose was very well tolerated. In a trial of 100 Gambian infants who received MVA85A (Ota et al., 2011) at a dose of 5×10^7 PFU and in a further study of 100 infants who received MVAmalaria (Afolabi et al., 2016) at a dose of $1-2 \times 10^8$ PFU, there was a tolerable safety profile. The adverse event profile with MVA-BN would be expected to be identical to the profile with these tuberculosis and malaria candidate vaccines and therefore provides some reassurance of its use in children (UKHSA, 2022).

Safety and efficacy of Jynneos® is currently not established in children, but data with similar vaccines including the MVA-based vaccines used in the vaccination campaigns in the 70's for smallpox are reassuring. If Jynneos is used in the paediatric population, the adult regimen should be considered and data collected to confirm a positive benefit/risk profile (EMA, 27/06/2022).

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 or Jynneos® - US)

5 Transitional emergency measures due to the lack of vaccines in Belgium

If the RAG (Sciensano) and the Federal Public Service (FPS) Health consider that the Belgian epidemiological situation is not under control with the measures currently in place and that the supply of vaccines in Belgium is too limited, the Council **proposes two transitional emergency measures to temporarily increase the availability of doses in the short term.**

ATTENTION

- These transitional emergency measures apply only to immunocompetent individuals. The standard regimen recommended by the EMA should be used when in doubt or for clearly immunocompromised patients.
- These transitional emergency measures should end as soon as the Belgian epidemiological situation is under control or as soon as sufficient vaccines are available.
- These emergency measures are not (yet?) supported by robust scientific, immunological and clinical evidence in humans. The safety, the individual clinical impact and the effectiveness of these measures in terms of public health for the control of the outbreak in Belgium are not (yet?) validated on a large scale.
- These emergency measures are not subject to conventional authorization by the EMA. They must therefore be accompanied by a systematic and controlled system of informed consent from the person (complete and transparent medical information).
- If the person refuses these transitional measures, the Council strongly recommends limiting close contact and sexual activity to one fixed partner until the epidemiological situation improves or the Belgian and global availability of vaccines increases. Condoms (latex or polyurethane) may protect your anus (butthole), mouth, penis, or vagina from exposure to MPX. However, condoms alone may not prevent all exposures to MPX since the rash can occur on other parts of the body (CDC, 05/08/2022).
<https://www.cdc.gov/poxvirus/monkeypox/prevention/sexual-health.html>

Notes: These emergency measures, if applied in Belgium, should be subject to validated clinical protocols allowing the collection, at least at the Belgian level, of new scientific data concerning the safety and clinical effectiveness of these vaccine strategies against MPX. Registration of the vaccines administered in the existing tools should be made mandatory and a centralized national database would be recommended (to allow follow-up and research).

Priority 1: Transitional emergency measure concerning intradermal (ID) administration of 1/5 of the dose normally administered in SC

For non-immunocompromised persons, the SHC could support an emergency vaccination strategy with two ID administration of 1/5 of the normal SC dose at 28 days of interval.

This strategy is supported by the FDA since 09/08/2022 and the EMA since 19/08/2022.

<https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-authorizes-emergency-use-jynneos-vaccine-increase-vaccine-supply>

https://www.ema.europa.eu/en/documents/other/considerations-posology-use-vaccine-jynneos/imvanex-mva.bn-against-monkeypox_en.pdf

It is essential to recognize the importance of proper ID administration to ensure that immune responses will be comparable to those obtained with a standard SC dose. Therefore, it is recommended that ID administration of the reduced dose be performed by professionals experienced in the ID administration of vaccines.

The use of low volume syringes is recommended to maximize dose withdrawal.

This ID approach also has some limitations due to the very limited safety data available (<200 people), the higher reactogenicity compared to the standard dose and route and the fact that there was a relatively high percentage of subjects (20%) that failed to receive the second vaccination during this unique controlled clinical study (Frey et al., 2015). This is well supported by others studies (Frey et al., 2021 ; Wilck et al., 2010).

