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Advice from the medical device Expert Panels

Mandate and Advice provided to the MDCG

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Contents

1. Legal basis for the request

Article 106 (10) (a) and (b) of Regulation (EU) 2017/745 on medical devices.

2. Party requiring the advice

The Medical Device Coordination Group (MDCG).

3. Scientific context and background information

In May 2022, multiple cases of monkeypox were identified in several non-endemic countries. This led to the placing on the EU market of several *in vitro* diagnostic medical devices intended to detect the monkeypox virus, typically to diagnose infection in context of clinical examination of the patient. The risk classification of these devices under Regulation (EU) 2017/746 depends on the characteristics of this infectious agent and the assessment of the risk associated with an erroneous result from a monkeypox detection device. This request concerns a number of scientific questions related to monkeypox virus in the context of the classification rules in Regulation (EU) 2017/746.

Relevant rules of Annex VIII of Regulation (EU) 2017/746 and elements of the IVD classification guidance MDCG 2020-16 Rev.2.

Rule 1 Annex VIII of Regulation (EU) 2017/746 lays down that devices intended to be used for the detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation are to be classified in class D. Examples of class D devices under this rule given in MDCG 2020-16 Rev.2 are tests detecting the presence or the exposure to HIV, haemorrhagic fever viruses or SARS-CoV-2 (NAT, antigen and antibody when applicable).

Rule 3a of Annex VIII of Regulation (EU) 2017/746 lays down that devices for detecting the presence of, or exposure to, a sexually transmitted agent are classified in Class C. The guidance MDCG 2020-16 Rev.2 mentions that Rule 3a applies to devices detecting agents whose main mode of transmission is sexual. Sexually transmitted infections are a group of infections that may be transmitted through vaginal, oral and anal sexual intercourse. The agents that cause sexually transmitted infections may pass from person to person through blood, semen, vaginal or other bodily fluids. Thus, for example, devices intended for the detection of human papilloma virus (HPV) or *Chlamydia trachomatis* are classified in C according to rule 3a. On the other hand, rule 3a does not apply to devices intended for the detection of *Sarcoptes scabiei* (genital scabies). These are then classified in class B according to rule 6 of Annex VIII.

Rule 3c of Annex VIII of Regulation (EU) 2017/746 lays down that devices intended to detect the presence of an infectious agent are classified in class C if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring. The guidance MDCG 2020-16 Rev.2 lists for example devices intended for the detection of *Legionella* spp. or *Haemophilus influenzae* type B meningitis as class C according to rule 3c.

4. Relevant medical field and areas of competence required

In vitro diagnostic medical devices, virology, monkeypox, infectious disease epidemiology.

5. Specific thematic panel or panel sub-group best suited to address the request for advice (if applicable)

In vitro diagnostic medical devices (IVD).

6. Scope of the advice

Addressing the following questions:

1) Should monkeypox virus be considered, today, as a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation?

2) Should monkeypox virus be considered a sexually transmitted agent, i.e. that its main mode of transmission is sexual?

3) Can it be considered that there is a significant risk that a false negative result of a monkeypox detection device would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring?

7. Timelines for providing the advice

Start of the advice: 26/06/2023

Advice sent for ECDC for comments: by 08/09/2023

Advice delivered to the MDCG: by 09/10/2023

8. Consultation or collaboration with other scientific bodies for the preparation of the advice (if necessary)

The European Agency for Disease Prevention and control (ECDC) is to be consulted on the draft advice.

9. Advice provided by the IVD Expert Panel

9.1. Background information

9.1.1. The monkeypox virus

The monkeypox virus (MPXV) is a zoonotic virus, which was first isolated in 1958 in Denmark from pox lesions during an outbreak of vesicular disease among captive cynomolgus macaques imported from Singapore for polio-vaccine-related research[1].

MPXV belongs to the family of Poxviridae, genus Orthopoxvirus. It is an enveloped virus with a double-stranded DNA. Other members of the Orthopoxvirus genus include vaccinia virus (the virus used for smallpox vaccination), cowpox virus, variola virus (smallpox agent), and several other animal pathogenic poxviruses[1]. Two distinct clades are known for MPXV: clade I, formerly known as the Congo Basin (Central African) clade, and clade II, formerly known as the West African clade, now called clade IIa. In these areas, the virus is enzootic.

Since 1958, over the following 10 years 8 outbreaks in monkeys in captivity were reported in the US and the Netherlands. There were no reports of MPXV infections in the natural habitat of the monkeys or in humans. Despite the name of the virus and its suggested epidemiological link, monkeys are not the natural host for the virus. MPXV has been further identified in rodents like squirrels, Gambian pouched rats, or dormice[2].

