

# Monkeypox multi-country outbreak - first update

8 July 2022

## Key messages

Since early May 2022 and as of 7 July, cases of monkeypox (MPX) have been reported in non-endemic countries. Twenty-six European Union/European Economic Area (EU/EEA) countries have reported 4 908 cases, representing 65% of all cases reported worldwide in 2022.

In the current outbreak in non-endemic countries, most of the cases have been detected in males between 18-50 years, and primarily among men who have sex with men (MSM). Particular sexual practices have facilitated the transmission of MPX among MSM groups with multiple partners. However, there is also the potential for further transmission in other population groups. In endemic areas, MPX virus has been detected in a broad range of animal species, and the occurrence of zoonotic transmission events cannot be excluded, but there is no documented evidence of human-to-animal or animal-to-human transmission in the EU/EEA to date.

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 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 hospitalisations reported. Severity of MPX may be higher among young children, pregnant women, and immunocompromised individuals.

Based on the 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 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 MSM) and low for the broader population. The risk of establishment of an enzootic cycle and spill-over events to humans is considered to be low.

Early diagnosis, isolation, effective contact tracing, and vaccination strategies are key for the effective control of this outbreak. It is essential to underpin all response measures with risk communication and community engagement efforts. Until recently, MPX was quite rare in the EU/EEA, with only sporadic imported cases reported. This, along with the fact that clinical presentations in the current outbreak are not typical, makes diagnosis by the average clinician difficult. Activities to increase awareness of health professionals across specialties should continue, providing information on the range of clinical presentations of currently diagnosed cases, testing recommendations and testing procedure, advice on infection prevention and control in primary care, public health measures in place in the country, as well as risk communication tips and advice for outreach in their communities. In addition, countries should review their diagnostic capacity and increase the availability of testing.

At this point, mass vaccination for MPX is not required nor recommended. Unless contact tracing can successfully identify a high proportion of infected contacts, mathematical modelling results indicate that targeted pre-exposure prophylaxis (PrEP) of individuals at high risk of exposure would be the most effective strategy to use vaccines to control the outbreak. Therefore, prioritising groups of MSM 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 PrEP vaccination would be the most efficient strategy when there is less effective tracing. The modelling also suggests that post-exposure prophylaxis (PEP) 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 PEP vaccination is still lower than with PrEP vaccination. In settings where higher vaccine uptake is expected, PEP 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 prioritised.

Targeted national vaccination programmes should be implemented within a framework of collaborative research and clinical trial protocols with standardised data collection tools for clinical and outcome data. Targeted health promotion interventions and community engagement are also critical to ensuring vaccine uptake and reaching out to those most at risk of exposure. Antivirals for the treatment of MPX should preferably be used in the framework of a clinical trial to obtain harmonised safety and efficacy data.

### What is new in this update

This updated rapid risk assessment includes new information on the different clinical picture of MPX cases in the ongoing outbreak. It includes novel insights from a stochastic mathematical model developed collaboratively by ECDC and the European Health Emergency preparedness and Response Authority (HERA) to assess vaccination strategies as outbreak response measures. It also contains references to all the recently produced technical documents on contact tracing and risk communication and community engagement developed in collaboration between ECDC and the World Health Organization (WHO) Regional Office for Europe and civil society organisations.

## Event background

Since early May 2022 and as of 7 July, 7 553 cases of monkeypox (MPX) have been reported in non-endemic countries. As of 7 July, 26 EU/EEA countries have reported 4 908 cases, representing 65% of all cases reported in this outbreak worldwide.

Most of the cases have been detected in males between 18-50 years, and primarily among men who have sex with men (MSM). As of 4 July 2022, 21 cases in women and four cases in children in Spain, France, the Netherlands and the United Kingdom have been reported, and are under investigation [1].

A detailed summary and analysis of case-based data reported through The European Surveillance System (TESSy) since 2 June 2022 by all the countries and areas of the WHO European Region, including the 27 countries of the EU, Western Balkans countries, and an additional three countries of the EEA, can be found in the Joint ECDC-WHO regional Office for Europe Surveillance Bulletin published weekly [1].

As of 7 July 2022, 2 645 confirmed cases of MPX have been reported from 29 non-EU/EEA countries: the United Kingdom (1 350), the United States (560), Canada (358), Switzerland (131), Brazil (76), Israel (52), Australia (20), Ghana (19), Peru (15), United Arab Emirates (13), Mexico (11), Chile (8), Argentina (6), Colombia (5), Serbia (5), Singapore (2), South Africa (2), the Bahamas (1), the Dominican Republic (1), Ecuador (1), Georgia (1), Gibraltar (1), Jamaica (1), Lebanon (1), Morocco (1), Puerto Rico (1), South Korea (1), Turkey (1), and Venezuela (1).

## Disease background

In the ongoing outbreak of MPX, several differences in the clinical presentation compared to those available in the literature have been noticed and reported from countries in various ECDC-organised webinars. Most frequently reported differences include: no prodromal symptoms or very mild; rash appearing before prodrome; rash presenting with very few lesions and/or limited only in genital or peri-anal areas; and lesions that do not evolve synchronously [2, 3].

A recent study in Belgium, available as a preprint, retrospectively examined anorectal and oropharyngeal swabs collected for sexually transmitted infection (STI) screening. The authors identified three cases with no reported symptoms and a positive anorectal MPX PCR, among 224 men [4]. The results were confirmed by seroconversion in all three cases. However, there are some notes of caution in interpreting these findings, such as the potential for recall bias and the inability of confirmation of the positive result from another anatomical site. In addition to this study, other countries (Italy, Portugal) have reported a very small number of subclinical cases of MPX in the

current outbreak in webinars jointly organised by the WHO Regional Office for Europe and ECDC. The finding of subclinical or asymptomatic MPX cases and their role in transmission needs to be further studied.

Whether transmission of monkeypox virus (MPXV) through genital secretions can occur is currently unclear. MPXV DNA was identified during this outbreak in seminal fluid samples of young adult male patients in Italy who reported condomless sexual intercourse [5]. Human-to-human transmission through close physical contact in sexual networks is a significant factor in the current outbreak, but further research is needed to clarify whether MPXV can be sexually transmitted through genital fluids rather than through contact with skin lesions, droplets, or fomites. The presence of MPXV nucleic acid alone cannot be considered definitive evidence of infectivity. In addition, the permanence of MPXV in semen and its public health relevance should be further studied.

