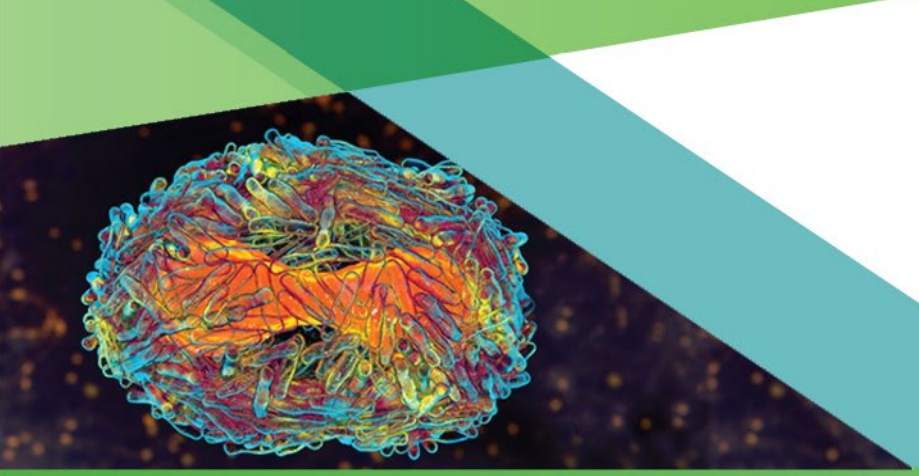


RAPID RISK ASSESSMENT

Monkeypox multi-country outbreak – second update

18 October 2022

Key messages

Since early May, and as of 11 October 2022, 20 455 confirmed cases of monkeypox (MPX) have been reported from 29 European Union/European Economic Area (EU/EEA) countries, including four deaths. As of 30 September, MPX confirmed cases reported from EU/EEA countries represented almost one third (29.7%) of the cases reported to the World Health Organization (WHO) globally (68 267 cases). The weekly number of MPX cases reported in the EU/EEA peaked in July 2022 and a steady declining trend has been observed since, with only a few cases being reported at the time of this update. Multiple factors have probably contributed to the decline of this outbreak, including efforts in risk communication and community engagement, increasing immunity in the most affected population due to natural immunity and vaccination, and a decrease after the summer in large cultural and social events frequented by the main risk groups for this outbreak.

The majority of cases continue to be detected in males between 18 and 50 years (87%), and primarily among men who have sex with men (MSM). Summer mass gatherings and specific sexual practices have facilitated the transmission of MPX among MSM groups until now. Sporadic cases in women and children have also been reported. Cases in the current outbreak continue to present with a spectrum of symptoms and signs that differs from what has been described in past outbreaks of MPX in endemic countries. In general, cases have presented in this outbreak with relatively mild symptoms although some patients describe significant discomfort, pain and complications. From the total number of cases reported in the EU/EEA, 1.1% have required hospitalisation for clinical care and five cases were admitted to intensive care.

Based on evidence in the current outbreak and the declining number of new infections, the overall risk of MPX infection is assessed as moderate for MSM and low for the broader population.

Early diagnosis, isolation, and effective contact tracing, supported by appropriate vaccination strategies remain key for the effective control of this outbreak. Mass vaccination against MPX is currently not required nor recommended. Considering limitations in vaccine supplies, primary preventive vaccination (PPV) and post-exposure preventive vaccination (PEPV) strategies may be combined focusing on individuals at substantially higher risk of exposure and close contacts of cases, respectively. PPV strategies should prioritise gay, bisexual, or other men or transgender people who have sex with men who are at higher risk of exposure based on epidemiological or behavioural criteria. Individuals at risk for occupational exposure should be considered based on risk assessment. Vaccination strategies will need to be kept under review as evidence on effectiveness is accumulated and adapted to the situation in each country according to the trajectory of the outbreak.

While some encouraging preliminary evidence is emerging on the performance of the MVA-BN vaccine, more robust data on vaccine efficacy and effectiveness is needed. 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. Health promotion interventions and community engagement are also critical to ensure effective outreach and high vaccine acceptance and uptake among those most at risk of exposure.

Suggested citation: European Centre for Disease Prevention and Control. Monkeypox multi-country outbreak – second update, 18 October 2022. ECDC: Stockholm; 2022.

Despite the improving epidemiological situation, it is important to continue active risk communication and community engagement efforts with the affected population to prevent a resurgence. Activities to increase awareness of health professionals across specialties should also continue in order to ensure prompt diagnosis and the appropriate management of cases and contacts. Testing services for orthopoxvirus should be available, while support to sexual health services is important to the continuation of case detection, contact tracing, and management of cases.

Future considerations for the evolution of the MPX outbreak and for preventing similar outbreaks are outlined, including the scenario that the outbreak resurges, it causes a continued low number of new cases almost exclusively among MSM, which is considered more likely currently, MPX wanes and finally it is eliminated in EU/EEA countries through concerted efforts in the European region.

What's new in this update

This update was triggered by the continuous decline of case numbers since the end of July 2022. It includes an updated risk assessment for the most affected sub-population and health professionals based on evidence from this outbreak and new information on MPX vaccine effectiveness. It reinforces the need for continued investment in the response to the MPX outbreak and finally, it includes a section on considerations for the evolution of the outbreak and for preventing similar outbreaks with qualitative scenarios.

Event background

Since early May, and as of 11 October 2022, 20 455 confirmed cases of monkeypox (MPX) have been reported from 29 EU/EEA countries, including four deaths. From the total number of cases reported, 1.1% have required hospitalisation for clinical care and five cases were admitted to intensive care unit. According to WHO, 68 267 confirmed MPX cases have been reported globally, of which 20 265 (29.7%) were from EU/EEA countries (data updated on 12 October 2022) [1].