9.1.2. MPXV infection of humans

The first human infection was reported in 1970 in a 9-month-old infant, hospitalized in the Democratic Republic of Congo under suspicion of smallpox infection[3]. After 1970, MPXV infections occurred sporadically in Central and East Africa and West Africa. In 2003, an outbreak in humans in the US was linked to imported wild animals. This US outbreak affected 81 human cases among people who had close contacts with pet prairie dogs imported from Ghana[1]. There is no evidence that the virus became enzootic in the US.

Since 2005, thousands of suspected cases are reported every year. In 2017, mpox re-emerged in Nigeria and continued to spread between people across the country and in travelers to other destinations.

9.1.3. Mpox outbreak in 2022

In May 2022, an mpox outbreak appeared and rapidly spread across Europe, the Americas and beyond. This was the largest outbreak of Mpox so far worldwide. The first case was identified in the UK in April

[1] Factsheet for health professionals on mpox (monkeypox). ECDC. 1 June 2023. https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals

[2] Mpox (monkeypox). WHO. https://www.who.int/health-topics/monkeypox#tab=tab_1

[3] Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ. 1972;46(5):593-7. PMID: 4340218; PMCID: PMC2480792.

2022 in a returned traveler from Nigeria[4]. The last update of epidemiological situation provided by WHO from 115 Member States across all 6 WHO regions reported in total more than 90,000 cases and 157 associated deaths, as of 11 september 2023. During the 4 weeks prior to 11 September June 2023, 1131 cases were reported and 5 related death from in 22 countries[5]. These data confirm the downward trend of the outbreak and the relative low mortality compared to previous mpox infections in endemic regions. The outbreak decreased in intensity at the end of 2022, probably due to a set of measures including vaccination with a vaccinia-based vaccine. However, the decrease already started before the vaccine became more widely available, suggesting that other factors contributed to this decline and absence of an epidemic pattern. The global pattern of decrease was also shown in Europe, where up to 6 July 2023, 25,935 mpox cases from 45 countries were reported, including only 30 cases from 8 countries in the 4 weeks before 6 July[6].

The global outbreak has affected primarily (but not exclusively) men who have sex with men (MSM) and has spread person-to-person through sexual networks.

The mpox outbreak of 2022 is based on a clade II strain, classified as clade IIb. This strain is closely related to the one that was observed for the first time during the 2017–2019 Nigeria, Singapore, UK, and USA outbreaks[1]. MPXV is genetically stable with a relatively low mutation rate[7].

Genetic stability hampers epidemiological research as transmission routes are more difficult to delineate, with limited identification of epidemic clusters with geographic consistency[5].

9.1.4. Diagnosis of MPXV infections in humans

It is important to distinguish MPXV from other infections with similar symptoms (rash, skin lesions), e.g., from chickenpox, measles, bacterial skin infections, scabies, herpes, syphilis, other sexually transmissible infections, and from medication-associated allergies; and to differentiate potential coinfections, e. g. herpes. For these reasons, accurate diagnostics is key for early case detection, treatment and prevention of further spread.

Detection of viral DNA by polymerase chain reaction (PCR) is the most relevant laboratory test for MPXV detection. Specimens are optimally taken directly from the rash – skin, fluid, or crusts – collected by swabbing. In the absence of skin lesions, testing can be done on oropharyngeal, anal, or rectal swabs. Testing of blood markers is not recommended. Serological tests have limited value in diagnostics due to immunological cross-reactivity between human orthopoxviruses, although they can be useful for excluding a recent or past orthopoxvirus (although rare in humans) infection.

[4] Monkeypox - United Kingdom of Great Britain and Northern Ireland. Disease Outbreak News. WHO. 16 May 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON381

[5] Emergency situation reports. WHO. https://www.who.int/emergencies/situation-reports

[6] Joint ECDC-WHO Regional Office for Europe Mpox Surveillance Bulletin. ECDC and WHO. 12.01.2014. https://monkeypoxreport.ecdc.europa.eu/

[7] Scarpa F, Sanna D, Azzena I, Cossu P, Locci C, Angeletti S, Maruotti A, Ceccarelli G, Casu M, Fiori PL, Petrosillo N, Ciccozzi M. Genetic Variability of the Monkeypox Virus Clade IIb B.1. J Clin Med. 2022 Oct 28;11(21):6388. doi: 10.3390/jcm11216388. PMID: 36362616; PMCID: PMC9695420.