For more details on MPX's disease characteristics, please refer to ECDC's updated factsheet [6].

For more information about MPXV infection in animals, please consult the European Food Safety Agency (EFSA) [7] and the World Organisation for Animal Health (WOAH) questions and answers [8].

## Mathematical modelling of the MPX outbreak

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. We investigated the potential impact of MPX outbreak response strategies for achieving outbreak control, particularly of vaccination strategies used pre- or post-exposure. The model built on a previously published branching process model [9], which was substantially adapted to the current MPX situation.

We modelled two groups of contacts of MPX cases (regular versus non-regular contacts) to allow different parameter values and interventions (e.g. contact tracing and vaccination strategies) for each group separately. The classification into regular and non-regular contacts reflects the context of potential exposures, in distinction from the contact classification reflecting the likely risk of exposure. The model allows for a diverse interpretation of 'regular' and 'non-regular' contacts, which makes the model results generalisable to various settings. One can consider regular contacts as household members and a small number of regular sex partners, and non-regular contacts as sporadic contacts at events with a larger number of individuals who have had no or infrequent contact before. The fact that some individuals have a larger number of contacts is modelled through relevant heavy-tailed probability distributions (e.g. the number of secondary cases is generated from a negative binomial distribution). More technical details on the modelling approach have been summarised in the caption beneath Figure 1 and in the ECDC technical report 'Considerations for contact tracing during the monkeypox outbreak in Europe' [10].

For this rapid risk assessment update, we present novel modelling insights on the following questions:

- How likely is outbreak control within 12 weeks through different interventions and vaccination strategies (defined here as no new secondary cases)?
- What is the added contribution of vaccination strategies in achieving outbreak control within 12 weeks over the isolation of cases and contact tracing alone? (i.e. the difference of outbreak control achievable with a strategy of isolation and tracing when adding vaccination expressed per vaccinated individual).

We considered the following vaccination strategies:

- PEP vaccination of contacts of cases;
- PEP vaccination of contacts of cases, and contacts of contacts;
- PEP vaccination of contacts of cases, and PrEP vaccination of at-risk individuals; and
- PrEP vaccination of at-risk individuals.

We modelled all vaccination strategies in addition to the isolation of cases and contact tracing, and for each we explored two scenarios of 20% or 80% vaccine uptake. We assumed near-perfect isolation of cases at ~90% effectiveness in preventing new secondary cases (i.e. in the model we allowed that a few cases in isolation may generate a few secondary cases, just by chance, or due to imperfect adherence). The effectiveness of tracing (i.e. the probability of successfully identifying newly infected contacts) was assumed at 50% for regular contacts and 10% for non-regular contacts. Vaccinations were assumed to start six weeks after the first symptomatic case. Note that the model results can be seen as a reference point for the chosen vaccine uptake and the effectiveness of tracing. Results in terms of the probability of achieving outbreak control are expected to shift either higher or lower depending on the setting-specific vaccine uptake and the probability of finding infected contacts. For a broader spectrum of results for the effectiveness of isolation and contact tracing alone in 36 different combinations of scenarios please consult the ECDC technical report 'Considerations for contact tracing during the monkeypox outbreak in Europe' [10].

The modelling results suggest that the effective isolation of cases (at an assumed ~90% effectiveness in preventing new secondary cases) and tracing the infected contacts of cases (at a probability of successfully finding 50% of newly infected regular contacts and 10% of non-regular contacts) make the likelihood of outbreak control by week 12 a little more than 50%. Unless the effectiveness of tracing increases further to finding 80% of the

newly infected regular contacts and 20% of the newly infected non-regular contacts, the addition of PEP or PrEP vaccination at low uptake levels of 20% results in little increase of the chance to achieve outbreak control by week 12 (Figure 1, panel a). In contrast, a high uptake of 80% of PrEP vaccination increases the effectiveness to achieve outbreak control by week 12 to more than 75%. Where a higher effectiveness of contact tracing can be achieved and combined with high vaccine uptake levels of 80% (an upper bound estimate), the chance of outbreak control by week 12 can be maximised, with PrEP vaccination being the most effective strategy.

In terms of the efficiency of the added contribution of the vaccination strategies (meaning increasing the probability of outbreak control per vaccinated individual, and as compared to a strategy of isolation and tracing alone), the modelling suggests that PrEP vaccination would be most efficient at less effective tracing, as it would result in a relatively larger increase in the probability of outbreak control per vaccinated individual. PEP vaccination of contacts would offer a marginally more efficient approach, if there are both higher uptake levels and more effective tracing, although the absolute probability of outbreak control per vaccinated individual is lower with PEP vaccination than with PrEP vaccination (Figure 1, panel a). In addition, for PrEP vaccination, a higher efficiency can also be achieved by targeting a smaller group of individuals (Figure 1, panel b).

We derived two estimates for the PrEP vaccination, for a smaller and larger group of key populations: (i) an estimate for the number of individuals identifying as MSM who have ever tried to get PrEP for HIV infection [11, 12] and who may be willing to receive the smallpox vaccine, and (ii) an estimate for the number of healthcare workers at risk from exposure to disease or infections and physical proximity [13]. Please note that these groups are only used for calculating the efficiency of outbreak control with PrEP vaccination in general terms (fewer/more people vaccinated). If individuals at risk or who practise highly risky behaviour can be targeted more directly, the efficiency gain for outbreak control per vaccinated individual is expected to increase further.