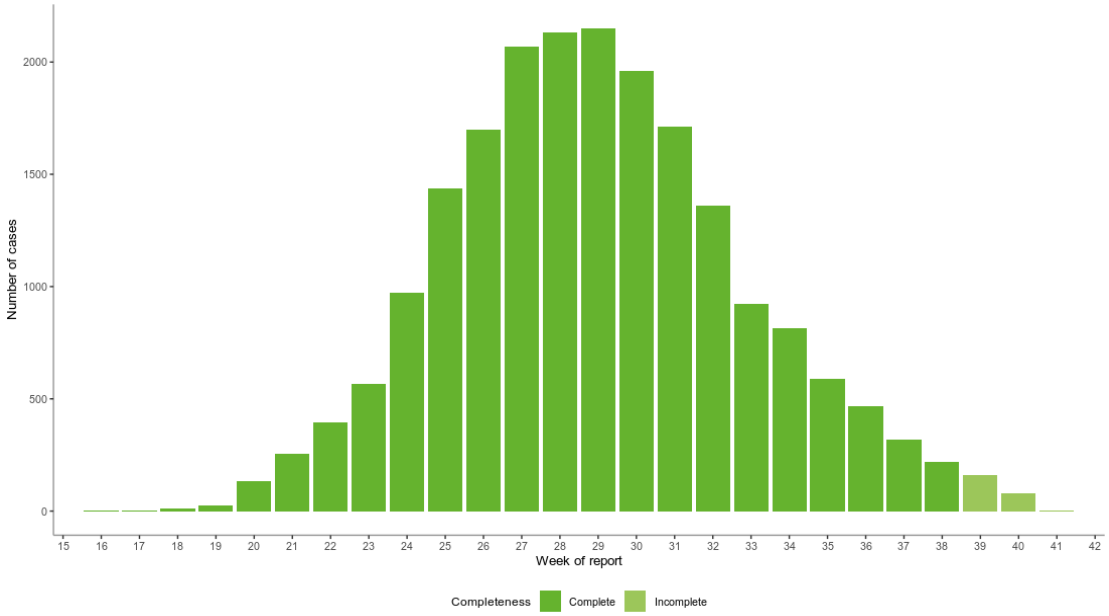
Most cases have been detected in males between 18–50 years (87%), and primarily among men who have sex with men (MSM). As of 11 October 2022, 1.6% and 0.3% of the total number of cases have been reported in women and children (0–17 years-old), respectively, with no observed increase over time. Two infections among healthcare workers with occupational exposure and one case with laboratory exposure were also reported to The European Surveillance System (TESSy). Moreover, a case of occupational exposure of a healthcare worker has been reported in the literature [2].

A detailed summary and analysis of case-based data reported through 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 [3].

The epidemiological curve of all MPX cases reported in the EU/EEA shows cases peaking in July 2022 and then a constant declining trend. From the peak of the cases in week 29 (18-24 July 2022) to week 38 (19-25 September 2022), the number of new MPX cases reported has decreased by 90% (Figure 1).

The MPX outbreak epidemiological trend is also decreasing globally, including in those regions, such as the south American and Western Pacific regions, where the summer events season is starting [1]. However, the current outbreak epicentre is placed in the Americas, as most of the new cases reported in the last month come from this region [1].

Figure 1. Number of confirmed MPX cases reported weekly in the EU/EEA, from 22 April 2022 to 11 October 2022



Data should be interpreted with caution due to notification delays. Please note that the data for recent weeks may be incomplete.

Disease background

In the ongoing outbreak of MPX, several differences in the clinical presentation have been reported compared to those available in the literature from past outbreaks of MPX in endemic countries. For more details on MPX's disease characteristics, please refer to ECDC's updated factsheet [4].

Few data are available on secondary attack rates in the current outbreak. The low number of cases in non-MSM population groups, the fact that the proportion of such cases increased only slightly since the start of the outbreak, and evidence from studies investigating possible routes of infection suggest a low probability of transmission through non-sexual routes, especially outside the household setting [5]. A small cluster has been described in a tattoo establishment involving a total of 54 exposed individuals and 20 confirmed infections, with an attack rate of 37%. This cluster was attributed mostly to environmental exposure and poor disinfection practices [6,7]. In addition, a case was described in the United States (US), in a person who attended multiple crowded outdoor events but reported no sexual exposure [8]. Finally, a study from the United Kingdom (UK) summarising data on MPX exposure in four different educational settings found no secondary cases among students or staff after prolonged exposure to an adult MPX case [9].

Among cases in the current outbreak, besides primary skin and mucosal lesions, monkeypox virus (MPXV) has been detected in several other body sites and bodily fluids, including nasopharyngeal swabs, saliva, urine, blood, semen and faeces and rectal swabs. The highest viral loads have been reported from specimens of skin and mucosa, including genital and rectal/anal sites compared to specimens from other sites [10-13]. Limited data on the duration of viral shedding (i.e. detection of MPXV DNA over time) show that positive samples are most frequent in the 2–3 weeks after symptom onset [11,13,14]. Cases with prolonged detection of MPXV DNA (up to 54 days for semen and up to 76 days for saliva) have also been described [15].

Current limited evidence points to the existence of a small percent of asymptomatic MPX infections [14,16] (1-3% of cases), but the public health relevance of asymptomatic and pre-symptomatic transmission of MPXV is yet to be determined.

For more information about MPXV infection in animals, please consult the European Food Safety Agency (EFSA) [17] and the World Organisation for Animal Health (WOAH) questions and answers [18].

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 [19]. 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 continuing transmission of MPX in EU/EEA countries?