9.1.5. Transmissibility of MPXV

The zoonotic reservoir of MPXV has not been identified so far[1,2]. Several mammalian species are suspected to be natural hosts, and MPXV has been identified in monkeys, mice, rats, porcupines, woodchucks, squirrels, etc. Until the 2022 outbreak the zoonotic route was considered the most important transmission for humans. In the 2003 outbreak in the US, it was concluded that transmission of the virus to non-African captive species, including prairie dogs, preceded human disease, and no human-to-human transmission was recorded[8]. The exact transmission route between animals and humans remains unclear, but proximity to an infected animal (through direct contact or fluid contact) seems to be the main source for infections[9].

Inter-human transmission can occur via direct contact with the mpox lesions, or the fluids contained within. People can also contract Mpox from contaminated objects such as clothing or linens, through sharps injuries in health care, or in community setting such as tattoo parlours. Vertical transmission, including foetal death has been reported prior to 2022[10]. A recent review did not establish a clear role for respiratory transmission of MPXV[11]. Characteristics for the 2022 clade IIb outbreak are mucosal lesions in the genital or anal areas, mouth, and eyes, with many affected individuals reporting close and sustained previous physical or sexual contact with infected individuals[12], resulting in pronounced human to human transmission, with cases identified primarily, but not exclusively, among MSM. Despite detectability of viral DNA at low level in blood of mpox disease cases, replication-competent virus was not successfully isolated from these cases so far. During the recent mpox epidemic two studies performed with investigational blood screening nucleic acid amplification tests (NAT) did not result in identification of MPXV-DNA positive cases among the limited number of blood donations tested[13,14].

Although MPXV is genetically stable, the strains isolated from the 2022 outbreak of MPXV (clade IIb) seem to have more mutations compared to the IIa clade. It is assumed that these mutations occurred due to human-to human transmission. The exact impact of these mutations is presently unknown. It is concluded that inter-human mpox circulation is associated with a higher mutation rate when compared to original strains[15].

[8] Reynolds MG, Yorita KL, Kuehnert MJ, Davidson WB, Huhn GD, Holman RC, Damon IK. Clinical manifestations of human monkeypox influenced by route of infection. J Infect Dis. 2006 Sep 15;194(6):773-80. doi: 10.1086/505880. Epub 2006 Aug 8. PMID: 16941343.

[9] Kaler J, Hussain A, Flores G, Kheiri S, Desrosiers D. Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation. Cureus. 2022 Jul 3;14(7):e26531. doi: 10.7759/cureus.26531. PMID: 35928395; PMCID: PMC9345383.

[10] Mbala PK, Huggins JW, Riu-Rovira T, et al. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. J Infect Dis 2017;216:824-828

[11] Beeson A, Styczynski A, Hutson CL, Whitehill F, Angelo KM, Minhaj FS, Morgan C, Ciampaglio K, Reynolds MG, McCollum AM, Guagliardo SAJ. Mpox respiratory transmission: the state of the evidence. Lancet Microbe. 2023 Apr;4(4):e277-e283. doi: 10.1016/S2666-5247(23)00034-4. Epub 2023 Mar 7. PMID: 36898398; PMCID: PMC9991082.

[12] Priya Venkatesan Monkeypox transmission—what we know so far. The Lancet Respiratory Medicine, 2022, 10;11: E101

[13] Knight C, Andreani J, Garrett N, Winter M, Golubchik T, Breuer J, Reynolds C, Brailsford SR, Harvala H, Simmonds P (2023) Absence of detectable monkeypox virus DNA in 11,000 English blood donations during the 2022 outbreak. Transfusion 63, 690-695. https://doi.org/10.1111/trf.17266

[14] Groves JA, Tonnetti L, Self D, Yadav MC, Livezey K, Linnen JM, Stramer SL (2023) Nucleic acid testing for monkeypox in United States blood donor specimens. Transfusion (in press).

https://doi.org/10.1111/trf.17500

[15] Groves JA, Tonnetti L, Self D, Yadav MC, Livezey K, Linnen JM, Stramer SL (2023) Nucleic acid testing for monkeypox in United States blood donor specimens. Transfusion (in press).

Human-to-human transmission also increases the transmission rate, compared to zoonotic transmission[16], most relevant for the at-risk groups rather than the general population[17]. Close contact thus seems the main driver for transmission, which was also shown in the 2003 outbreak in the US[18].

The role of asymptomatic infections in transmission currently remains unclear[1,19,] although different analyses suggested that it may have played a role in the 2022 outbreak[20,21,22].