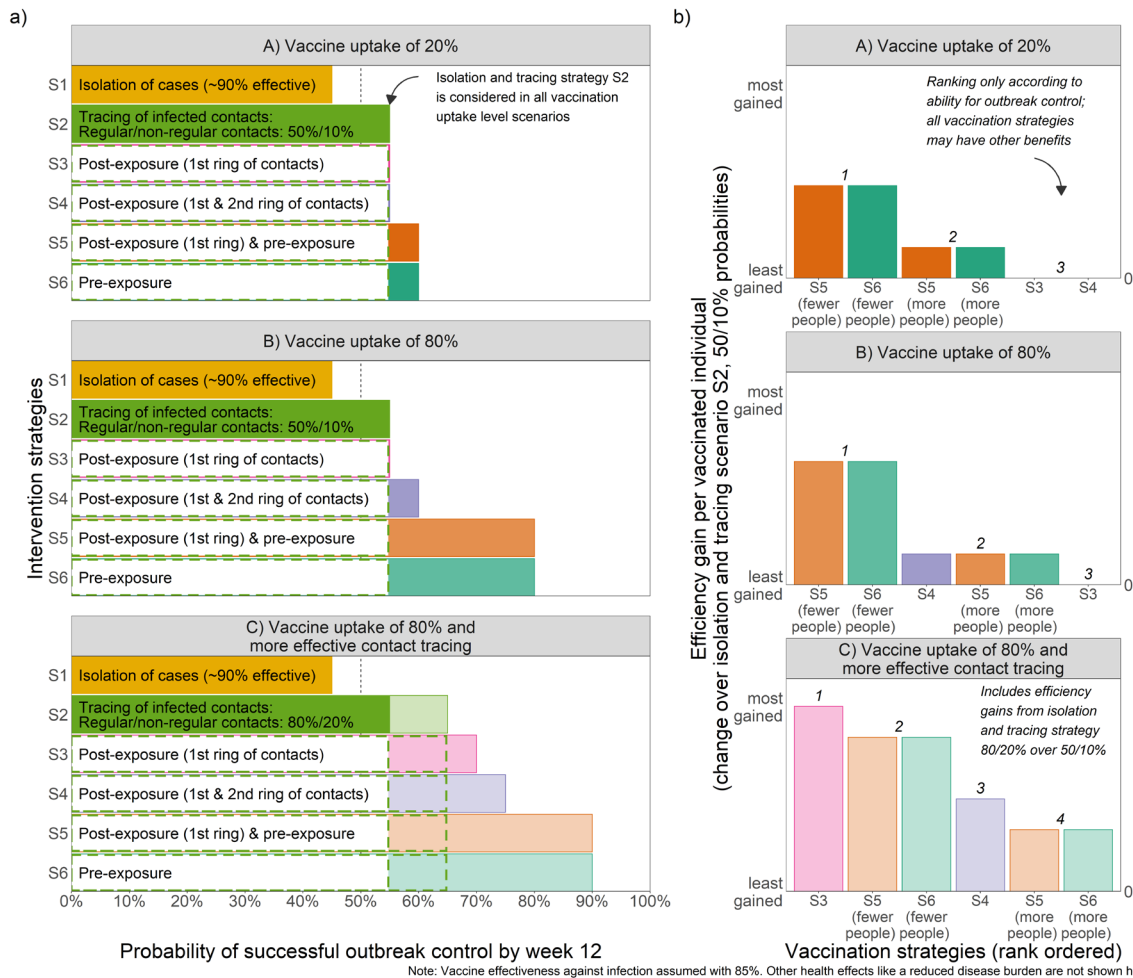
These findings emphasise the impact of vaccination strategies as a complement to the isolation of cases and effective contact tracing for controlling the outbreak. Effective isolation of cases and contact tracing are key when aiming to bring the outbreak under control. Adding vaccination can increase the chances of outbreak control by breaking transmission chains, especially when combined with more effective tracing, and with the most efficient use of vaccines in PEP vaccination of contacts of cases and focused PrEP vaccination targeting individuals with a substantial risk of exposure in the current epidemic context (e.g. individuals with multiple casual sexual contacts and/or sexual partners, or health workers at risk of exposure).

Limitations of this model include that we only consider the effect against transmission to achieve outbreak control, and a vaccine effectiveness against infection of 85%. In addition, the results do not account for the potential health impact of the vaccines on cases and vaccinated individuals (e.g. vaccines may reduce the severity of MPX in vaccinated individuals, while there is also the potential for adverse events following immunisation; for more details see below under 'Vaccination'). More details on the assumptions and limitations of this model are included in the caption of Figure 1.

The model reflects the current uncertainties regarding the MPX epidemiology in the EU/EEA in 2022 and it may be updated in accordance with new evidence or a change in the epidemiological situation.

**Figure 1. The effectiveness and efficiency of MPX outbreak control by week 12 with different response measures combining isolation of cases, contact tracing, and vaccination strategies**

**Panel a)** shows the simulation results for the effectiveness of successful outbreak control at week 12. **Panel b)** shows the efficiency gain of the vaccination strategies over isolation and tracing to achieve outbreak control at week 12



Intervention strategies S1-S6 all include the isolation of cases, and intervention strategies S2-S6 all include contact tracing. The scenarios labelled with A) and B) in rows 1-2 show a lower value for the effectiveness of tracing (i.e. the probability of finding newly infected contacts), at lower and higher values for the vaccine uptake, while scenarios labelled with C) in row 3 show a higher value for the effectiveness of tracing and at higher values for the vaccine uptake (an upper-bound estimate). Each intervention strategy was evaluated for 2 000 simulated MPX outbreaks. All simulations started with one initial case, and we sampled from relevant heavy-tailed probability distributions that reflected a mean incubation period of 10 days (range 5-21 days), a mean delay until case isolation of 2.5 days (range 1.5-3.5 days), and a combined value for  $R_0$  of 2.5 (with a dispersion parameter of 0.5 for non-regular contacts and of 1.0 for regular contacts), which we separated in the baseline for the regular and non-regular contacts by assuming 60% of secondary cases to arise among non-regular contacts and 40% among regular contacts. We assumed near-perfect isolation (i.e. in the model just by chance, or due to imperfect adherence, a few cases in isolation may generate secondary cases, too, based on  $R_0 = 0.1$  and a dispersion parameter of 1.0 that were used to inform the number of secondary cases from a negative binomial distribution). If the isolation of cases was at much lower levels of effectiveness or adherence, the incremental benefit of vaccines would increase (as more new secondary cases that would have been prevented through isolation may then be prevented through the protection from the vaccines). We used reasonable base-case (or in the absence of those, worst-case) parameter values in the baseline (e.g. we assumed a proportion of 10% of infections being asymptomatic or 'mild', which do not isolate but can be traced in the model). Sensitivity of parameter values have been explored before (with a higher initial number of undetected cases and higher  $R_0$  being the most influential in explaining larger outbreak sizes) [10]. We present maximum outbreak durations of up to 12 weeks, as the modelling framework may need to be updated for longer durations (e.g. with more evidence or a change in community transmission). The values used for the effectiveness of tracing, and for the vaccine uptake, can be read as a reference point for interpretation and they are indicative of the range that one could expect the impact to fall in terms of outbreak control (i.e. if the isolation of cases, contact tracing, or the vaccine uptake or vaccine effectiveness was lower than we assumed here the probability of outbreak control would decrease; likewise, higher values would shift results further to the right). Similarly, all simulations started with one case, and if there is more than one case at the start of the vaccination then the chance for outbreak control by week 12 would be expected to decrease, too. The effectiveness and efficiency would also increase further after 12 weeks, and at much higher rates for the strategies involving PrEP vaccination. We have also looked over only 12 weeks here, while the benefit from vaccinating individuals may be much longer-lived and protect to a certain degree from future MPX infections, too. To reduce the effect of stochastic noise, we present the model results in discrete categories. The differences between strategies in panel b) is indicative of the numeric differences between strategies, and we have ranked strategies across all three scenarios. Note that we quantified the efficiency as the difference of outbreak control achievable with the vaccination strategies against the strategy of isolation and tracing without vaccination; results are expressed per vaccinated individual, but the efficiency may decrease if more than one dose is used per individual. Stochastic models like the one used here are the most appropriate and robust type of mathematical model in the early stages of infectious disease outbreaks, where 'randomness' has a large effect. In addition, note that these scenarios assume one sequential outbreak, and it is possible that countries may observe multiple cases being imported over time to cause separate, localised outbreaks which may appear as one ongoing outbreak having started with one initial case. Our results could be interpreted for each such introduction separately. Not shown here is the potential health impact of the vaccines on cases and vaccinated individuals. For vaccination, we assumed a vaccine effectiveness against transmission of 85%; that the vaccine needs to be given up to 14 days after exposure; and the effective vaccine protection takes 7 days (range 2-14) to establish. For more details on the vaccines and the considerations around their use as an option for response, see below under 'Vaccination'.



