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Vaccination for monkeypox prevention in persons with high-risk sexual behaviours to control on-going outbreak of monkeypox virus clade 3.

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Since January 2022, and as of 15th June 2022, a total of 2103 laboratory-confirmed cases of monkeypox, including one death, have been reported to the WHO from 42 countries in five of six WHO regions (WHO 2022a; ECDC 2022). The majority (84%) of confirmed cases (n=1773) are in the WHO European Region, and only a few have a travel history to endemic countries in Africa.

The unprecedented outbreak of monkeypox primarily affect men who have sex with men (MSM) with new or multiple partners. A new nomenclature has been proposed to distinguish recurring local cases in known enzootic regions from the current outbreak, with the previous Congo Basin lineage as clade 1, the West African local cases (and incidental travellers) as clade 2, and the current outbreak outside of the African region as clade 3 (Happi et al. 2022).

A recent estimate of the R_0 of the ongoing outbreak of MPXV clade 3 suggests it may be substantially higher than 1, thus sustaining an expanding outbreak in this high-risk population of young men who are too young to have had a smallpox vaccine in their childhood (Endo et al. 2022). The priority should be on stopping further spread and protecting frontline health-care workers (Ntoumi et al., 2022).

The immunity against pox viruses is limited to people over 40 years of age since smallpox was eradicated around 1980 and the vaccination programs ended. Thus, any immunity from prior smallpox vaccination would only be present in persons over the age of 40 years. Thus, the successful smallpox eradication and cessation of vaccination has created an ecological niche where the MPXV can easier spread outside its natural rodent reservoir, from human to human (Petersen et al., 2019). The MPXV has not radically changed and remains a zoonosis – but is now spreading effectively in a highly sexually active network of young men without immunity. If surveillance was strengthened and response timely the outbreak could be stopped at the source. Judging from the high HIV prevalence among at least some subset of recent monkeypox cases, it appears to be a particularly risk-averse subset of the MSM population that is at risk in this unprecedented monkeypox outbreak. Fifty percent of cases in early reports from Portugal and Italy were HIV-positive (Perez Duque et al. 2022; Ferraro et al. 2022).

Pre-Exposure prophylaxis, PrEP, and Post-Exposure Prophylaxis, PEP

It took time for the idea of pre-exposure prophylaxis (PrEP) to be translated into a prevention strategy for MSM at high risk of HIV infection. Outside clinical trials, PrEP with antiretrovirals is estimated to reduce transmission by approximately 50% (Jourdain et al. 2022) with proven cost-effectiveness in real-world setting (Ten Brink et al. 2022). We did not have PrEP when the HIV pandemic started, but we would undoubtedly have used it if we had had it.

Vaccination against the now eradicated smallpox virus has been shown to be 85% cross-protective against monkeypox (Fine et al., 1988). Still, it is not clear how long the protection lasts. The 85% protective efficacy was obtained with the first-generation vaccinia virus vaccines against transmission through droplet spread (Fine et al., 1988).

In a new WHO interim guidance on vaccine use for MPX, the WHO proposes post-exposure prophylaxis (PEP) with a vaccine offered to contacts of cases within four days of first exposure (WHO 2022b). PrEP in the form of a vaccine is recommended for health workers at risk, laboratory personnel working with orthopoxviruses, clinical laboratory staff performing diagnostic testing for monkeypox, and others who may be at risk as per national policy (WHO 2022a). The latter is in line with the recommendations of the USA CDC Advisory Committee on Immunization Practices (ACIP) from June 25, 2015, revised by the CDC on June 1st (CDC 2022a) advising routine vaccination with live smallpox (vaccinia) vaccine (ACAM2000®) for laboratory personnel who directly handle cultures or animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola).

Epidemiologically, the assessment is that it should be possible to contain monkeypox infection through active tracking of cases, isolation and quarantine, supplemented with PEP vaccination of high-risk contacts.

The WHO has stated that a smallpox vaccine should not be used widely to fight monkeypox. Director-General Tedros Adhanom Ghebreyesus said during a WHO meeting that "While smallpox vaccines are expected to provide some protection against monkeypox, there is limited clinical data, and limited supply" (WHO 2022b).