The risk of infection seems associated with prior exposure to smallpox vaccination or putative prior infection [2,23,24,25]. Individuals born after termination of the smallpox vaccination campaigns are more at

https://doi.org/10.1111/trf.17500

[16] Branda F, Pierini M, Mazzoli S. Monkeypox: Early estimation of basic reproduction number R0 in Europe. J Med Virol. 2023 Jan;95(1):e28270. doi: 10.1002/jmv.28270. Epub 2022 Nov 9. PMID: 36319946.

[17] Kile JC, Fleischauer AT, Beard B, Kuehnert MJ, Kanwal RS, Pontones P, Messersmith HJ, Teclaw R, Karem KL, Braden ZH, Damon I, Khan AS, Fischer M. Transmission of monkeypox among persons exposed to infected prairie dogs in Indiana in 2003. Arch Pediatr Adolesc Med. 2005 Nov;159(11):1022-5. doi: 10.1001/archpedi.159.11.1022. PMID: 16275790.

[18] Kile JC, Fleischauer AT, Beard B, Kuehnert MJ, Kanwal RS, Pontones P, Messersmith HJ, Teclaw R, Karem KL, Braden ZH, Damon I, Khan AS, Fischer M. Transmission of monkeypox among persons exposed to infected prairie dogs in Indiana in 2003. Arch Pediatr Adolesc Med. 2005 Nov;159(11):1022-5. doi: 10.1001/archpedi.159.11.1022. PMID: 16275790.

[19] Yang, S., Guo, X., Zhao, Z. et al. Possibility of mpox viral transmission and control from high-risk to the general population: a modeling study. BMC Infect Dis 23, 119 (2023). https://doi.org/10.1186/s12879-023-08083-5

[20] De Baetselier I, Van Dijck C, Kenyon C, Coppens J, Michiels J, de Block T, Smet H, Coppens S, Vanroye F, Bugert JJ, Girl P, Zange S, Liesenborghs L, Brosius I, van Griensven J, Selhorst P, Florence E, Van den Bossche D, Ariën KK, Rezende AM, Vercauteren K, Van Esbroeck M; ITM Monkeypox study group. Retrospective detection of asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. Nat Med. 2022 Nov;28(11):2288-2292. doi: 10.1038/s41591-022-02004-w. Epub 2022 Aug 12. PMID: 35961373; PMCID: PMC9671802.

[21] Ferre VM, Bachelard A, Zaidi M, Armand-Lefevre L, Descamps D, Charpentier C, et al. Detection of Monkeypox Virus in Anorectal Swabs From Asymptomatic Men Who Have Sex With Men in a Sexually Transmitted Infection Screening Program in Paris, France. Ann Intern Med. 2022;175(10):1491-2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35969863 (link is external)

[22] Agustí C, Martínez-Riveros H, Hernández-Rodríguez À, Casañ C, Díaz Y, Alonso L, et al. Asymptomatic Monkeypox virus infection: A self-sampling screening Intervention Adressed to gay, bisexual and other men who have sex with men and trans women in Spain medRxiv. 2023:2023.02.20.23286168. Available at https://www.medrxiv.org/content/medrxiv/early/2023/02/22/2023.02.20.23286168.full.pdf

[23] Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Muyembe Tamfum JJ, Nguete B, Hughes CM, Monroe BP, Reynolds MG. Vaccinating against monkeypox in the Democratic Republic of the Congo. Antiviral Res. 2019 Feb;162:171-177. doi: 10.1016/j.antiviral.2018.11.004. Epub 2018 Nov 14. PMID: 30445121; PMCID: PMC6438175.

[24] Kriss JL, Boersma PM, Martin E, Reed K, Adjemian J, Smith N, Carter RJ, Tan KR, Srinivasan A, McGarvey S, McGehee J, Henderson D, Aleshire N, Gundlapalli AV. Receipt of First and Second Doses of JYNNEOS Vaccine for Prevention of Monkeypox - United States, May 22-October 10, 2022. MMWR Morb Mortal Wkly Rep. 2022 Oct 28;71(43):1374-1378. doi: 10.15585/mmwr.mm7143e2. PMID: 36301741; PMCID: PMC9620573

[25] Zaeck LM, Lamers MM, Verstrepen BE, Bestebroer TM, van Royen ME, Götz H, Shamier MC, van Leeuwen LPM, Schmitz KS, Alblas K, van Efferen S, Bogers S, Scherbeijn S, Rimmelzwaan GF, van Gorp ECM, Koopmans MPG, Haagmans BL, GeurtsvanKessel CH, de Vries RD. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat Med. 2023 Jan;29(1):270-278. doi: 10.1038/s41591-022-02090-w. Epub 2022 Oct 18. PMID: 36257333; PMCID: PMC9873555.

risk of infection. One conclusion might be that a more substantial proportion of the at-risk population has developed antibodies either through vaccination or infection.