# ECDC risk assessment for the EU/EEA

This assessment is based on evidence available to ECDC at the time of publication. It follows the ECDC rapid risk assessment methodology, where the overall risk is determined by a combination of the probability of infection and the impact of the disease on the affected population [14]. ECDC will continue monitoring the event and will reassess the risk depending on its evolution and the implemented response measures.

## What is the risk of further spread of MPX in EU/EEA countries?

### Risk in persons with multiple sexual partners, including some MSM

Human-to-human transmission of MPX occurs through close contact with infectious material from skin lesions of an infected person, through respiratory droplets in prolonged face-to-face contact and through fomites. In the current outbreak in non-endemic countries, cases of MPX are still identified primarily among groups of MSM. Data from virus sequencing show that the outbreak is characterised by the expansion of one specific virus clade (MPXV clade 3, formerly 'West African clade') with no evidence of multiple introductions. MPXV shows signs of microevolution during human-to-human transmission in the current outbreak without significant mutation affecting its transmissibility or severity[15].

Particular sexual practices (e.g. having multiple casual sexual encounters and/or multiple sexual partners, including being a sex worker, participation in chemsex<sup>1</sup>) are very likely to have facilitated and could further facilitate the transmission of MPX among MSM groups. Outbreaks of other infections (meningococcal meningitis, hepatitis A, and multi-drug resistant *Shigella sonnei*) have been linked to travel abroad and to social events attracting an MSM audience (e.g. Pride events [16], large summer music festivals, etc). Several such events are currently taking place in Europe and may be conducive environments for the transmission of MPXV. ECDC and the WHO Regional Office for Europe, in collaboration with community organisations, have developed advice to public health authorities regarding these events [17]. Most of the currently detected cases are in males between 18-50 years of age [1], who have therefore not received the smallpox vaccine, which confers cross-protection to MPXV (according to older studies, it is estimated to be up to 85% effective in preventing infection). The probability of further spread of MPXV among people with multiple sexual partners in interconnected sexual networks in EU/EEA countries and globally, in the coming months, is therefore assessed as high.

As regards the severity of the disease in this outbreak, it presents with mild to moderate symptoms. Relatively few hospitalisations are reported (about 10%, for the cases with available data), which, according to information from countries in ECDC-organised webinars, are mostly for isolation purposes or for the management of pain and secondary bacterial infections [1]. The impact of MPX for people with multiple sexual partners, including some MSM, is still assessed as low, which combined with the high probability of infection leads to an overall moderate risk for people with multiple sexual partners. A significant percent of the cases detected to date have been people living with HIV (PLHIV) (39%) [1] undergoing anti-retroviral treatment. The impact of MPXV infection on PLHIV who are not on appropriate anti-retroviral treatment in the at-risk groups could be higher.

### Risk for the broader population

Despite the current focus of circulation of MPXV among groups of MSM with multiple partners, the potential exists for transmission in other population groups. Severity may be higher among young children, pregnant women, and immunocompromised individuals, therefore resulting in a higher impact at the individual level. People older than 65 years, despite ageing immune systems, are probably protected from developing severe disease due to maintenance of T-cell immunity from past smallpox vaccination or illness. To date, only sporadic and mild MPX cases have been diagnosed in the broader population, including 21 women and four children [1]. Such cases are expected, and sporadic cases have been observed in the broader population during outbreaks of other infectious diseases among MSM (e.g. hepatitis A [18]). Nevertheless, these cases still need to be thoroughly investigated and traced, as they may reveal valuable transmission information.

Based on the evidence from the cases reported in this outbreak to date, the probability of further spread of MPXV among the broader population in EU/EEA countries in the coming months is assessed as very low, leading to an overall low risk for the general population.

### Risk for health professionals

The assessment of risk for health professionals including laboratory personnel has not changed since ECDC's first rapid risk assessment on MPX from 23 May [19]. The risk depends on the type of exposure and ranges from low (when wearing appropriate PPE) to high when exposed for prolonged time to a case without appropriate PPE, performing an aerosol generating procedure without PPE, or suffering an occupational exposure in a laboratory

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<sup>1</sup> Chemsex is defined as using certain substances immediately before or during sexual activity to facilitate, prolong, and/or intensify sexual experience. Ref: Bourne A, Reid D, Hickson F, et. al, The Chemsex Study: Drug Use in Sexual Settings Among Gay and Bisexual Men in Lambeth, Southwark and Lewisham. Technical Report. London: Sigma Research, London School of Hygiene & Tropical Medicine (2014).

without appropriate PPE or equipment [19]. No cases of transmission to health professionals through occupational exposure have been reported to date in this outbreak.

