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Growing shreds of evidence for monkeypox to be a sexually transmitted infection

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The largest monkeypox virus (MPXV) outbreak identified in non-endemic countries started in May 2022 [1]. Initially, that was linked to Gay Pride parties in the Canary Islands and rave parties in Madrid, Spain, and Berlin, Germany, where sexual activities took place [2]. However, those who attended the parties had neither a history of travel nor contact with persons returning homes from endemic areas. In addition, they reported no contact with any animals whose relationship to the disease is known or unknown [3]. Since then, cases have been increasingly reported from different parts of the Western world, mainly amongst men who have sex with men (MSM) seeking care in primary care and sexual health clinics [1]. Up to June 29, 2022, 5115 cases have been reported in 51 countries [4].

Genomic and phylogenetic analyses of the first outbreak-related MPXV genome, publicly released on May 20, 2022, by Portugal, as well as additional sequences released on the National Center for Biotechnology Information (NCBI) before May 27 2022, [Portugal (n=10), USA (n=1), Germany (n=1), France (n=1), Switzerland (n=1), Slovenia (n=1)] confirmed that the 2022 outbreak virus belongs to the West African (WA) clade [3]. All outbreak MPXV sequenced are tightly clustered together, forming a divergent branch descendant from a branch with viruses associated with the exportation of MPXV virus in 2018 and 2019 from an endemic country (Nigeria) to the United Kingdom (UK), Israel and Singapore, with genetic linkage to a large outbreak occurring in Nigeria in 2017-2018 [5,6]. The emergence of the epidemic among LGBTI+ communities and the predilection of MSM to acquire the disease raise multiple questions. We hypothesize answers to most of these questions, which need further research to prove or disprove.

Monkeypox might have emerged into the human experience through "spillover". The spillover into a new permissive host with a more cosmopolitan distribution could - in theory - contribute to the virus emerging as a threat to humans [7]. Spillover of the novel monkeypox is assumed to occur through a long intersection of the West African monkeypox virus clade with animals, wild/pets, vectors, or even the surrounding environment.

The monkeypox virus has existed in the Western world since 2003. Between May and July 2003, an outbreak of monkeypox infection appeared in the United States for the first time outside Africa. Genetic studies revealed the identity between

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the outbreak strain and monkeypox virus isolated from humans in West Africa and non-human primates in primate colonies. However, it is to be emphasized that no human-to-human transmission was documented, and all cases were due to contact with infected prairie dogs [8].

In 2018-2019, cases of monkeypox were imported to Israel, Singapore and UK [5]. In addition, human-to-human transmission resulted in a nosocomial infection case in the latter country [9]. The human-to-human transmission was reported on a small scale in endemic countries [10].

So, across the globe, there were loci from which the virus could spread to the whole world. Theoretically, this could be achieved through maritime navigation by ships roaming the earth for passengers and goods transport. Ships provide conditions suitable for the survival and growth of pest populations, arthropods and rodents. All these creatures can transmit illness on board or introduce diseases in new areas. Moreover, the USA outbreak source in 2003 was prairie dogs (*Cynomys* spp.) shipped from Ghana with various ill exotic African rodents, which might also be reservoirs (*Funiscuirus* spp., *Heliosciurus* spp., *Cricetomys* spp., *Atherurus* spp., *Graphiurus* spp., and *Hybomys* spp.) [8]. So, at some points, sources of infection may be cohoused with susceptible carriers, or shipping containers loaded with fomites from previously transported infected animals/reservoirs were used, without appropriate decontamination procedures, to accommodate items liable to carry infectious microorganisms. In this context, we should remember that the three plague pandemics plus several epidemics that ravaged the role shipping characterized the world played in their spreading [11].

The Canary party was carried out May 5-15, 2022. All cases reported by/at the end of this date were MSM [12]. Compatible with Gomes et al., a prolonged period of cryptic dissemination in a non-endemic area may appear acceptable [3]. However, many factors make it more logical to be in animals and not humans. 1) Silent human-to-human transmission looks less likely given the known disease characteristics of the affected persons, usually involving localized or generalized skin lesions. 2) Although the MPXV reservoir is not yet established, the virus is capable of infecting a broad range of hosts. Studies revealed that MPXV could have more than one reservoir host in Africa, likely to be a non-human primate (NHP), e.g., *Cercopithecus* sp. and *Colobus* sp. [13-15]. It has been observed that these monkeys mix with various rodents, giving a basis for interspecies transmission [13]. Even though some African rodents shipped to the USA from Ghana with the infected prairie dogs (*Cynomys* spp.) responsible for the USA outbreak in 2003 became ill and died after arrival, other species of rodents inhabiting the USA and Europe, can carry and even disseminate the infection to humans in artificial settings [8,16-18]. Besides, rabbits and white mice found worldwide appeared to be the most susceptible species, and young animals are more vulnerable than adults [19]. 3) The existence of insects in the natural life cycle of MPXV may be worth evaluating. The seropositivity for MPVX antibodies identified in *Petrodromus tetradactylus* (four-toed elephant-shrew) suggests that a role of insects in the natural lifecycle of MPXV may exist. The presence of MPXV antibodies in so many distinct species and virus detection in specimens from *Funisciurus* sp., *Cricetomys* sp. *and Graphiurus* sp. suggests that the natural lifecycle is a complex interaction of reservoir hosts and incidental species [20].