9.1.6. Mpox symptoms and disease

Symptoms of mpox are similar to smallpox, although much less severe. Smallpox was officially declared eradicated in 1980[26].

Signs and symptoms usually begin within a week but can start 1–21 days after exposure[5.] Prodromal clinical symptoms are unspecific, including fever, headache, lymphadenopathy, myalgia, and fatigue, lasting 1–5 days, after which single or multiple highly infectious lesions on the skin or mucosa appear that may last between 2–4 weeks. Some patients also develop a rash.

Although most patients will fully recover within a few weeks, complicated courses can occur, including secondary bacterial infections of the skin lesions, pneumonia, sepsis, encephalitis, myocarditis, proctitis, balanitis, urethritis, or death (0.17%). Persons with immune suppression due to medication or medical conditions are at higher risk of serious illness and death. People living with HIV that is not well-controlled more often develop severe disease[5], not observed for controlled HIV co-infections[25,27].

In the 2022 outbreak, most patients presented usually mild symptoms, sometimes with very few lesions. Some locations of the lesions (proctitis, oropharyngeal) were more debilitating. Hospitalization for isolation, pain management, or for complications such as secondary skin infections, abscesses, and difficulty in swallowing was recorded in a minority of cases (1–13%). Serious complications were rare and included epiglottitis, myocarditis, and encephalitis. The case fatality in the EU was less than 0.1%[2].

9.1.7. Mpox treatment

The goal of treating mpox is to take care of the rash, manage pain and prevent complications. Early care is important to help manage symptoms and avoid further problems. Getting an mpox vaccine can help prevent infection. The vaccine should be given within 4 days of contact with someone who has mpox (or within up to 14 days if there are no symptoms, post-exposure vaccination).

Pre-exposure vaccination is recommended for people at high risk (men who have sex with men, health workers at-risk of exposure, people with multiple sex partners, sex workers).

Several antivirals, such as tecovirimat, have also been used, although no data are available on the effectiveness of tecovirimat in treating mpox infections.

[26] Declaration of global eradication of smallpox WHA33.3. WHO. 08.05.1980. https://iris.who.int/bitstream/handle/10665/155528/WHA33_R3_eng.pdf?sequence=1

[27] Estévez S, Vara M, Gamo M, Manzano S, Troya J, Botezat E, Jiménez E, Pedrero-Tomé R, Martin MÁ, de la Cueva P, Fernández E, Fernández B, Brown DE, Palma E, Simón A. Epidemiological and Clinical Characteristics of Patients Admitted to a Secondary Hospital with Suspected MPOX Virus Infection: Is HIV Playing a Role? J Clin Med. 2023 Jun 18;12(12):4124. doi: 10.3390/jcm12124124. PMID: 37373818; PMCID: PMC10299369.

9.2. Questions and Answers

This advice is based on the evidence and experience gained so far with the clade IIb MPXV strain, estimated as most relevant for the current EU setting. Clade I and clade IIa infections are considered incidental import infections, with no or limited risks for human-to-human infection and thus spread within the EU community.

9.2.1. Should monkeypox virus be considered, today, as a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation?

Until the 2022 outbreak, MPXV was considered an enzootic infection in defined geographic areas in Africa. Incidental outbreaks occurred outside these endemic areas, usually confined to transmission from animal to human. The basic reproductive rate of these clades is therefore low (≤ 1). The 2022 outbreak has shown that the virus is able to more efficiently transmit from human to human, particularly in specific at-risk groups. Due to implementation of countermeasures and potential unknown factors, the transmission declined significantly since the end of 2022, without evidence of widespread transmission or of high risk of propagation.

Specific background

Generally, infections with the clade IIb virus have a mild to moderate course of disease, with limited risk of complicated disease and a low case fatality rate. Case-based data for 25,800 cases from 41 European region countries, reported a hospitality rate of 6%, 8 admissions to ICU units and 7 deaths[13]. Currently, incidental infections in the EU region are reported (n=37 in the prior 3 weeks). At the same time, the Western pacific region shows increased numbers, albeit numbers are still low (n=158, in the prior 3 weeks). WHO assesses the global risk as moderate[28].

Based on the currently available evidence one can thus conclude that mpox is a transmissible agent that does not causes a life-threatening disease in Europe with a high or suspected high risk of propagation. However, epidemiological surveillance is required because the risk of propagation can change over time.