## Risk of transmission through substances of human origin (SoHO)

To date, no cases of MPXV transmission through substances of human origin have been documented. Besides animal studies, studies of the recent human cases also show presence of the pathogen in the human tissues and body fluids [5, 20, 21]. In addition, as mentioned above, MPXV was detected in the semen of patients with confirmed infection, but the available data are insufficient to form conclusions on the infectivity of semen, particularly as regards the potential permanence of MPXV [5]. The assessment of the risk of transmission through substances of human origin remains unchanged as low, with the overall risk for recipients in the EU/EEA as also low [19].

## Risk of establishment of an enzootic cycle and spill-over to humans

Detection of the MPXV or antibodies has been shown in a broad range of animal species, including non-human primates, opossums, different types of African squirrels and rats, dormice, African bush-tailed porcupines, and African hedgehogs, among others. Other species found susceptible to the infection that are more likely to be kept as pets are rabbits, hares, prairie dogs, and pet rodents. As MPX is an emerging disease in Europe, little is known about the susceptibility of animal species endemic to Europe. In addition, there is no documented evidence of domestic animals, such as cats and dogs, and livestock being affected by MPXV.

To date, there is no documented evidence of human-to-animal or animal-to-human transmission of MPXV in EU/EEA countries. However, the occurrence of (reverse-) zoonotic transmission events cannot be excluded. Should susceptible wild animals come in contact with the virus, an enzootic cycle might establish; as a consequence, the disease could eventually become an endemic zoonosis in the EU/EEA. The current likelihood of the disease to become enzootic among EU/EEA wild animal species and subsequently to observe spill over event to humans is considered to be low. Considering that in the coming weeks/months, human-to-human transmission of the virus is expected to remain the primary mode of transmission, the impact of such events is estimated to be low. As a result, the risk of establishment of an enzootic cycle and spill-over events to humans is considered to be low.

# Options for response

The number of MPX cases by country in the EU/EEA countries varies and may not be explained only by differences in the size of the at risk populations [1]. Other factors that may explain these differences include: countries being in different phases of the outbreak, underdiagnosis and/or underreporting at the national level (including the effects of misdiagnosis and stigma), differing socioeconomic status which does not allow for participation in international mass gatherings or differences in behaviour of at-risk populations.

Early diagnosis, isolation, effective contact tracing and vaccination strategies are key for the effective control of this outbreak, as supported by ECDC modelling presented in this risk assessment and former reports [10].

These priorities require continuing significant preparedness and response activities, including:

- The review of laboratory diagnostic capacity and increase of the availability of testing for orthopoxviruses;
- The continuing activities to increase awareness of health professionals around the ongoing outbreak;
- The development, review and implementation of vaccination strategies;
- The monitoring of antiviral use for the treatment for severe cases; and
- Strong risk communication and engagement with at-risk groups, as well as the broader public.

## Overall preparedness and response

### Laboratory diagnostics and sequencing

Countries should review their molecular diagnostic testing capacities and capabilities for MPXV. Increasing availability of testing sites and increasing overall testing capacity will facilitate the prompt diagnosis of MPX cases, particularly in countries which have currently diagnosed a low number of cases.

Several countries have developed and validated PCR assays for the detection of MPXV [22-24] and commercial PCR kits are under development but are not currently widely available [25-27]. If there is limited experience in MPX diagnostic testing, laboratories are encouraged to refer specimens for confirmatory testing. Countries not having national reference laboratory capacity for MPX should refer specimens from at least the first suspected case(s) for confirmatory testing to an experienced laboratory in another country. The European laboratory network for emerging viral diseases (EVD-LabNet) facilitates the sharing of protocols and confirmatory testing support through their network members [28]. The European Virus Archives (EVAg) can provide positive control materials for diagnostic testing [29]. EU/EEA countries in need of diagnostic and/or sequencing support should contact EVD-LabNet ([EVD.outbreak@ecdc.europa.eu](mailto:EVD.outbreak@ecdc.europa.eu)) and ECDC ([ECDC.microbiology@ecdc.europa.eu](mailto:ECDC.microbiology@ecdc.europa.eu)).

Sequencing of MPXV assists in general understanding of the outbreak as well as providing potential data to better understand transmission chains and patterns of spread [15]. It is recommended that whole genome or partial genome raw reads and assemblies are deposited into available databases designed for sequence data sharing.

## Increase awareness of health professionals

Monkeypox is a tropical disease and until recently was quite rare in EU/EEA, as only sporadic imported cases were diagnosed. This, coupled by the fact that clinical presentations in the current outbreak are not typical of what has been reported in previous outbreaks, makes the diagnosis challenging for clinicians that do not have specialist training or experience related to such cases. Information presented in the ECDC organised webinars speaks about frequent and even multiple events of misdiagnosis of the MPX cases before they are finally confirmed. Continuing awareness activities targeting health professionals should be undertaken. Mild or subclinical cases may be missed or misdiagnosed as STIs or other exanthematous diseases (e.g. varicella, herpes simplex virus infections, impetigo) or the diagnosis of a case may be delayed leading to further transmission and jeopardizing control activities. Availability of sexual health services varies in EU/EEA countries, therefore, information should target and reach different specialties, including dermatologists, sexual health specialists, internal medicine and infectious disease specialists particularly if working with HIV, urologists, as well as general practitioners and paediatricians depending on the existing structures of the country. Cases in the broader population are expected, even if there is no widespread transmission among them (such as the four paediatric MPX cases detected to date) but such cases prompt the need to increase awareness among all medical practitioners [30-32]. Information provided to medical practitioners should include the range of clinical pictures of currently diagnosed cases, testing recommendations and testing procedure, advice on infection prevention and control in primary care, an outline of the public health measures in place in the country, as well as risk communication tips and advice for health professionals for outreach to their communities.

Awareness activities targeting clinicians should be a priority in all countries but particularly in those which have diagnosed a low number of cases to address misdiagnosis and under-reporting.

WHO has developed interim guidance for the management of MPX cases [33].