Risk in the most affected subpopulation (currently men who have sex with men)

The majority of MPX cases reported since the beginning of the 2022 outbreak in non-endemic countries have been in men between 31 and 40 years old. Of the cases with known sexual orientation, 96% are men who have sex with men (MSM), who have been exposed through close sexual contact [3]. Receptive anal sex has been described as a higher risk practice [20]. Modelling studies in the US based on behaviour survey data indicate that men with more than one partner in the three weeks prior to their diagnosis of MPX have 1.8–6.9 higher risk of infection. However, one-time sexual encounters accounted for more than 50% of daily transmission of MPXV, even though they represent <3% of the daily partnerships. Therefore, decrease in one-time sexual encounters can render more significant decreases in transmission [21].

Since week 30 2022, there has been a continuous decline in the number of new MPX reported cases in EU/EEA countries. Multiple factors may be responsible for this, including:

- Efforts in risk communication and community engagement, resulting in sexual behaviour changes at the individual level, including a decreased number of sexual partners, as well as in the wider MSM group, reducing their risk of infection and increasing vaccine acceptance [22];
- The end of the summer in the northern hemisphere and a significant decrease in leisure travel and large cultural and social events;
- Increasing immunity in the most affected population group as a combination of natural immunity and vaccination of those most at risk of exposure (e.g. people with multiple sexual partners);
- Decreased testing either due to saturation of services (overburdening of sexual health clinics and decreased offer of testing) or decreased willingness to test, from anecdotal references. This last point has been mentioned as a potential cause of the decreasing number of cases, as patients are deterred by stigmatisation and/or the long isolation period (usually up to 28 days), and in addition are aware that in most cases no specific treatment is needed.

The probability of the further spread of MPXV among MSM with random one-time sexual encounters or multiple sexual partners is currently assessed as moderate.

A significant percentage (38%) of the MPX cases in this outbreak have been diagnosed in people living with HIV (PLHIV) [3]. Most PLHIV in the EU/EEA (range 67–87%) are receiving antiretroviral treatment and are not severely immunocompromised [23]. An international case series from the current MPX outbreak, where 44% of MPX cases were HIV-positive, reported that PLHIV were more likely to have diarrhoea, perianal rash, and more skin lesions. However, no differences in the severity of illness were noted in men who are living with HIV [24]. The impact of MPXV infection in PLHIV who are not on appropriate antiretroviral treatment in the at-risk groups could be higher.

The severity of MPX in this outbreak as inferred by hospitalisations remains rather low (6.3% total hospitalised patients, of which only 1.1.% for healthcare reasons in the EU/EEA countries) [3], although on a personal level patients describe significant discomfort, pain, and complications (e.g. secondary skin infections, rectal pain, mental health issues, etc). Severe complications have been rare, including myocarditis [25] and encephalitis [26], and hospitalisation in ICU accounts only for 0.1% of cases. Four deaths have been reported to date in EU/EEA countries, due to severe complications such as encephalitis in combination with immunosuppression.

As a result, the impact of the disease in MSM groups is assessed as low, with the overall current risk from MPX infection for this population remaining as moderate.

Risk for the broader population

MPX cases in the broader population reported as of 11 October 2022 include relatively few cases in women (1.6%), with an even smaller number of cases reported in children <17 years of age (0.3%), all mild with no reported deaths in this population. As outlined in the 'Event background' section, cases in the broader population have only increased slightly throughout the ongoing outbreak and very few cases have been documented through community transmission without sexual contact.

Severity is expected to be higher in young infants, pregnant women, and immunocompromised individuals [27-29].

As the likelihood of infection for the broader population is assessed as very low and the disease impact in general as low, the overall risk for the broader population remains low.

Risk for health professionals

To date, four cases of MPXV transmission to health professionals through occupational exposure have been reported in the EU/EEA, three cases among healthcare workers and one case in a laboratory worker following laboratory exposure. All these cases of infection followed an accidental exposure (e.g. needle sticks or splash). However, probable occupational exposure through fomites was also described in the case of community healthcare workers in Brazil [30]. A study in the US showed that healthcare personnel exposed to MPX cases, even when not wearing the recommended PPE or not receiving the post-exposure preventive vaccination, didn't become infected after documented contact with MPX cases [31].

Given these findings, ECDC assesses the risk for health professionals as low when wearing appropriate PPE to moderate when exposed for a prolonged time to a case without appropriate PPE, performing an aerosol-generating procedure without PPE, or suffering an occupational exposure in a laboratory without appropriate PPE or equipment [32]. For healthcare workers wearing appropriate PPE, the probability of exposure is very low, and the overall risk from MPX is low (Table 1).

For laboratory personnel, the risk assessment remains unchanged as in the first MPX risk assessment (see Table 1) and depends on their having the appropriate PPE and if they follow appropriate laboratory protocols [32].

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 recent human cases also show the presence of the pathogen in human tissues and body fluids [33-35]. MPXV DNA was detected in blood up to day 18 after the onset of symptoms. In addition, as mentioned in the 'Disease background' section , MPXV was detected in the semen of patients with confirmed infection [13]. Seminal shedding of MPX virus has been confirmed up to 16 days after symptom onset. The available data are insufficient to form conclusions on the infectivity of semen, particularly as regards the potential permanence of MPXV in semen after recovery [34]. The assessment of the overall risk for recipients of SoHO in the EU/EEA remains low [32].

Risk of (reverse-)zoonotic transmission and establishment of an enzootic cycle among wild animals

Detection of 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. 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.

More than six months after the start of the outbreak and the occurrence of over 68 000 cases globally, there have been only two reports of a possible MPX transmission to pet animals, in France and in Brazil, in both cases to dogs that lived with one or more MPX-confirmed human cases [36,37]. In France, the animal tested PCR MPX-positive by cutaneous and mucosal swabs, but the serological test remained negative [38]. The dog in Brazil was tested positive by PCR; there is no information on sampling and serological analysis. In the UK, despite an enhanced syndromic surveillance over 3.5 months among pets owned by confirmed human MPX cases, no cases of animals with MPX-compatible clinical signs were detected. Based on these observations and that there are currently about <100 new cases per week (compared to >2 000 cases weekly three months ago), the risk of MPX transmission to pet animals is considered to be very low. Considering the lack of data, it is currently not possible to estimate the risk of MPX transmission among pets and from infected pets to humans.