This is in strong contrast to the related smallpox agent, variola virus, which was characterized by both higher risk for propagation and much higher fatality rate (around 30% of infections).

9.2.2. Should monkeypox virus be considered a sexually transmitted agent, i.e. that its main mode of transmission is sexual?

The recent mpox outbreak is characterized by transmission of the virus within specific communities. As commented in section "1e) Transmissibility of mpox virus", it appears that particularly close contact is important for human-to-human transmission.

[28] Multi-country outbreak of mpox, External situation report#27 – 14 August 2023. WHO. https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-27---14-august-2023

The risk of infection following sexual exposure is high – in a contact tracing study in connection with the 2022 outbreak, 66% of exposed sexual contacts were 'definitely or possibly' infected compared to only 14% of non-sexual contacts[29].

The ECDC case-based data reported that 98% of cases reported were male and a majority of cases were from the 31-40 years age category. Of those with data reported on sexual orientation, 96% self-identified as MSM.

In a study of high-risk individuals, daily anorectal, genital and saliva sampling confirmed presymptomatic viral shedding with associated risk of transmission during sexual contact[30]. Although the sexual transmission route for monkeypox virus was mainly associated with clade II virus, the recent strong increase in mpox in DRC mainly with clade I is also related to sexual contacts in both men and women. This change in transmission route is of concern since it also shows the potential of efficient human to human transmission in case of close (sexual) contact which is also reflected in a different clinical presentation comparable to that observed for clade IIb[31] . The change of transmission is also associated geographic changes adaptation from efficient rural zoonotic transmission to urban human to human transmission (CDC, WHO). ECDC recently published a risk assessment in which the sexual transmission of the clade I was confirmed; however, as no clinical cases of clade I mpox are yet detected in the EU, the associated risk is currently considered low[32].

A recent systematic review confirmed the presence of Mpox in semen[33], which has also been cultured[34] providing further evidence of possible Mpox transmission through semen. This was also supported by

[29] Brosius I, Van Dijck C, Coppens J, Vandenhove L, Bangwen E, Vanroye F, Verschueren J; ITM MPOX Study Group; Zange S, Bugert J, Michiels J, Bottieau E, Soentjens P, van Griensven J, Kenyon C, Ariën KK, Van Esbroeck M, Vercauteren K, Liesenborghs L. Presymptomatic viral shedding in high-risk mpox contacts: A prospective cohort study. J Med Virol. 2023 May;95(5):e28769. doi: 10.1002/jmv.28769. PMID: 37212312.

[30] Brosius I, Van Dijck C, Coppens J, Vandenhove L, Bangwen E, Vanroye F, Verschueren J; ITM MPOX Study Group; Zange S, Bugert J, Michiels J, Bottieau E, Soentjens P, van Griensven J, Kenyon C, Ariën KK, Van Esbroeck M, Vercauteren K, Liesenborghs L. Presymptomatic viral shedding in high-risk mpox contacts: A prospective cohort study. J Med Virol. 2023 May;95(5):e28769. doi: 10.1002/jmv.28769. PMID: 37212312.

[31] Kibungu EM, Vakaniaki EH, Kinganda-Lusamaki E, Kalonji-Mukendi T, Pukuta E, Hoff NA, Bogoch II, Cevik M, Gonsalves GS, Hensley LE, Low N, Shaw SY, Schillberg E, Hunter M, Lunyanga L, Linsuke S, Madinga J, Peeters M, Cigolo JM, Ahuka-Mundeke S, Muyembe JJ, Rimoin AW, Kindrachuk J, Mbala-Kingebeni P, Lushima RS; International Mpox Research Consortium. Clade I-Associated Mpox Cases Associated with Sexual Contact, the Democratic Republic of the Congo. Emerg Infect Dis. 2024 Jan;30(1):172-176. doi: 10.3201/eid3001.231164. Epub 2023 Nov 29. PMID: 38019211; PMCID: PMC10756366.

[32] Implications for the EU/EEA of the outbreak of mpox caused by Monkeypox virus clade I in the Democratic Republic of the Congo. ECDC. 5 December 2023. https://www.ecdc.europa.eu/sites/default/files/documents/Implications-mpox-drc-TAB-erratum.pdf

[33] Barboza JJ, León-Figueroa DA, Saldaña-Cumpa HM, Valladares-Garrido MJ, Moreno-Ramos E, Sah R, Bonilla-Aldana DK, Rodriguez-Morales AJ. Virus Identification for Monkeypox in Human Seminal Fluid Samples: A Systematic Review. Trop Med Infect Dis. 2023 Mar 14;8(3):173. doi: 10.3390/tropicalmed8030173. PMID: 36977174; PMCID: PMC10057446.