The broad host range of MPXV is a cause for concern, as it may facilitate the adaptation of MPXV to new hosts in new regions. Reports from the USA concluded that the host range of MPXV can include animals from pan-geographical locales, namely, North America, South America, Asia, and Africa [20].

After settlement in the non-endemic areas, MPXV was supposed to have ample time to replicate and accumulate the necessary mutations and microevolution characters required to have a new host tropism and overcome restriction factors. During the hypothesized prolonged period of cryptic dissemination, many events might occur. Primarily, multiple sequences of the genetic evolution of the monkeypox virus resulted in the epidemic strain's emergence. Deep analysis of the 2022 monkeypox virus revealed ~46 single nucleotide polymorphisms (SNPs) divergent from 2018-2019 related viruses. Such divergence, in the light of previous estimates of substitution rate (1-2 substitutions per site per year) identified in *Orthopoxviruses*, represents unexpected rapid evolution [3,21].

Moreover, a strong mutation bias in the 2022 monkeypox virus has been determined that probably carries the signature of potential action of

apolipoprotein B mRNA editing catalytic polypeptide-like 3 (APOBEC3) enzymes in the viral genome editing [3]. In addition, a mutation in monkeypox immunogenic surface glycoprotein B21 has been recognized. Moreover, 15 SNPs have been identified carrying the same mutation bias mentioned before during the human-to-human transmission and suggesting the first signs of microevolution within the 2022 outbreak virus. It has been assumed that progressive gene loss events have been the inciting force behind the evolution of pox viruses [22]. Therefore, identifying a subcluster of two sequences within the 2022 monkeypox virus sharing a 913bp frameshift deletion in a gene coding for an Ankyrin/Host range protein has been hypothesized to associate with adaptation to human-to-human transmission [3].

At the end of this cryptic dissemination, a genetically modified virus with new characters emerged. It is postulated that the emergent virus can perpetuate in the micro-environment created by intimate contact between male external genitalia and rectal mucosa due to factors that need further study. Evidence is that MPXV infection has emerged mainly among MSM, not WSW (women who have sex with women), which may be due to the female different sex practice procedures and positions that are mainly superficial. It may then expand to the LGBTI community through bisexual individuals. The faecal microbiota of MSM has been extensively studied in HIV infection and was concluded to differ from the faecal microbiota of MSM with women. The authors identified its influence on immune activation and proposed an influx of CD103+ and CCR5+ CD4+ T cells into the colon as a potential link between the MSM microbiota and HIV transmission. Similar studies are needed for MSM who develop MPXV infection [23].

"Spillover" was supposed to follow the cryptic dissemination. A massive super spreading event (MSSE) of the genetically modified virus proceeds. When a natural zoonotic virus spillover into a human host, subsequent human-to-human transmission is often not possible or unsustainable, an example is the Avian Influenza. However, if the virus acquires enough of the right mutations, such a way of transmission can occur [24]. It is well documented that the genetic structure of MPXV responsible for the 2022 epidemic differs, as explained before.

A similar example is that of HIV. The evolutionary process of HIV shows its ancestor was the simian immunodeficiency virus (SIV). Despite multiple independent spillover events, SIV was not fit to maintain transmission in a human host. Early in the 20th century, blood-to-blood contact following the handling of bushmeat from an infected primate was believed to have occurred, which was assumed to create the right environment for virus perpetuation. The result was an initial spillover of a variant of SIV that could sustain itself in a novel host, humans, leading to the HIV pandemic [25].

The hypothesis of a massive super spreading event (MSSE) that occurred during the festival in which large numbers of people gathered may explain two questions. First, the single origin of all viruses that caused the outbreak, and second, there was an index case that transmitted the infection. During the festival, many factors have been reported to shape MSSE, including environment crowding, frequent and lengthy contact, and co-infection with other sexually transmitted infections (STI), e.g., HIV [26]. In addition, almost all the attendees were under 40 years. A group of the population lacks cross-protective immunity since they were born only after the smallpox eradication campaigns had been discontinued [27]. The lack of knowledge of the disease was an important factor supporting the MSSE assumption.

The clinical presentation of the monkeypox disease supports the postulation that it is an STI. Contrary to the classical clinical presentation of monkeypox explained in textbooks or described by seniors who experienced the past smallpox epidemic, the clinical presentation of monkeypox is much more subtle, especially signs of rash [28]. Some patients have only one or two small lesions. The rash typically begins on the thighs, external genitalia or the anus, coinciding with the MSM practice positions. And sometimes, it does not spread to other parts of the body. Sometimes it is not even a pox but rather an ulcer or a crater; however, it can be painful. Flu-like symptoms sometimes don't appear or can emerge after the skin lesions [29]. Sometimes patients have a single swollen lymph node, particularly inguinal and sometimes do not [30]. Some patients have inflammation of the rectum. All these signs support the way of MPXV spread, primarily through close contact with an infected person, including contact with the rash or skin lesions. Contact with one an-

other and with more than one partner during sex, usually skin to skin for an extended period, especially in rough sex practice and Chemsex, increases the risk of virus transmission. MSM, especially those with intense sexual networks, might be seeing an increase in these cases because of their potential behaviour and the number of contacts they have.

The situation with this emerging primarily zoonotic disease, now apparently occurring as an STI, is highly concerning, deserving more research, to understand the multiple consequences of this virus now affecting multiple continents, and with possible new routes of transmission, even during the COVID-19 pandemic that still is not over [31-36].

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