Excerpts from the EMA document: "***Intradermal delivery of vaccines, allowing antigen sparing, is approved for several vaccines, notably BCG (tuberculosis vaccine), influenza and rabies vaccines. Intradermal delivery of a reduced dose of MVA-BN has been investigated in a phase 2 clinical trial (NCT 00914732 – Frey et al., 2015). Vaccinia-naïve healthy adults (18-38 years) with no prior history of smallpox vaccination were randomised to receive either 2 subcutaneous [SC] doses (0.5 mL, 108 TCID50/dose) in the deltoid area or 2 intradermal [ID] doses (0.1 mL, 2x107 TCID50/dose) in the volar area of the forearm with a 4-week interval. The vaccine administered in the trial can be regarded as similar to the currently marketed product even though the description of the nominal strength is different. The lower ID dose of IMVANEX, one fifth of the SC dose, was immunologically non-inferior to the standard SC dose.*** As the study was conducted in healthy subjects, questions remain whether the reduced ID dose will be immunologically non-inferior to the standard SC dose in specific groups such as immunocompromised individuals or in people with HIV. The exact level of protection and duration of protection afforded by the vaccine regimens are unknown. **No data on cellular immunity have been reported.** As shown with another MVA vaccine, **the ID route resulted in significantly higher local adverse reactions (i.e., erythema, induration) than the SC route.** Around 30% more subjects for ID vs. SC administration reported symptoms of local reactogenicity after the first dose and around 20% more subjects after the second dose. Moderate/severe erythema and induration occurred after any vaccination in almost all subjects with the ID route, with higher rates of severe reactions after the second dose (80% vs. 40%). Following any vaccination, the proportion of subjects with erythema or induration at the local injection site graded as severe (>30 mm) was 58.1% for the SC group and 94.8% for the ID group. In addition, the proportion of subjects who experienced local reactogenicity lasting at least 30 days, unexpected nodules and skin discolouration at the vaccination site was 25% and 67.0% for the SC group and ID group, respectively. However, SC and ID groups did not significantly differ in systemic reactogenicity. There was no significant difference in the proportion of subjects with moderate/severe systemic reactions among groups after vaccination. No vaccine-related serious adverse events were reported during the study. It is also important to note that the available data on ID administration **are based on 2 doses of vaccine**, which are deemed critical to achieve vaccine response and to maintain protection in the longer term. **There is no intradermal presentation authorised in the EU.** The EMA has neither information on the maximum number of 0.1 mL doses that can be effectively withdrawn from the authorised presentation nor information on vial stopper performance/integrity after repeated puncture since no feasibility study has been conducted on this. **However, the use of low-dead volume syringes is recommended to maximise dose withdrawal.** There is no information on storage conditions (e.g. time out of refrigeration) between multiple uses to support physico-chemical stability or stability from a microbiological perspective. **From a microbiological point of view, once opened, the product should be used immediately".**

Priority 2: Transitional Emergency Measure regarding the extension of the deadline

For non-immunocompromised individuals, the SHC could support a **two dose emergency strategy with a longer delay for the second dose**. As there are few data on the degree of protection and duration of effect after the first dose, **this extension of the 28-day interval between the two doses should be as limited as possible**. Depending on how the situation evolves in terms of vaccine supply, the second dose should be administered as soon as possible after the 28 days recommended by regulatory authorities.

This strategy is supported by extrapolation of some human immunological data and clinical evidence in animal models (Earl et al., 2008 ; Greenberg et al., 2016 ; Maclennan et al., 2019 ; Pittman et al., 2019 ; Osterholm et al., 2022). This strategy has also already partially implemented by some NITAGs for certain groups especially in case of PEPV vaccination.

On clinicatrials.gov the results of a phase 2 are interesting. It shows a rather strong anamnestic response to a booster dose 2 years after 1 or 2 doses. The data look re-assuring for longer term immunity after one dose.

[An Open-Label Phase II Study to Evaluate Immunogenicity and Safety of a Single IMVAMUNE Booster Vaccination Two Years After the Last IMVAMUNE Vaccination in Former POX-MVA-005 Vaccinees - Study Results - ClinicalTrials.gov](#)

However, some authors caution about this approach in view of the number and type of neutralising antibodies and thus their effectiveness in fully protecting the individual after a single dose (Townsend et al., 2013 ; Zaack et al., 2022). In addition, this approach is not currently supported by the FDA and WHO. EMA has not commented on this topic.

*Excerpts from the FDA document: "This option was determined to be **inadvisable**, particularly because it might both be insufficiently protective while at the same time providing individuals with a false sense of reassurance that they were protected against monkeypox when the actual level of protection would be unknown and quite possibly inadequate".*

Excerpts from the WHO document: "The third-generation vaccine MVA-BN is characterized by its lower reactogenicity, and as a consequence the vaccine is differentiated from other products by its recommended schedule of two doses to be administered 4 weeks apart. While some authorities may consider offering PEP as a single dose, there is as yet little data on the relative effectiveness of this approach."