Considering the current number of new cases, the likelihood of wild peri-domestic animals becoming infected via direct contact with infected humans or pet animals, contaminated wastewater, and other waste, is considered very low. In the coming weeks/months, human-to-human transmission of MPX virus is expected to remain the primary mode of transmission. As a result, the risk of establishment of an enzootic cycle, potentially leading to spill-over events to humans, is considered to be low.

Table 1. Overview of the risk assessment for MPX infection in the ongoing multi-country outbreak, 2022

Population/route	Probability	Impact	Risk
Risk in the most affected subpopulation of MSM	Moderate	Low	Moderate
Broader population	Very low	Low	Low
Health professionals without proper PPE performing general patient care	Low	Low	Low
Health professionals without proper PPE performing an aerosol generating procedure	Moderate	Low	Moderate
Health professionals with proper PPE in all types of care and procedures	Very low	Low	Low
Laboratory staff with proper PPE and using proper laboratory protocols	Very Low	Low	Low
Laboratory staff without proper PPE and/or not following laboratory protocols	Moderate	Moderate	Moderate
Risk of transmission through SoHO	Low	Low	Low
(Reverse-)zoonotic transmission and establishment of an enzootic cycle among wild animals in Europe	Very low	Low	Low

Options for response

Early diagnosis, isolation, effective contact tracing, and vaccination strategies remain key for the effective control of this outbreak. This entails continued investment in:

- Awareness activities for health professionals around the ongoing outbreak and support of sexual health services, together with appropriate management of cases and contacts;
- The availability of testing for orthopoxvirus;
- The development, implementation, and review of vaccination strategies;
- Risk communication and community engagement activities with the affected population and the general public.

Awareness of health professionals

Although MPX remains quite rare in the EU/EEA, it is important to continue awareness-raising activities targeting health professionals. In addition, support for sexual health services, which have carried the weight of this outbreak, is urgently needed [39-41]. Information provided to medical practitioners should include the range of clinical presentation 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. Although the number of reported infections following occupational exposure of health professionals to MPX in the current outbreak is very small, guidance and training should be enforced as regards sampling (e.g. avoid de-roofing MPX lesions, reinforce hand hygiene in all contacts and regular needle safety practices).

Awareness activities targeting clinicians should be a priority in all countries but particularly in those which that have diagnosed a low number of cases to address misdiagnosis and under-reporting. WHO has developed interim rapid guidance for clinical management and infection prevention and control of MPX cases [42] and the ECDC has produced guidance on infection prevention and control for primary care and acute care settings [43].

Management of cases

MPX cases should be isolated if hospitalised. Ambulatory MPX cases should be advised to self-isolate in their home, if possible, particularly if they experience a large number of skin lesions. Skin lesions have consistently shown the highest concentration of live MPXV compared to other sample sites; patients should therefore ideally remain in isolation until they do not experience systemic symptoms and their skin has completely healed. Instructions for the cases in self-isolation on behaviour, cleaning, and disinfection remain the same [32]. Due to the prolonged isolation period, patients may require mental health and/or financial support to comply with isolation guidance.

Ambulatory MPX cases experiencing only solitary or very few lesions in areas that can be covered by clothing can be excused from isolation, provided they are advised to cover their lesions well, to practice rigorous hand hygiene and wear a well-fitted medical mask when in close contact with others. Cleaning and disinfection instructions for their home and workplace environments remain the same as with the isolated cases [32]. All cases should be advised to abstain from sex until full recovery, and after that use a condom for a total of 12 weeks, as an

additional precaution, and in addition, they should avoid contact with very young children, pregnant women, and immunocompromised people. This change in guidance is supported by the very low likelihood of transmission in community settings observed until now [9] (see 'Disease background section').

As mentioned above, severe cases have been quite rare, however, their occurrence reinforces the need of monitoring ambulatory cases for deterioration of their condition and offering prompt treatment with antivirals (i.e. the EMA-approved tecovirimat) or referral for hospitalisation. Antivirals can also potentially provide rapid relief from some of the MPX symptoms (e.g. the proctitis syndrome). A joint procurement of limited quantities of this pharmaceutical has been implemented in the EU/EEA countries. Use of tecovirimat and other antivirals (e.g. brincidofovir) in the ongoing MPX outbreak should be undertaken in the framework of a clinical study to obtain efficacy data. An international core protocol for a randomised clinical trial of the safety and efficacy of treatments for patients with MPX virus disease has been developed by WHO and can be used by countries [44]. The use of antivirals for post-exposure prophylaxis remains to be investigated.

Management of contacts

Contact tracing remains important for informing those exposed and the prompt diagnosis of potential secondary cases. It can also help identify settings or population groups where targeted interventions are needed. 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 and informed. Close collaboration with civil society and community-based organisations is important to ensure that contact tracing/partner notification strategies and accompanying risk communication are adapted to the affected groups, building trust in the processes while diminishing stigmatisation.

Close contacts of cases do not require quarantine, as long as they have no symptoms. ECDC has published a technical report, 'Considerations for contact tracing during the MPX outbreak in Europe, 2022' [45], and WHO has issued interim guidance [46].

Waste management

Clinical waste from MPX patients is classified as category A (UN3549) under the UN classification; this does not distinguish between clades of the virus. During the current outbreak, some national authorities [47] have decided to classify waste from patients infected with the currently circulating clade of MPXV as regular medical waste, but these are decisions made at the national level and reflect that national authorities' decisions depend on their respective national risk assessments.