[34] Lapa D, Carletti F, Mazzotta V, Matusali G, Pinnetti C, Meschi S, Gagliardini R, Colavita F, Mondi A, Minosse C, Scorzolini L, Cicalini S, Maffongelli G, Specchiarello E, Camici M, Bettini A, Baldini F, Francalancia M, Mizzoni K, Garbuglia AR, Nicastri E, Girardi E, Antinori A, Vaia F, Maggi F; INMI Monkeypox Study Group. Monkeypox virus isolation from a semen sample collected in the early phase of infection in a patient with prolonged seminal viral shedding. Lancet Infect Dis. 2022 Sep;22(9):1267-1269. doi: 10.1016/S1473-3099(22)00513-8. Epub 2022 Aug 2. PMID: 35931095; PMCID: PMC9629691.

the observation of other concomitant sexually transmitted infections (STIs)[35]. In a subset of patients in which semen and blood samples were available[36], 22/36 also tested positive for Mpox in semen and 24/36 in serum/plasma. Positive semen samples were also observed in subjects without genital lesions, which was hypothesized to be a result of bloodstream dissemination of the virus.

The focus on importance of the sexual transmission route is also reflected in the WHO recommendations for high-risk groups for preventive measures[37,38], including vaccination, i.e. health workers at risk of exposure; men who have sex with men (MSM); people with multiple sex partners and sex workers.

Based on the currently available evidence and the characteristics of the MPXV clade IIb and recent clade I transmission patterns, the conclusion is that mpox can be considered a sexually transmitted agents.

9.2.3. Can it be considered that there is a significant risk that a false negative result of a monkeypox detection device would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring?

The risk associated with a false-negative MPXV detection test result causing death or severe disability in an adult depends on the severity of the disease in the absence of treatment. As mentioned above, most patients fully recover within a few weeks after being infected and the mortality rate is very low (<2/1,000). This implies that the impact of a false negative result is extremely limited. However, one should consider that a false negative result for an infected individual may not prevent secondary infections in sexual partners.

There is very limited evidence of increased risk of complicated disease during pregnancy, or risk of vertical transmission resulting in severe disability or death pre- or postpartum. Probably as precaution, WHO includes pregnant women in the group of those at increased risk for complications from MPXV[2].

In conclusion, the potential impact of a false-negative test result on the risk of death or severe disability is considered low.

Specific background

[35] Candela C, Raccagni AR, Bruzzesi E, Bertoni C, Rizzo A, Gagliardi G, Canetti D, Gianotti N, Mileto D, Gismondo MR, Castagna A, Nozza S; Centro San Luigi (CSL) Working Group. Human Monkeypox Experience in a Tertiary Level Hospital in Milan, Italy, between May and October 2022: Epidemiological Features and Clinical Characteristics. Viruses. 2023 Mar 2;15(3):667. doi: 10.3390/v15030667. PMID: 36992376; PMCID: PMC10051371.

[36] Raccagni AR, Candela C, Mileto D, Canetti D, Bruzzesi E, Rizzo A, Castagna A, Nozza S. Monkeypox infection among men who have sex with men: PCR testing on seminal fluids. J Infect. 2022 Nov;85(5):573-607. doi: 10.1016/j.jinf.2022.07.022. Epub 2022 Jul 29. PMID: 35914609; PMCID: PMC9556608.

[37] Allan-Blitz LT, Klausner JD. Current Evidence Demonstrates That Monkeypox Is a Sexually Transmitted Infection. Sex Transm Dis. 2023 Feb 1;50(2):63-65. doi: 10.1097/OLQ.0000000000001705. Epub 2022 Oct 28. PMID: 36098576; PMCID: PMC9855745.

[38] Allan-Blitz LT, Gandhi M, Adamson P, Park I, Bolan G, Klausner JD. A Position Statement on Mpox as a Sexually Transmitted Disease. Clin Infect Dis. 2023 Apr 17;76(8):1508-1512. doi: 10.1093/cid/ciac960. PMID: 36546646; PMCID: PMC10110265.

Data on MPXV infection during pregnancy are limited. An increased risk for severe disease has not been quantified so far. Adverse pregnancy outcomes have been reported, including pregnancy loss, stillbirth, preterm birth, or neonatal infection, but an association between severity of maternal illness and adverse perinatal outcomes is unclear. Limited data do suggest transmission of MPXV from pregnant women to children in utero during pregnancy or by close contact with the newborn during and after birth. Despite the virus DNA has been detected in seminal fluid there is currently no information of virus spread through semen, vaginal fluids, or breast milk.