## Vaccination

Currently no vaccine is authorised for use against MPX in the EU, but the 3rd generation smallpox vaccine Imvanex™ (Modified Vaccine Ankara - MVA) has been authorised by the European Medicines Agency (EMA) for the EU market against smallpox [34]. MVA has shown protection in primate models challenged with lethal doses of MPXV [35] and is considered a potential vaccine for MPX because of the similarity between the MPXV and the smallpox virus. Older generation smallpox vaccines have significant side effects and in addition, are no longer authorised and should not be used. The MVA is authorised in adults against infection and disease caused by both smallpox and MPXV in the USA (Jynneos™) and Canada (Imvamune™) as well as other related orthopoxviruses (Canada only). There are minor differences in terms of manufacturing process and quality specifications between the various marketing authorisations in the different countries, which are due to differences in the datasets submitted for marketing authorisation, but which do not affect the final quality of the vaccine [36]. MVA is administered as a subcutaneous injection, preferably in the upper arm, with a 2-dose regimen, with the second dose given at least 28 days after the first. However, data from human and animal studies suggest that a single dose of MVA offers fast protection against MPX, and that the second dose mainly serves to extend the durability of protection [37].

As Imvanex™ is not authorized for use against MPX in Europe, there is urgent need for an emergency authorisation. The EMA has started a review of data to extend the use of Imvanex™ to include protecting people from MPX disease [38]. Considering the limited availability of Imvanex™, EMA's Emergency Task Force recommended that Jynneos™ can be used to provide protection against MPX in the EU if national authorities decide, as a temporary measure, to import Jynneos™ from the US. In order to address the limited supply in the EU/EEA and to make vaccines rapidly available, the European Commission's Health Preparedness and Response Authority (HERA) has purchased 109 090 doses of Jynneos™ for distribution to Member States [39]. The vaccine delivery to Member States is conducted on a pro-rata basis and has already started, prioritising the countries with highest number of cases which have granted all national authorisations for the vaccine.

It is important to note that scientific evidence on the vaccine effectiveness of MVA against MPX is lacking. Evidence on the extent by which the vaccine can prevent or modify disease when given as PEP vaccination as well as data on long-term immunogenicity are scarce. MVA can be used in people living with HIV, although vaccine response among those with CD4 cell count <100 cells/m<sup>3</sup>, has not been established [40,41]. The limited clinical data on use in pregnancy and the animal studies on fertility and developmental toxicity did not identify any specific reason for concern. Safety and efficacy of the MVA 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 [42]. In the UK, MVA was offered as part of the public health response after several cases of MPX were imported in the recent period, including to children and infants, with no known adverse events. If MVA is used in the paediatric population, the adult regimen should be considered and data should be collected to confirm a positive benefit/risk profile.

In the EU/EEA, few countries recommend vaccination with MVA to prevent MPX for certain risk groups either as PrEP and/or PEP vaccination. However, there is no unified approach across the Member States. According to an Health Security Committee survey conducted on 10 June 2022 and an ECDC desk review, 12 countries (Cyprus,



Denmark, France, Germany, Greece, Ireland, Italy, Latvia, Luxembourg, Portugal, Slovakia, Spain) are currently discussing recommendations to vaccinate at-risk contacts for PEP and certain healthcare professionals for PrEP or PEP. One country (Romania) is considering the vaccination of at-risk contacts on a case-by-case basis, but currently does not recommend vaccinating healthcare professionals. As per 4 July, at least six countries (Denmark, France, Germany, Ireland, Italy, Spain) have published official documents recommending vaccination with MVA as PEP to people who have been in close contact with MPX cases. Germany is considering PrEP vaccination with MVA for people with an increased risk of exposure and/or infection such as MSM or personnel in special laboratories.

At this point in time, mass vaccination for MPX is not required nor recommended [43]. The following preliminary considerations on vaccination strategies can be understood as options for response.

### *Pre-exposure prophylaxis*

- Based on the modelling results, PrEP vaccination is the most effective strategy for the use of vaccines to control the outbreak. Mathematical modelling indicates that vaccination, if uptake is sufficiently high and when used in addition to effective isolation of cases and tracing of contacts, substantially increases the potential to control the outbreak.
- Use of PrEP vaccination is most efficient (i.e. increasing the probability of outbreak control per vaccinated individual) in settings with less effective tracing, and highly efficient in settings with more effective tracing.
- Targeted PrEP vaccination of smaller groups of individuals may have a high efficiency in outbreak control. Therefore, the prioritisation of individuals at substantially higher risk of exposure can be considered. MSM may be offered PrEP vaccination based on a risk assessment according to certain criteria and behaviours (e.g. recent history of multiple casual sexual contacts and/or sexual partners, attending sex on premises venues, or group sex or chemsex practices, or a proxy marker such as recent bacterial STI). PrEP vaccination for occupational risk exposure can also be considered for staff members who work in sex on premises venues, such as saunas, if they are regularly exposed to items (e.g. linens) or surfaces likely to be contaminated with body fluids or skin cells.
- Also, professionals in healthcare or laboratory settings and outbreak response team members may be targeted for PrEP vaccination based on risk assessment.

### *Post-exposure prophylaxis*

- Based on the modelling results, PEP vaccination of contacts of cases would be the most efficient vaccination strategy (i.e. increasing the probability of outbreak control per vaccinated individual) in settings with more effective tracing and higher vaccine uptake levels. The absolute probability of outbreak control per vaccinated individual is expected to be lower with PEP vaccination than with PrEP vaccination.
- The priority target groups for PEP vaccination are close contacts of cases (e.g. sexual partners, household contacts, HCWs and individuals with other prolonged physical or high-risk contact as defined in the recent ECDC publication on contact tracing [10]). Among these, contacts with a high risk of developing severe disease like children, pregnant women and immunocompromised individuals, should be prioritised for PEP vaccination.
- PEP vaccination of contacts and of contacts of contacts, according to a ring vaccination scheme as conducted during recent Ebola outbreaks, could also be considered. The time of vaccination should be as close as possible to the potential date of exposure.
- Ideally, PEP vaccination should be administered within four days of first exposure (and up to 14 days in the absence of symptoms). For individuals who had received a live replicating first or second generation smallpox vaccine in the past and sustain a high-risk exposure to a probable or confirmed MPX case, a single dose of MVA may be offered (i.e. as a booster dose). Community engagement efforts for the identification of contacts around cases should be put in place in order to achieve a significant impact in terms of lowering disease burden and transmission. Data on effectiveness and safety of PEP vaccination should be collected to refine benefits and risks in the context of MPX prevention strategies.

### *Combined pre-exposure and post-exposure prophylaxis*

- Another option to prevent infection in the context of limited vaccine supply and mild symptoms, would be to offer PEP vaccination to close contacts of cases and, in addition, to consider targeted PrEP vaccination of individuals at substantially higher risk of exposure when more vaccines become available.