Cleaning and disinfection

Orthopoxviruses persist in the environment but are sensitive to common disinfectants. Guidance for the cleaning and disinfection of patient rooms, utensils, and household items are included in ECDC's first MPX risk assessment [32]. A cluster of MPX cases connected to a tattoo parlour was recently described in Spain potentially connected to unsafe tattoo practices and poor hygiene [6,7]. Single use needles and piercing equipment is recommended for tattooing to avoid transmission of blood-borne pathogens. Cleaning and sterilisation of the non-single use equipment should be performed according to manufacturer guidelines with a virucidal agent.

Laboratory diagnostics and sequencing

Countries should review their molecular diagnostic testing capacities and capabilities for MPXV. Increasing overall testing capacity will facilitate the prompt diagnosis of MPX cases.

If there is limited experience in MPXV diagnostic testing, laboratories are encouraged to refer specimens for confirmatory testing. Countries not having national reference laboratory capacity for MPXV can refer specimens 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 [48]. The European Virus Archives (EVAg) can provide positive control materials for diagnostic testing [49].

Several countries have developed and validated PCR assays for the detection of MPXV [50-52] and commercial PCR kits are available [53-55]. False-negative PCR test results have been reported for a few cases in the US and preliminary data indicate this to be caused by a deletion affecting the target regions of two published MPXV-specific PCR assays [56]. Laboratories diagnosing MPX should consider reanalysing PCR-negative samples from patients with MPX symptoms and exposure using PCR assays targeting another region of the MPXV genome [57]. To prevent false positive test results, laboratories should consider performing repeated testing to verify positive PCR test results for specimens with high Cycle Threshold (Ct) values from people without known epidemiologic link.

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 [58]. We recommend that whole genome or partial genome raw reads and assemblies are deposited into available databases designed for sequence data-sharing.

Vaccination and vaccination strategies

Authorised vaccine against MPXV and considerations for use

Since 22 July 2022, the third-generation non-replicating smallpox vaccine Imvanex™ (Modified Vaccine Ankara – Bavarian Nordic or MVA-BN) has been authorised by the European Medicines Agency (EMA) for protection against MPX in adults [59,60]. MVA-BN is administered as a subcutaneous injection (0.5 ml), preferably in the upper arm, with a two-dose regimen, with the second dose given at least 28 days after the first. Data from human and animal studies suggest that a single dose of MVA may offer fast protection against MPX, and that the second dose mainly serves to extend the durability of protection [59]. A single booster vaccination dose (0.5 ml) may be considered for individuals previously vaccinated against smallpox, MPX, or vaccinia viruses, although there are inadequate data to determine the appropriate timing of the booster doses [61]. The safety profile of MVA-BN is favourable, with mild to moderate side effects. Older generation smallpox vaccines have significant side effects and are not authorised by EMA.

MVA-BN is currently authorised for use against infection and disease caused by both smallpox and MPXV in the US (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 [62]. Considering the limited availability of Imvanex™ , the EMA Emergency Task Force (ETF), together with the Committee for Medicinal Products for Human Use (CHMP) Biologics Working Party (BWP) and the European Directorate for the Quality of Medicines and HealthCare (EDQM), evaluated the specificities of the FDA-approved Jynneos™ and released a statement including safety, efficacy, and manufacturing considerations in case Jynneos™ is used as a replacement of Imvanex in the EU to provide protection against MPX disease [62].

In addition, in August 2022, EMA's ETF reviewed data on MVA-BN used as an intradermal injection at a lower dose of 0.1 ml (i.e. fractional dose) showing similar immunogenicity to the subcutaneous administration [63] and advised national authorities to consider using MVA-BN as an intradermal injection at a lower dose to protect at-risk individuals during the current MPX outbreak as a temporary urgent measure while supply of the vaccine remains limited [64]. Nevertheless, the ETF also cautioned about a higher risk of local reactions (e.g. longer-lasting redness, and thickening or discoloration of the skin) after intradermal injections, recommended the use of low-dead volume syringes to optimise the number of doses that can be extracted from each vial, and emphasised that the administration should only be carried out by healthcare professionals experienced with intradermal injection administration.

Additional considerations regarding the use of MVA-BN in special populations (children and adolescents, pregnant women, and immunocompromised individuals) have been previously discussed [32] and may be found in the EMA's Summary of product characteristics [61].

Review of evidence of performance of MVA-BN vaccine against MPX disease

Robust data on the clinical efficacy or effectiveness of the third-generation vaccines against MPX disease are still lacking, but some initial assessments of the performance of MVA-BN in the current outbreak are becoming available while clinical trials and effectiveness studies are being implemented [65]. A few observational studies published as preprint reported data on breakthrough infection after the first dose of the vaccine.

In Israel, an observational, retrospective population-based cohort study used data obtained from the electronic medical records of Clalit Health Services (CHS) (52% of the Israeli population). The cohort included all CHS members eligible for the MVA vaccine per the Israeli Ministry of Health's guidelines when the study commenced. The MVA eligibility criteria were: (a) males aged 18 to 42 years who were dispensed HIV-PrEP at least for one month since 1 January 2022, or (b) males aged 18 to 42 years who were diagnosed with HIV and also were diagnosed with one or more of the following STIs since 1 January 2022: active syphilis, chlamydia, or gonorrhoea. Subjects who were infected with MPXV prior to the study period were excluded. Results found that among 1 970 subjects who met the study eligibility criteria (0.04% of CHS members), 873 (44%) were vaccinated with MVA and completed at least 25 days of follow-up. A total of 18 infections were confirmed in CHS during the study period, three in vaccinated and 15 in unvaccinated status (40.0 versus 6.4 per 100 000 person days). Vaccine effectiveness was estimated at 79% (95% CI: 24% to 94%). Results suggest that a single dose of MVA is associated with a significantly lower risk for MPXV infection in high-risk individuals [66].