However, the evolution of the outbreak is worrisome as there does not seem to be much slowing down of the epidemic yet. Reports suggest significant challenges in the tracing of

contacts due to lack of information or hesitancy to share contact information (Vivancos et al. 2022). Therefore, it seems prudent to consider PEP vaccination in high-risk individuals as well, but the time window is short as post-exposure vaccination with the present recommendations should be given not later than four days after exposure. The current shortage of vaccines will require prioritization unless there is scaling up of production. Also, it seems to us that the risk of infection in healthcare workers using appropriate Personal Protection Equipment (PPE) is much lower than MSM, where the R_0 is above 1 and even much higher depending on the number of partners (Endo et al. 2022). The use of smallpox vaccine as PrEP in MSM at high risk of monkeypox virus exposure and may also reduce transmission into the general population.

The 21st of June 2022 the UK Health Security Agency published a statement saying that "some gay and bisexual men at higher risk of exposure to monkeypox should be offered vaccines to help control the recent outbreak of the virus" and that "an individual's eligibility would depend on a number of factors but would be similar to the criteria used to assess those eligible for HIV pre-exposure prophylaxis (PrEP) – but applied regardless of HIV status" (UK HSA 2022).

We believe that such a program should only be performed in the form of a proper clinical trial with follow up for instance for 12 months, registering clinical MPX cases and documenting adverse events.

Are the vaccines available for smallpox safe to be offered to populations at high risk of exposure?

The original first-generation smallpox vaccines used for the smallpox eradication program in the 1970s are no longer available. Second- and third-generation smallpox vaccines have been developed due to the concern for smallpox as a bioweapon. These new vaccines have an improved safety profile and one of them has been approved by the FDA and EMA for prevention of monkeypox. WHO has issued interim guidelines for vaccines and immunization for monkeypox (WHO 2022b).

Two vaccines are licensed by the FDA in the U.S.A., ACAM2000® (IMVAMUNE®) and JYNNEOS® (IMVANEX®) (CDC 2019) for smallpox, but only JYNNEOS® for monkeypox (in September 2019). ACAM2000® contains replication competent vaccinia virus, belonging to the poxvirus family and is manufactured by Emergent BioSolutions Inc. Gaithersburg,

Maryland, U.S.A. (FDA 2007). ACAM2000® may cause rash, fever, and head and body aches. In certain people, particularly those who are immunocompromised and who have eczema and atopic dermatitis, complications from the vaccinia virus can be severe and person-to-person spread of the vaccinia vaccine virus can occur.

JYNNEOS®/IMVANEX®, is a live vaccine produced from the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) strain, an attenuated, non-replicating orthopoxvirus manufactured by Bavarian Nordic, Hellerup, Denmark. As a replication-deficient vaccine, it can be used for vaccination of people 18 years and older with certain immune deficiencies or conditions, such as HIV or atopic dermatitis (FDA 2019). The European Health Emergency Preparedness and Response Authority (HERA) has ordered 110,000 doses of the JYNNEOS®/IMVANEX® vaccine to be made available to EU Member States (Eur Phar Rev 2022). Given the difference in the safety profiles between the ACAM2000®/IMVAMUNE® and JYNNEOS®/IMVANEX®, only the latter should be used as PrEP or PEP against MPXV infections.

The optimal strategy to offer vaccine as PrEP needs to be considered**.**

A possibility is to recommend a vaccine to MSM who self-identify as having multiple partners or to those who are already under treatment for other STDs, such as HIV, syphilis, gonorrhoea. The UKHSA proposes to target persons qualifying for HIV PrEP (UK HSA 2022). We do not know if immunization with a smallpox vaccine like JYNNEOS®/IMVANEX® will provide protective immunity against sexually transmitted MPXV. Therefore, the use of a vaccine as PrEP against MPXV must be in the form of a randomized, controlled trial with another vaccine used in the control arm.

Conclusion

Since the expanding unusual global outbreak of monkeypox has so far primarily been limited to MSM, at least the safest smallpox vaccine should be offered to this group on a strictly voluntary basis as pre-exposure prophylaxis (PrEP) as part of a clinical trial to document protective efficacy and monitor adverse reactions. Clinical trials are needed to inform about protective efficacy against sexual transmission before use can be advocated.

The scale of PrEP could be decided in reference to the exposure risk level in each respective jurisdiction. This will facilitate a controlled roll-out of vaccines, and should be implemented

when vaccine production has been ramped up to meet demand. No doubt vaccine production must be increased to ensure access and equity also outside Europe and North America.

If vaccination can reduce sexual MPXV transmission, it will limit the outbreak and would be an important tool to prevent further spread within and beyond the initial high-risk population. When the WHO Emergency Committee convened by Dr. Ghebreyesus meets June 23rd, we anticipate and hope that PrEP will be addressed.