All decisions around immunization should be based on an assessment of risks and benefits on a case-by-case basis. Finally, considering the lack of clinical data on protection against disease from these different vaccination strategies, national vaccination programmes should be implemented within a framework of collaborative research and clinical trial protocols with standardized data collection tools for clinical and outcome data. Targeted health promotion interventions and community engagement are also critical to ensure uptake and reach those most at risk of exposure.

### *Vaccination Strategies Adopted Outside EU/EEA*

Outside the EU/EEA the following vaccination strategies have been recommended: the UK Health Security Agency (UKHSA) based on the currently available vaccine supply and advice from the Joint Committee on Vaccination and Immunisation (JCVI) recommends that a reactive selective vaccination strategy with the aim of interrupting transmission in the subset of individuals at increased risk of exposure should be deployed [44]. PrEP vaccination

with MVA should be offered to MSM at highest risk due to a large number of contacts. High risk criteria include a recent history of multiple partners, participating in group sex, attending sex on premises venues or a proxy marker such as recent bacterial STI. The initial priority is to deliver first doses to as many MSM in the highest risk group as possible. Subject to the evolving epidemiology, a second dose may be advised around 2-3 months later to provide longer lasting protection. UKHSA have also advised that vaccination may also be offered to staff members who work in sex on premises venues, such as saunas, if they are regularly exposed to items (e.g. linens) or surfaces likely to be contaminated with body fluids or skin cells. This offer could be combined with supplementary approaches to provide outreach vaccination to high risk MSM who may not be in contact with sexual health services. Other population groups to be prioritised for PrEP vaccination include individuals with high occupational risk of exposure such as HCWs providing care to MPX cases, staff in sexual health clinics, and laboratory workers handling pox viruses. As the evidence on vaccine effectiveness of post-exposure vaccination with MVA is very limited, vaccine should be prioritised for those most likely to benefit based in time between exposure and vaccination (vaccination between 4 -14 days after exposure) and risk of severe disease. Risk groups to be prioritised include children below 10 years, pregnant women, immunosuppressed individuals.

The US CDC and the Advisory Committee on Immunization Practices (ACIP) are recommending vaccination with MVA or the ACAM2000 vaccine as PrEP to certain clinical and research laboratory personnel and to certain healthcare and public health response team members designated by public health authorities to be vaccinated for preparedness purposes. PEP vaccination is recommended to close contacts of MPX cases [45,46]. The Canadian National Advisory Committee on Immunization (NACI) also recommends vaccination with MVA as PrEP for adults at high risk of occupational exposure in laboratory research setting but, due to the currently limited supply, not to personnel in clinical diagnostic laboratory settings. PEP vaccination is recommended to individuals with high-risk exposures to a probable or confirmed case of MPX, or within a setting where transmission is ongoing [47]. On 5 July the US government announced its first phase of the national MPX vaccination strategy that aims to rapidly deploy vaccines in the most affected communities [48]. To date, vaccines have only been provided to those who have a confirmed MPX exposure. With newly available doses, CDC is recommending that vaccines be provided to individuals with confirmed MPX exposures and presumed exposures. This includes those who had close physical contact with someone diagnosed with MPX, those who know their sexual partner was diagnosed with MPX, and MSM who have recently had multiple sex partners in a venue where there was known to be MPX or in an area where MPX is spreading. As additional doses will be received from the manufacturer, they will be made available to jurisdictions to expand availability to the vaccine for individuals with elevated risk.

## Antivirals

Tecovirimat is the only antiviral drug with an indication for the treatment of orthopoxvirus infections, including MPX, authorised by EMA, but remains in short supply, although a joint procurement for the EU/EEA countries is underway. Brincidofovir and cidofovir are the only other antiviral drug options for severe MPX cases, but particularly the latter has significant side effects [2]. Use of tecovirimat and other antivirals in the ongoing MPX outbreak should be preferably undertaken in the framework of a clinical study to obtain efficacy data. A common treatment protocol has been discussed with EMA and should be started soon with the participation of several member states. Additional clinical trial protocols, including randomised trials, are under development and discussed also with WHO.

Health authorities should consider prioritisation of patient groups that could be offered treatment. Use of antivirals for post-exposure prophylaxis could be additionally investigated.

## Management of cases

Advice for the management of ambulatory MPX cases in isolation can be found in ECDC's first rapid risk assessment on MPX [19].

In healthcare settings, prevention of transmission is based on appropriate infection prevention and control measures. MPX is considered to be predominantly transmitted through direct contact with body fluids or lesion material, through prolonged face-to-face contact or through contact with fomites (e.g. contaminated clothing or linens). There is still uncertainty about the role of respiratory droplets and aerosols and the risk to healthcare workers through this transmission route. WHO recommends placement of the patient in a well-ventilated, single room with dedicated bathroom or toilet. In addition to applying standard precautions, including meticulous hand hygiene, healthcare workers providing care to suspected or confirmed cases in the hospital should wear PPE including gloves, gown, a respirator (such as FFP2) and eye protection [33]. Aerosol-generating procedures should be performed in an airborne isolation room or, if not available, in a well-ventilated single room with closed door by personnel wearing appropriate PPE.

The patient room and other areas where patient care activities occur should be cleaned and disinfected in accordance with the national or facility guidelines. A recent study in healthcare setting revealed extensive environmental contamination in patient rooms including furniture, and bathroom area [49]. Surfaces should first be cleaned with detergent and water and then disinfected with an approved hospital disinfectant with virucidal properties. Disposable or dedicated patient care equipment should be used. Patient care equipment should be cleaned and disinfected in accordance with manufacturer instructions before use for other patients [33]

Clothing and linen should be handled with care to avoid infectious dust suspension in the air. Waste from MPX cases (such as dressings or other material soaked with lesion fluid or containing scabs) should be handled as infectious waste.

Cleaning staff should wear PPE including gloves, gown, respirator (FFP2) and eye protection when cleaning and disinfecting the patient room or patient care equipment. Healthcare facility cleaning staff can also be considered for pre-exposure vaccination with the smallpox vaccine.