In France, an observational study identified 12 (4%) confirmed cases of MPXV infection among 276 individuals vaccinated with one dose of MVA-BN after exposure with a confirm case of MPX (median delay of 11 days after exposure). The median time between vaccination and the first symptoms of MPX was four days, ranging from one to 25. Ten of 12 patients developed MPX in the five days following vaccination and two had a breakthrough infection at 22 and 25 days [67].

In the US, the performance of the rollout of vaccination campaigns against MPX is being assessed monitoring rates of MPX cases by vaccination status [68]. Data analysis across 32 US jurisdictions showed that MPX incidence among males aged 18–49 years eligible for MVA-BN vaccination was 14 times higher among unvaccinated males compared with those who had received a first vaccine dose ≥14 days earlier. Rates are not adjusted for time since vaccination, underlying medical conditions (such as HIV status), or other factors (risk behaviours) [69]. In addition,

data from Illinois identified 90 MPX infections among 7 339 individuals who had received their first dose of MVA-BN. Thirty-seven and 32 cases occurred one to seven and eight to 14 days after vaccination, respectively, comprising 77% (69/90) of all postvaccination cases. The median time between vaccination and infection was 8.5 days (IQR, 4-13; range, 1-58 days) [70].

Vaccination strategies

In the context of the current multi-country outbreak, mass vaccination against MPX is not required nor recommended. MPX vaccines can be used as post-exposure vaccination (PEPV) or as primary preventive vaccination (PPV) [71].

Primary preventive (pre-exposure) vaccination

Primary preventive (pre-exposure) vaccination (PPV) refers to the vaccination of individuals at risk of exposure to MPXV infection. Mathematical modelling presented in the previous ECDC rapid risk assessment has indicated that PPV, assuming 80% vaccine effectiveness, 80% vaccine uptake, 90% isolation of cases, and effective tracing of contacts, would be the most effective vaccination strategy to control the 2022 multi-country outbreak [72]. PPV would also be the most efficient vaccination strategy (i.e. increasing the probability of outbreak control per vaccinated individual) even when there is less effective contact tracing. Targeting PPV to population groups at highest risk of exposure may further increase vaccination efficiency in outbreak control.

Based on the results of modelling, in the context of the 2022 multi-country outbreak, countries should prioritise PPV among individuals at substantially higher risk of exposure to MPX, such as individuals identifying themselves as gay, bisexual, or other men or transgender people who have sex with men according to a risk assessment based on certain epidemiological or behavioural criteria (e.g. recent history of multiple sexual partners or plans to engage with multiple partners, attending sex on premises venues, or group sex or chemsex practices, use of or eligibility for pre-exposure prophylaxis for HIV, recent history of bacterial sexually transmitted infections, etc). In addition, PPV could be considered for workers in sex-on-premises venues, such as saunas, if they are regularly exposed to items (i.e. linens) or surfaces likely to be contaminated with body fluids or skin cells, and other groups at higher risk, such as sex workers.

PPV for occupational exposure of health workers, especially those at repeated risk of exposure, laboratory personnel (e.g. laboratory staff working with orthopoxviruses or in clinical laboratories performing diagnostic testing for MPXV), and outbreak response staff should also be considered based on risk assessment.

Targeted health promotion interventions and community engagement are critical to ensure effective outreach, high vaccine acceptance, and uptake among those most at risk of exposure. In the context of limited vaccine supply, the assessment of risk of exposure and MPXV infections between and within population groups may guide more targeted PPV strategies at local level.

Post-exposure preventive vaccination

Post-exposure preventive vaccination (PEPV) refers to the immunisation against MPXV of close contacts of cases to prevent the onset of disease or mitigate disease severity. Based on mathematical modelling [72], in the context of the 2022 multi-country outbreak PEPV of contacts of cases would be the most efficient vaccination strategy 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 PEPV than with PPV vaccination.

The priority target groups for PEPV are close contacts of cases (i.e. sexual partners, household contacts, healthcare workers, and individuals with other prolonged physical or high-risk contact) as defined in the recent ECDC publication on contact tracing [45]. In the context of limited supply, contacts with a high risk of developing severe disease if infected, such as children, pregnant women, and immunocompromised individuals, should be prioritised for PEPV based on a case by cases risk assessment.

Ideally, PEPV should be administered within four days of first exposure (and up to 14 days after exposure in the absence of symptoms) [73]. To increase the effectiveness of PEPV, community engagement efforts for the identification of contacts around cases should be put in place.

In the context of the 2022 multi-country outbreak and limited vaccine supplies, PPV and PEPV may be combined focusing on individuals at substantially higher risk of exposure (for PPV) and close contacts of cases (for PEPV), especially with a high risk of developing severe disease if infected, until more vaccines become available.

Finally, considering the lack of clinical data on protection against infection and disease from these different vaccination strategies, 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.

Vaccination strategies and rollout in the EU/EEA

In the EU/EEA, as of 12 October 2022, at least 20 countries (Austria, Belgium, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Norway, Portugal,

Spain, and Sweden) have a national policy on vaccination against MPXV in place[1]. Among these, all 20 EU/EEA countries with policies provide MPXV vaccines for PEPV to contacts of cases and 16 also for primary (pre-exposure) preventive vaccination to individuals at high risk of exposure.

In the context of the 2022 multi-country outbreak, primary (pre-exposure) preventive vaccination is being prioritised for MSM at high risk, including individuals on or eligible for HIV pre-exposure prophylaxis (16 countries), sex workers (seven countries), healthcare workers (five countries), laboratory personnel (four countries), and less frequently other groups considered at risk (e.g. people with HIV at risk, staff working in sex-on-premises venues, and transgender people). Post-exposure vaccination is being offered to close contacts of cases (20 countries), primarily sexual contacts (18 countries), household contacts (16 countries), healthcare workers (11 countries), and less frequently other regular contacts or other close contacts (not sexual or household).