References

Centers for Disease Control.a. Smallpox/Monkeypox VIS. 1st June 2022 https://www.cdc.gov/vaccines/hcp/vis/vis-statements/smallpox-monkeypox.html (Accessed 21 June 2022).

Centers for Disease Control. Vaccines.b. Last updated the 2nd Dec 2019. https://www.cdc.gov/smallpox/clinicians/vaccines.html (Accessed 18 June 2022).

Endo A, Murayama H, Abbott S, Ratnayake R, Pearson CAB, John Edmunds W et al. Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions, May 2022. medRxiv 13 June 2022. https://doi.org/10.1101/2022.06.13.22276353.

European Centers for Disease Control. Epidemiological update: Monkeypox multi-country outbreak. https://www.ecdc.europa.eu/en/news-events/epidemiological-update-monkeypox-multi-country-outbreak-15-june (Accessed 16 June 2022)

European Pharmaceutical Review. Bavarian Nordic to supply EU Member States with monkeypox vaccine. https://www.europeanpharmaceuticalreview.com/news/172246/bavarian-nordic-to-supply-eu-member-states-with-monkeypox-vaccine/ (Accessed 20 June 2022).

Federal Drug Agency. ACAM2000 (Smallpox (Vaccinia) Vaccine, Live) 2007. https://www.fda.gov/media/75792/download (Accessed 18 June 2022).

Federal Drug Agency. JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating). 2019. https://www.fda.gov/media/131078/download. (Accessed 18 June 2022).

Ferraro F, Caraglia A, Rapiti A, Cereda D, Vairo F, Mattei G et al. Multiple introductions of MPX in Italy from different geographic areas. Euro Surveill. 2022;27(23): pii=2200456. https://doi.org/10.2807/1560-7917.

Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. Int J Epidemiol. 1988;17:643–50.

Happi C, Adetifa I, Mbala P, Njouom R, Nakoune E, Happi A et al. Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus. https://virological.org 10 June 2022. https://virological.org/t/urgent-need-for-a-non-discriminatory-and-non-stigmatizing-nomenclature-for-monkeypox-virus/853 (Accessed 20 June 2022).

Jourdain H, de Gage SB, Desplas D, Dray-Spira R. Real-world effectiveness of pre-exposure prophylaxis in men at high risk of HIV infection in France: a nested case-control study. Lancet Publ Hlth. 2022;7(6):e529-e536. doi: 10.1016/S2468-2667(22)00106-2.

Perez Duque M, Ribeiro S, Martins JV , Casaca P, Leite1 PP, Tavares M et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. Euro Surveill. 2022;27(22):pii=2200424. https://doi.org/10.2807/1560-7917.

Petersen E, Abubakar I, Ihekweazu C, Heymann D, Ntoumi F, Blumberg L et al. Monkeypox - Enhancing public health preparedness for an emerging lethal human zoonotic epidemic threat in the wake of the smallpox post-eradication era. Int J Infect Dis. 2019 Jan;78:78-84.

Ten Brink DC, Martin-Hughes R, Minnery ME, Osborne AJ, Schmidt HA, Dalal S et al. Cost-effectiveness and impact of pre-exposure prophylaxis to prevent HIV among men who have sex with men in Asia: A modelling study. PLoS One. 2022;17(5):e0268240. doi: 10.1371/journal.pone.0268240.

UK Health Security Agency (UKHSA). Monkeypox: vaccine to be offered more widely to help control outbreak. 21 June 2022. https://www.gov.uk/government/news/monkeypox-vaccine-to-be-offered-more-widely-to-help-control-outbreak (Accessed 22 June 2022).

Vivancos R, Anderson C , Blomquist P, Balasegaram S, Bell A, Bishop L et al. Community transmission of monkeypox in the United Kingdom, April to May 2022. Euro Surveill. 2022;27(22):pii=2200422. https://doi.org/10.2807/1560-7917.

WHO 2022a: WHO situation update: Multi-country Monkeypox outbreak: situation update https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393 -accessed June 18, 2022

WHO 2022b. Vaccines and immunization for monkeypox: Interim guidance, 14 June 2022. https://www.who.int/publications/i/item/who-mpx-immunization-2022.1

Zumla A, Valdoleiros SR, Haider N, Asogun D, Ntoumi F, Petersen E et al. Monkeypox outbreaks outside endemic regions: scientific and social priorities. Lancet Infect Dis. 2022 May 27:S1473-3099(22)00354-1. doi: 10.1016/S1473-3099(22)00354-1.