People who have already received the first SC dose with an extended delay for the second one **may be eligible to receive the second ID injection as soon as possible**
(cf. Priority 1).

The SHC therefore has a clear preference for priority 1 in this context.

6 Drugs (for information only)

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).

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 (AMM) 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)".
- 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-vaccine pour des populations particulières, lorsque les antiviraux ne peuvent pas être utilisés : femmes enceintes, jeunes enfants avec poids de moins de 13 kg. »

Recently, Webb and collaborators (2022) produce a systematic review of clinical guidelines for MPX. Treatment guidance was mostly limited to advice on antivirals. Seven guidelines advised cidofovir (7/14 - 50% - four specified for severe MPX only), 29% (4/14) tecovirimat, and 7% (1/14) brincidofovir (Webb et al., 2022).

In Germany: "Administration of human vaccinia immunoglobulin may also be considered as PEPV 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>

7 Other NITAGs recommendations for information (Sciensano, 29/07/2022)

1. International recommendations with regards to monkeypox vaccination, as of 26 July

Agency	Post-exposure	Pre-exposure	Date	Reference
WHO	For contacts of cases, post-exposure prophylaxis is recommended with an appropriate second- or third-generation vaccine	Pre-exposure prophylaxis is recommended for: <ul style="list-style-type: none">• <u>health workers</u> at risk• <u>laboratory personnel</u> working with OPXV• clinical laboratory staff performing diagnostic testing• <u>others who may be at risk</u> as per national policy	June 14	Vaccines and immunization for monkeypox: Interim guidance, 14 June 2022 (who.int)
ECDC	Effective for outbreak control in settings with effective contact tracing and high vaccine uptake levels The priority target groups are: <ul style="list-style-type: none">• <u>close contacts of cases</u> (e.g. sexual partners, household contacts, HCWs and individuals with other prolonged physical or high-risk contact)• among these, <u>contacts with a high risk of developing severe disease</u> like children, pregnant women and immunocompromised individuals, <u>should be prioritized</u>	Most efficient vaccination strategy to control the outbreak, in particular when there is less effective contact tracing Prioritization of individuals at substantially higher risk of exposure can be considered: <ul style="list-style-type: none">• <u>MSM</u> based on a risk assessment according to certain criteria and behaviors• <u>staff members who work in sex on premises venues</u>, if they are regularly exposed to items or surfaces likely to be contaminated with body fluids or skin cells• <u>professionals in healthcare or laboratory settings</u> and outbreak response team members, based on risk assessment	July 8	Monkeypox multi-country outbreak - first update (europa.eu)
CDC	'It is important that states and other jurisdictions identify <u>contacts of confirmed or probable monkeypox cases</u> to offer vaccine for PEP' Expanded PEP is also possible: includes <u>people with certain risk factors</u> of having been recently exposed, <u>even if they have not had documented exposure</u>	'people whose jobs may expose them to orthopoxviruses, such as monkeypox, get vaccinated with either ACAM2000 or JYNNEOS to protect them if they are exposed to an orthopoxvirus': <ul style="list-style-type: none">• Clinical <u>laboratory personnel</u> who perform testing• <u>Research laboratory workers</u> who directly handle cultures or animals contaminated or infected	June 30 (PEV)/ June 2 (PrEV)	Considerations for Monkeypox Vaccination Monkeypox Poxvirus CDC Monkeypox and Smallpox Vaccine Guidance Monkeypox Poxvirus CDC
		• Certain <u>healthcare and public health response team members</u> designated by public health authorities to be vaccinated for preparedness purpose		

Guidelines in a number of selected countries

Country	Post-exposure	Pre-exposure	Date	Reference
Netherlands	All high- and intermediate-risk contacts (as per definition of contacts)	MSM and transgender people receiving HIV-PrEP, on ART, or known to be at high risk for STI (for example sex workers) (estimated at +/- 32.000 people)	July 8	Risico-inschatting contacten en maatregelen LCI richtlijnen (rivm.nl) advisiebrief-mpx-prep-vaccinatie-6-juli-2022.pdf
France	All adult contacts at risk of having been exposed (as per definition of contacts)	Only if sufficient vaccine supply; Otherwise PEP of contacts has priority Populations at very high risk of exposure, in particular: <ul style="list-style-type: none">• <u>MSM and transgender people</u> reporting multiple sexual partners (about 250.000 people);• <u>people in prostitution</u>;• <u>professionals working in sexually oriented venues</u> People with a <u>very high risk of occupational exposure</u> to Monkeypox (only on individual basis if the risk is very high)	May 20 (PEV) July 7 (PrEV)	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 (has-sante.fr) Haute Autorité de Santé - Monkeypox : une vaccination préventive proposée aux personnes les plus à risque d'exposition (has-sante.fr)
Germany	<ul style="list-style-type: none">• After close physical contact via non-intact skin or mucous membranes or with prolonged unprotected face-to-face contact <1m• After contact without adequate personal protective equipment• For personnel in laboratories with accidental unprotected contact with laboratory samples containing non-inactivated monkeypox material	Only if sufficient vaccine supply; Otherwise PEP of contacts has priority <ul style="list-style-type: none">• <u>MSM with changing partners</u>;• <u>Personnel in special laboratories</u> with targeted activities with infectious laboratory samples containing orthopox material, <u>after individual risk assessment</u> by safety officers	June 9	RKI - Recommendations of the STIKO - Press release of the STIKO on the monkeypox vaccination recommendation