## Waste management

In ECDC's rapid risk assessment from 23 May [19], it is mentioned that 'waste should be assessed depending on risk and handled in accordance with healthcare facility policies and local policy and regulations'. The UN classification of waste classifies clinical waste from MPX patients as category A (UN3549) and it does not distinguish between clades of the virus. Recently, some national authorities [50] have decided to classify waste contaminated with the currently circulating clade of MPXV as regular medical waste, however these are decisions made at the national level, and reflect that national authorities' decisions depend on their respective national risk assessment.

## Management of contacts

Contact tracing consists of the prompt identification of contacts of a MPX case to allow for management of those exposed and prompt diagnosis of potential secondary cases. It can also help identify settings or population groups where targeted interventions are needed. However, countries have reported that they face several challenges for contact tracing during the ongoing MPX outbreak including the fact that multiple anonymous contacts need to be traced, resources are limited at the regional or national levels, the stigma associated with MPX and varying levels of trust in public health authorities in different countries. Collaboration between public health and clinical service providers, particularly sexual health professionals where they exist, who are already experienced and have established procedures for partner notification for STIs, is critical to ensure that as many close contacts as possible are identified. Partner notification methodology, as used for STIs, can support contact tracing in the context of the MPX outbreak. Close collaboration with civil society and community-based organisations is important to build trust in contact tracing strategies and to ensure these strategies and accompanying risk communication are adapted to the affected groups, while diminishing stigmatisation.

ECDC has recently published a technical report on 'Considerations for contact tracing during the MPX outbreak in Europe, 2022'. This document provides additional information for the prioritisation of efforts to identify and manage close contacts of MPX cases as well as indicators for public health authorities in the EU/EEA that can be used for monitoring the efficacy of their contact tracing activities [10].

## Substances of Human Origin (SoHO)

In the donor assessment process, attention should be paid to the differing clinical presentation deviations from the course of illness in the current as compared to earlier outbreaks, in particular the asynchronous appearance and evolution of the skin lesions.

In inconclusive cases, confirmatory testing should be performed using nucleic acid amplification testing (NAAT), such as real-time or conventional polymerase chain reaction (PCR), preferable specific to MPXV. The recommended testing sample is skin lesion material [51]. In the absence of the skin lesions, an oropharyngeal swab can be taken, however, a negative oropharyngeal swab should be interpreted with caution [51,52] and taking into consideration the clinical history and picture. Sampling and interpretations of the results of commercial tests available on the EU/EEA market should be according to the test package insert.

## Mitigation of the risk of human-to-animal transmission

Probable and confirmed MPX cases should avoid close direct contact with animals including pet animals, livestock and wild (captive) animals. Similarly, close contacts of cases should avoid being in close direct contact with animals for 21 days after the last exposure to the virus.

To mitigate the risk of wild animals entering in contact with the virus, ensure that waste, including medical waste, is disposed of in a safe manner and is not accessible to rodent and other scavenger animals. Implementing actions to minimise the presence of the virus in the sewage system, where numerous rodents are living, should be considered.

## Risk communication and community engagement

Risk communication and community engagement (RCCE) strategies are a core element of any outbreak response and are essential to achieve results across all the proposed measures. In the context of the current monkeypox outbreak, ECDC, in collaboration with WHO Regional Office for Europe and civil society organisations, has produced several documents that address RCCE [17, 51-53] and provide examples of ongoing RCCE activities in the EU/EEA countries [54].

Public health authorities should partner with affected communities, including through civil society and community-based organisations already working with affected communities. This can include organisations working on testing and access to HIV care, or LGBT+ sexual health rights, and even organisers of summer events such as music festivals

or Pride events. This collaboration should focus on formulating adapted risk communication messages, selecting and using appropriate communication channels, and designing outreach strategies, which will also help to avoid and prevent stigmatisation. Such collaboration facilitates public health authorities in building trust with affected groups, which can be essential for contact tracing or increasing vaccine acceptance. The importance of such approaches has been seen in the recent COVID-19 pandemic, as well as in other epidemics such as Ebola [54, 55].

RCCE strategies may be informed by social listening, the monitoring of understanding, perceptions, concerns, and questions that circulate both in online and offline environments. Understanding these narratives and the sentiments behind them may help public health organisations design adapted and targeted risk communication messages, either to prevent the circulation of misinformation, or respond to it if necessary, including identifying any increase in stigma against affected groups. Stigma and fear can hamper public health responses, whether this drives people to hide their illness, avoid seeking care, or fail to adopt healthy preventive behaviour [56]. To limit stigma, it is essential to use respectful and inclusive language that does not link disease transmission to sexual orientation. Furthermore, risk communication methods should focus on amplifying and sharing facts about MPX and this outbreak in an understandable and accessible format.

Given the level of risk to the general population, most affected groups, such as MSM, healthcare workers, commercial sex workers, and those at risk of severe disease (immunocompromised people, pregnant women, children) should be considered a priority for RCCE strategies. A toolkit to support RCCE strategies, including key messages, has been jointly developed by ECDC and the WHO Regional Office for Europe and is available for adaptation and use by public health authorities [57].

## Limitations

This assessment is undertaken based on facts known to ECDC at the time of publication and several gaps in our knowledge still exist as regards MPX, including:

- The duration of viral shedding and the infectivity (including viral loads) of genital secretions and other body fluids.
- A more precise estimate of the infectious period, particularly the start of it.
- The documentation of pre-symptomatic and asymptomatic transmission of MPXV and investigation of the potential for transmission.
- The relative importance of the different transmission routes (skin vs. droplets vs. fomites vs. genital tract secretions).
- Studies on the potential risk of transmission through SoHO and studies on viremia among pre-symptomatic or asymptomatic patients.
- Operational research on the effectiveness of contact tracing.
- Estimates of secondary attack rates associated with different categories of contacts in various settings in Europe.
- Behaviour insights in the at-risk groups on their vaccination confidence as well as their compliance with public health advice.
- Information on the current residual cross protection from smallpox vaccination in the EU/EEA population.
- Efficacy and effectiveness data of the currently available MVA smallpox vaccine against MPX, and safety data for the use of the smallpox vaccine in young children, pregnant women and immunocompromised. Efficacy and effectiveness of MVA smallpox vaccine used pre-exposure and post-exposure.
- Efficacy data and safety profile of the available antiviral agents for the treatment of severe cases.
- Studies on the vulnerability of European rodent and other mammal species to MPXV.

## Source and date of request

ECDC internal decision, 28 June 2022.

## Consulted experts

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

## Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.



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