WHO has provided an overview of all available evidence about clinical management and prevention of mpox during and after pregnancy[39]. Before the 2022 outbreak, seven cases of severe symptomatic mpox during the 1st or 2nd trimester of pregnancy with hospitalization were described in the literature from the Democratic Republic of the Congo and Nigeria[39]28. Five pregnancies resulted in pregnancy losses before 26 weeks of gestation. One foetus had hydrops fetalis and generalized maculopapular skin rashes, including on the palms and soles, with no congenital malformations or deformities, nor gross abnormalities in the placenta, placental membranes, or umbilical cord. Two pregnancies resulted in liveborn neonates, of which one baby had generalized skin rash consistent with mpox and died of malnutrition six weeks after birth.

With the 2022 mpox outbreak 58 pregnancies were recorded as of 19 July 2023 in the global surveillance data (mainly Brazil and US): 5 cases were in their first trimester, 12 in their second trimester, and 10 in their third trimester, 31 with unknown trimester. Thirteen patients were hospitalized with no ICU admission or death[40]. No information is available on pregnancy outcomes, although 2 infants were reported to have been infected in utero or at birth.

In the USA, 21 cases of mpox during pregnancy were reported, all among cisgender women. Rash was present in all cases. Genital lesions were reported by four cases, however none reported genital lesions near the time of childbirth. Four were hospitalized due to symptoms; none required intensive care, intubation, or unplanned delivery. Limited data on in utero infected pregnancy outcomes were available (2 healthy infants, one spontaneous abortion). For 3 women with clinical symptoms 3-4 days after birth, the neonates developed lesions within one week later. In Brazil, 22 pregnant women with confirmed or probable mpox have been reported. Two pregnant women were hospitalized, one for clinical management and the other for isolation.

A case of neonatal MPXV infection after peripartum transmission within a family cluster was also reported in the UK. In this case, transplacental transmission could not be ruled out. A similar case has been reported in June 2023 from the WHO South-East Asia Region. The observed risk of vertical transmission and perinatal infection is also mentioned by CDC[41].

[39] Multi-country outbreak of mpox. External Situation Report 25. 24 June 2023. https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report--25---24-june-2023

[40] 2022-23 Mpox (Monkeypox) Outbreak:Global Trends. WHO. 23.02.2024. https://worldhealthorg.shinyapps.io/mpx_global/#32_Trends_in_cases

[41] Clinical Considerations for Mpox in People Who are Pregnant or Breastfeeding. CDC. 27.03.2023. https://www.cdc.gov/poxvirus/mpox/clinicians/pregnancy.html

Furthermore, in literature incidental cases are described, but firm conclusions on risks cannot be made[42,43]. This is also true for the possible mechanism of vertical transmission, which is also not elucidated[44].

Overall, there is some, albeit scarce, evidence of vertical transmission of MPXV from mother to child both pre- and perinatal. Except for the case reports with the original clades, there is no clear evidence of a causal relation between the infection during pregnancy and inadvertent outcome. However, data are too limited for any firm conclusion. There are however some reports of early postpartum infection of the neonates, which can have a serious, complicated course of disease. Considering the rarity of cases reported, the diagnostic risk associated is more related to the specificity of a detection test, i.e., risk of false positive result, than to the sensitivity. It cannot be excluded that a false negative result may have an associated risk of death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring, but these risks cannot be really estimated and are likely to be small.

[42] Sampson MM, Magee G, Schrader EA, Dantuluri KL, Bukhari A, Passaretti C, Temming L, Leonard M, Philips JB, Weinrib D. Mpox (Monkeypox) Infection During Pregnancy. Obstet Gynecol. 2023 May 1;141(5):1007-1010. doi: 10.1097/AOG.0000000000005170. Epub 2023 Mar 15. PMID: 36928418.

[43] Cuérel A, Favre G, Vouga M, Pomar L. Monkeypox and Pregnancy: Latest Updates. Viruses. 2022 Nov 14;14(11):2520. doi: 10.3390/v14112520. PMID: 36423129; PMCID: PMC9693336.

[44] Dashraath P, Nielsen-Saines K, Rimoin A, Mattar CNZ, Panchaud A, Baud D. Monkeypox in pregnancy: virology, clinical presentation, and obstetric management. Am J Obstet Gynecol. 2022 Dec;227(6):849-861.e7. doi: 10.1016/j.ajog.2022.08.017. Epub 2022 Aug 17. PMID: 35985514; PMCID: PMC9534101.