Country	Post-exposure	Pre-exposure	Date	Reference
United Kingdom	<ul style="list-style-type: none"> All high and medium-risk contacts <p>When supplies are limited, priority for:</p> <ul style="list-style-type: none"> health staff contacts at higher risk of severe disease contacts at high risk of ongoing exposure, for example GBMSM with multiple sexual partners 	<p><u>MSM</u> at highest risk due to a large number of contacts (believed to be around 40,000)</p> <p><u>HCWs</u>:</p> <ul style="list-style-type: none"> staff expected to provide care to monkeypox cases in high consequence infectious disease (HCID) units staff in sexual health clinics designated to assess suspected cases staff in additional hospitals outside HCID units designated to care for monkeypox patients workers in laboratories where pox viruses are handled, and others who work in specialist and reference laboratories staff regularly undertaking environmental decontamination around cases of monkeypox <p>Only first dose, second dose when more vaccines have arrived</p>	June 21	Monkeypox outbreak: vaccination strategy - GOV.UK (www.gov.uk) Recommendations for the use of pre and post exposure vaccination during a monkeypox incident (publishing.service.gov.uk)
Spain	High-risk contacts (as per definition of contacts)	Currently not recommended because of limited quantity	June 9	Propuesta vacunacion Monkeypox.pdf (sanidad.gob.es)
Denmark	Contacts with a moderate or high risk of infection after a concrete and individual health professional assessment by a specialist in infectious medicine	Not recommended yet	July 12	Guidelines for the management of monkeypox in Denmark - Danish Health Authority (sst.dk)

03/08/2022: NACI – CA

<https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/guidance-imvamune-monkeypox.html>

22/08/2022: CDC – USA

<https://www.cdc.gov/poxvirus/monkeypox/health-departments/vaccine-considerations.html>

8 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-ehrlich-institute9edbb432-b6ad-46da-9708-b458b3b4eb7a.pdf?sfvrsn=fdc398ff_1&download=true

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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.

BLUMENTAL Sophie	Pediatric Infectious Disease	HUDERF
CALLENS Steven	Infectiology, Internal medicine	UZ Gent
CARILLO SANTISTEVE Paloma	General medicine, vaccination	ONE
CORNELISSEN Laura	Epidemiology, Obstetrics, Gynaecology	Sciensano
DE SCHEERDER Marie-Angélique	Travel Medicine, HIV, Infectiology	UZ Gent
DE SCHRYVER Antoon	Family Medicine and Population Health	UZA
DOGNE Jean- Michel	Pharmacovigilance	UNamur, EMA
FRERE Julie	Pediatrics, Infectiology	CHU Liège
HULSTAERT Frank	Epidemiology, Health Economics	KCE
MAERTENS Kirsten	Vaccinology	UAntwerpen
PELEMAN Renaat	Infectiology, Vaccinology	UZ Gent
SOENTJENS Patrick	Infectiology, Tropical diseases, Vaccinology	ITG Defense
VAN DAMME Pierre	Epidemiology, Vaccinology	UAntwerpen
VANDEN DRIESSCHE Koen	Pediatric infectious diseases	UZA
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine, HIV	CHU Saint-Pierre, ULB
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.

MAHIEU Romain	Inspection d'hygiène CCC Gezondheidsinspectie GGC	CCC Brussels
MALI Stephanie	Coordinator, center of excellence for vaccines	AFMPS-FAGG
THEETEN Heidi	Vaccinology	VAZG

TOP Geert

WUILLAUME Françoise

Manager vaccination program

Vaccine vigilance

VAZG

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.).

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