In order to address the limited supply of vaccines against MPXV in the EU/EEA and to make vaccines rapidly available, the European Commission's Health Preparedness and Response Authority (HERA) purchased 334 540 doses of MVA-BN for distribution to Member States [74,75]. The vaccine distribution to Member States was conducted on a pro rata basis and has already started, prioritising countries with highest number of cases which have granted all national authorisations for the vaccine [74].

In the context of limited supplies, countries have been adopting dose sparing approaches, such as the administration of one vaccine to people previously vaccinated against smallpox, one dose with delayed second dose as interim measure until more vaccines are available, and the intradermal administration of a fractional dose of vaccine when indicated and feasible.

As of 12 October 2022, based on data reported to ECDC by National Focal Points from 25 countries, up to 18 countries had initiated the administration of vaccines against MPX between 15 June and 21 September 2022. Since the beginning of the rollout of MPX vaccination campaigns in response to the 2022 multi-country outbreak, a total of 140 007 doses have been administrated in 18 countries (partial data reported for September 2022). Considering data from 16 countries that were able to report vaccine doses by vaccination strategy, 92% of doses were used for PPV and 8% for PEPV. In addition, considering 15 countries that were able to report vaccine doses by dose number, 89% of doses to date have been administered as first doses and 11% as second doses.

Risk communication and community engagement

Risk communication and community engagement (RCCE) strategies are a core element of any outbreak response and are essential to achieving results across all the proposed measures. In the context of the MPX outbreak, ECDC, in collaboration with WHO Regional Office for Europe and civil society organisations, has produced several documents that address RCCE [76-79] and provide examples of ongoing RCCE activities in EU/EEA countries [80]. A toolkit to support RCCE strategies, including key messages for risk reduction, has been jointly developed by ECDC and the WHO Regional Office for Europe and is available for adaptation and use by public health authorities [81].

Risk communication strategies should still prioritise most affected groups, currently MSM, in addition to commercial sex workers, and those at risk for severe disease (immunocompromised people, pregnant women, young children). The level of risk of transmission has changed since the summer, and there is uncertainty as regards the evolution of the outbreak in the next months. The likelihood of infection to the general population remains very low, while the likelihood of infection for the most affected groups has changed. Still, it remains important to continue to clearly communicate measures that individuals can take to reduce exposure, in addition to possible symptoms, and how to seek care if there is a suspected case.

Focusing on the behaviours of people and how to reduce risk, instead of focusing on the characteristics of people infected (e.g. sexual orientation) may help reduce stigma. This may include recommendations to reduce the frequency of one-time sexual encounters and the number of sexual contacts and promoting the idea that individuals who suspect they may be infected take a break from sexual activities or events and promptly seek sexual healthcare before reengaging in such activities. Risk communication should continue to emphasise that stigma and discrimination harm response efforts and can negatively impact healthcare-seeking behaviour. It may be beneficial to undertake efforts to assess how experienced and perceived stigma impacts healthcare-seeking behaviour, to understand if stigma may be contributing to a decrease in cases reported through decreases in seeking care and testing.

While studies have shown high vaccine acceptance in most affected groups [82], it remains important to consider barriers to vaccination, including access and confidence [83]. Uncertainties on vaccine effectiveness should be communicated, as well as any limits of supply.

As incidence and the risk of sustained transmission changes, public and political interest and resources of community-based and civil society organisations may decrease, which may create more challenges for them to allocate time to collaborating with public health authorities. Nonetheless, engaging and maintaining dialogue with

[1] Information collected though a Health Security Committee survey conducted in August 2022, data on vaccine doses administered reported by National Focal Points to ECDC in October 2022 and ECDC desk review; some countries may be in the process of updating national policies and their decisions may have not been reflected by the time of publication of this report.

organisations representing affected groups remain important, both as a valuable source of information to understand needs and priorities, gaps in information or misinformation, as well as strengthening them as trusted communicators in and towards their communities. If and when evaluations of the response occur, it will also be essential to consider including these groups to understand their perspectives of the response [84].

Substances of human origin (SoHO)

In the donor assessment process, attention should be paid to the wide range of clinical presentations of the disease in the current outbreak, which also deviate from those observed in to earlier outbreaks, in particular the asynchronous appearance and evolution of the skin lesions and the presentation with a solitary lesion or mucosal lesions only [10].

In inconclusive cases, confirmatory testing can 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 [78]. In the absence of the skin lesions, an oropharyngeal swab can be taken, but a negative oropharyngeal swab should be interpreted with caution [78,79] 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.

Due to prolonged seminal shedding of the virus and unknown infectivity of the semen, in cases when there is a need to store semen (e.g. fertility preservation) it is advisable to perform PCR of semen sample and, if necessary, store it in the safe way (e.g. sealed straws).

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.

Front-line veterinary care (veterinary clinics and hospitals) should be aware of possible MPX transmission from humans to animals when dealing with pets that live in a household with people who are infected. People affected by MPX who suspect that their pet shows compatible clinical signs should inform their veterinary practitioner/clinic. If needed, they will alert the relevant national authorities, which will provide advice on the measures to take.

To mitigate the risk of wild animals coming 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.

Future considerations for the MPX outbreak and for preventing similar outbreaks

Significant uncertainties remain as to how the ongoing MPX outbreak will evolve. MPXV has not been easily transmitted from person to person outside of close sexual contact in this outbreak. Vaccination campaigns targeting people at risk and close contacts of cases, behaviour changes, and increasing immunity through infection in the most affected population group (especially in subgroups at very high risk of infection and transmission, such as those with multiple sexual partners) have probably all contributed with various degrees to the decline of cases observed in the EU/EEA. However, the magnitude and longevity of impact of each of these factors remains unclear.

As of 10 October 2022, ECDC modelling estimates that the median percentage of the MSM population across the EU/EEA still susceptible to MPX infection ranges between 55% and 95%. This range comes with a high degree of uncertainty, especially about the residual cross-protection from the historic smallpox vaccination programmes. These ballpark figures indicate that a large proportion of the MSM population remains susceptible to MPX and could become infected in subsequent resurgences of the disease. Furthermore, the estimated high proportion of MSM still unprotected from MPX infection may support reasons other than increasing levels of immunity responsible for the decline in incidence seen in recent weeks (i.e. behaviour change or reluctance to test).

Over the longer term, the number of individuals who practice sex with multiple partners in interconnected networks or casual one-time sexual encounters will increase again as behaviour will revert to pre-outbreak habits; in addition, young people who become old enough to engage in sexual activity may also start engaging in similar behaviours [21]. In this case the most effective strategy to break the transmission chains, and ideally prevent outbreaks before they even start, would be the early vaccination of those younger people at highest risk.

Four qualitative scenarios for the evolution of the current MPX outbreak in the next two months are discussed below, assuming no changes in the transmissibility of the MPXV or the severity of the disease are detected:

- **MPX resurges.** Several factors may play a role in the potential rise of MPX cases again. As interest in the outbreak wanes and RCCE activities diminish, gains from behaviour changes will also probably diminish [22]. As mentioned above, the number of susceptible individuals grows in the order of approximately one year, as young people come of age and start exploring their sexuality. In addition, the winter season festivities may present an opportunity to travel and connect and join networks with multiple sexual partners, which would

again facilitate contact with the virus. This is not considered the most likely mid-term scenario, but continuing strong case finding, contact tracing and RCCE activities, as well as prompt vaccination of individuals, needs to be maintained to prevent it.

- **MPX causes a continued low number of new cases with sporadic outbreaks, almost exclusively among MSM**, mostly transmitted during sexual contact. Cases could be concentrated in certain subgroups of MSM with multiple sexual contacts. Sporadic outbreaks can be expected when the susceptible population reaches a critical level, close contact between otherwise unlinked groups is facilitated (e.g. during mass gathering events) or after new introductions through travellers from endemic countries. In addition, outbreaks can be detected in populations living in congregate settings (e.g. prisons, dorms, homeless centres). We consider this a likely scenario, and including MPX in surveillance systems along with other STIs should be considered. The availability of testing for symptomatic MSM in sexual health clinics and other settings is also important for disease control purposes in this population. Whether screening of asymptomatic MSM, e.g. those presenting for STI screening regularly or those after high-risk exposure, would be effective in this scenario for case finding and disease control is not clear and would need to be investigated. PPEV (pre-exposure) vaccination through sexual health clinics for MSM presenting for STI screening and MSM diagnosed with an STI should be considered according to national recommendations (see also 'Vaccination strategies' above). Contact tracing and RCCE activities should still be supported.
- **MPX wanes.** In this scenario, the outbreak continues its steady decline started in week 30 2022, with the continuing reduction of susceptible individuals in the most affected population groups coupled with the known low transmissibility of the virus and changes in behaviour to the point of no new cases being reported. This may be the case, especially if those MSM at highest risk for infection and transmission reach sufficient immunity through infection or vaccination and the immunity is long-lasting. This scenario could be supported by historic experience from endemic countries, where it is documented, that transmission usually stops at secondary cases and chains are only four to six generations long [85,86]. The fact that a large proportion of MSM is still susceptible to MPX and the challenges to strengthen or even maintain adequate sexual health services and RCCE activities make this scenario less likely in the next two months.
- **MPX is eliminated in EU/EEA countries.** During the summer of 2022, the WHO Regional Office and the European Commission published a statement on the aim to prevent MPX becoming endemic in Europe by providing guidance, ensuring the availability of countermeasures, tackling stigma, and closing research and knowledge gaps [87]. Through concerted efforts from all EU/EEA countries on prompt identification, contact tracing, and vaccination, as well as wider global collaboration, the elimination of MPX in EU/EEA countries may be a possible scenario based on current knowledge of the characteristics of the disease, the pathogen, and the lack of reservoirs in EU/EEA countries. If the above scenario of a continuous decline of MPX cases becomes the most probable, public health authorities can truly aim for the complete elimination of the disease from EU/EEA countries with continuing RCCE activities, but most importantly early detection, contact tracing and vaccination. In the global health context, response efforts in the EU should also include supporting endemic countries to implement response activities to control MPX (increase capacity in testing, case finding and contact tracing, as well as RCCE), but also in particular making pharmaceuticals for MPX (antivirals and MVA vaccine) available to endemic countries.

Limitations/knowledge gaps

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

- Behavioural insights and up-to-date information about sexual contact patterns and risk reduction and healthcare-seeking behaviour among gay men, bisexual men, and other men who have sex with men in the EU/EEA is needed to better model and communicate risk and to understand healthcare-seeking and vaccine acceptance behaviour for this population in relation to MPXV risk. A repeat of studies like the European Men-Who-Have-Sex-With-Men Internet Survey (EMIS, last conducted in 2017) is needed [88].
- Understanding of the extent that community engagement and risk communication contributed to a change in behaviour and a resulting decline in the number of cases in Europe.
- MSM perception and the experience of stigma during the outbreak and how this might have affected health behaviour.
- Prevalence of (protective) immunity from past infection in the most affected groups to understand to what extent this contributed to the decrease in the number of cases and the underestimation of cases (due to under-ascertainment and underreporting).
- The impact of the response to the MPX outbreak on the detection, management, and reporting of other STIs (syphilis, gonorrhoea, HIV, etc).
- Information on the current residual cross-protection from smallpox vaccination in the EU/EEA population.
- Efficacy and effectiveness data of the currently available MVA vaccine against MPX, including for pre-exposure and post-exposure immunisation strategies, and safety data for the use in young children, pregnant women, and immunocompromised people.
- Efficacy data and the 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

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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.

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