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Editorial

The Never Ending Global Emergence of Viral Zoonoses After COVID-19? The rising concern of Monkeypox in Europe, North America and Beyond

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Since its emergence in early 2020 and up until the end of May 2022, the coronavirus SARS-CoV-2 has caused more than 524 million COVID-19 cases globally, with 6.2 million deaths (~1.2%, case fatality rate, CFR) [1,2]. Today, the risk for concurrent pandemics or the onset of future pandemics is inevitable. In fact, the history of mankind has been shaped by infectious diseases acting as independent forces of societal transformation. Zoonotic viruses represent the greatest threat impacting global health, including not only coronaviruses like the Middle East Respiratory Syndrome (MERS-CoV) [3] but also haemorrhagic fever viruses, hantaviruses, arenaviruses, arboviruses [4], and zoonotic influenza viruses [5-8]. In addition, re-emerging conditions are also a cause of concern, particularly those comprising multiple zoonotic viruses originating from both Africa and Asia.

Amid the COVID-19 pandemic, the increasing reporting of cases of monkeypox virus infection in humans spreading through many countries outside Africa is a major reason for concern [5-12]. Monkeypox virus is a double-stranded DNA virus of the Poxviridae family which also includes the variola virus, the causative agent of smallpox [14,15]. Cessation of vaccination against smallpox in most countries occurred after the World Health Assembly certified the eradication of Smallpox in 1980 [8]. Consequently, it is estimated that

more than 70% of the world's population is no longer protected against smallpox which also conferred some indirect degree of protection against other poxviruses including monkeypox [9]. It remains to be seen what the degree of protection is in those individuals who had prior smallpox vaccination over five decades ago.

The monkeypox virus has two distinct genetic clades: the Central African clade (Congo Basin) and the West African clade [16]. Monkeypox, has been circulating in Africa for decades. The virus was first discovered in 1958 during synchronous outbreaks on two colonies of research monkeys [17], and the first description of monkeypox in human's dates to 1970 in the Democratic Republic of Congo (DRC). While most circulation of Monkeypox occurs in Africa, there has been sporadic descriptions of cases outside Africa over the last two decades.

In 2003, the first outbreak outside of Africa was reported in the United States linked to exposure to pet prairie dogs which were housed together with Gambian pouched rats and dormice imported from Ghana [7]. The West African clade is known to have a more favourable prognosis with a CFR of less than 1% (Table 1). On the other hand, the Central Basin clade (Central African clade) is more lethal, with a CFR of up to 10% in unvaccinated children [12,18] (Table 1). Current genomic data from this outbreak has been made publicly available with full genomes accessible now from Belgium (https://bit.ly/3wEgQtE), Portugal (https://bit.ly/3Gd7zgz) and the USA. This multi-country outbreak most likely can be traced to a single origin, given that all sequences are clustering together within the West African clade (https://bit.ly/3Lz174F). These findings suggest very likely the exportation of the virus occurred from Nigeria in 2018 and 2019. Notably, viruses from the recent outbreak diverges a mean of 50 SNPs from those of 2018-2019, this divergence is high considering the estimated substitution rate for Orthopoxviruses (https://bit.ly/3Lz174F). Therefore, intensive genomic surveillance is still needed to rule out the origin and spread of the monkeypox virus causing this recent global outbreak.

Transmission of monkeypox to humans occurs mainly through contact with body fluids, skin lesions, or respiratory droplets from infected animals directly or indirectly through contaminated fomites [15-20]. Monkeypox can infect a taxonomically wide range of mammalian species; however, the virus has only been isolated once from a wild animal, a *Funisciurus* squirrel in the DRC in 1985, and a mangabey monkey found infected in Cote d'Ivoire in 2012 [21]. The extent of viral circulation in animal populations and the range of species that may harbour the virus has not been fully established, although several lines of evidence point to rodents as major potential reservoirs [22]. However, the primary reservoir for human infection remains unknown [23]. Several epidemiological studies from the DRC have implicated squirrels (especially *Funisciurus anerythrus*) inhabiting agricultural areas as primary candidates to sustain viral transmission among people in nearby settlements [24]. In one environmental survey, *Funisciurus* spp squirrels had a higher rate of monkeypox seropositivity (24%) than other any animals tested, including *Heliosciurus* spp squirrels (15%) and primates (8%) [25]. A subsequent seroprevalence study conducted to investigate the DRC outbreak back in February 1997, showed even higher positivity rates amongst these squirrels (39–50% in *Funisciurus* spp and 50% in *Heliosciurus* spp squirrels). In addition, 16% of Gambian giant rats tested in this study demonstrated serological evidence of MPV exposure [26].

The clinical manifestations of Monkeypox resembles that of smallpox [16] including non-specific clinical features such as fever, chills, myalgia, headache, lethargy, and lymphadenopathy followed by a vesiculo-pustular rash, with an incubation period ranging from 5 to 21 days [26-29]. Even though the incubation period for this current outbreak has not been established, its often long period of incubation suggests that

initial exposure events may have occurred in early April 2022. The differential diagnosis of monkeypox includes a variety of infections such as Rickettsialpox caused by *Rickettsia akari*, smallpox, measles, chickenpox, and syphilis, and others, depending also on the local epidemiology (e.g. Peruvian warts in some Latin American countries, or Buruli ulcer in Africa) [29-32]. A definitive diagnosis of monkeypox can only be established by laboratory testing. Therefore, the World Health Organization (WHO) recommends that the optimal specimens for diagnosis include direct sampling from lesions: smears of exudate from vesicular lesions or scabs stored in a dry, sterile, non-viral transport medium and cold test tube [16].

Endemic cases of monkeypox are common in Nigeria. According to the latest report from the Nigerian Centre for Disease Control (NCDC), the country recorded 558 cases of monkeypox and eight deaths between 2017 and 2022 [31]. The recent geographic spread of the ongoing monkeypox outbreak has expanded beyond the forests of central Africa, where patients were initially found, to other parts of the world [28]. The impact of monkeypox has been highlighted by the recent registration of 56 cases in the United Kingdom, 41 in Spain and 37 confirmed cases in Portugal, among other countries [29]. The alert of this zoonotic virus has caught by surprise even the European Centre for Disease Prevention and Control (ECDC), which until the weekend did not count Monkeypox as one of the potential threats within the European Union, but only observed the evolution of the alert in the British Isles.

As of May 23, 2022, multiple countries in Europe, in addition to United Kingdom, Spain and Portugal, have reported monkeypox (Figure 1). In North America, Canada and United States of America, have confirmed cases. Beyond Europe, Israel and Australia have also notified suspected and confirmed cases, with a suspected case in Argentina (Figure 1), for a total of 245 cases, 160 of them confirmed (65%).

The classic mode of transmission of this infection relies on exposure to live or dead animals through hunting or handling bush meat. The animal reservoir of the monkeypox virus is unknown; however, there is evidence that places native African rodents as a potential source, which may explain the spread of the disease outside this continent. Since the first reported case in Zaire in 1970, 95% of the informed cases to date are from the DRC. Since the 2000s, there has been an increased number of Monkeypox cases throughout the New World and outbreaks associated with contact with African rodents sold as pets. One of the factors related to the gradual increase in cases is the cessation of routine vaccination against Smallpox, which was mandatory until 1972 and ceased after its eradication in 1980 [32]. An interesting aspect about the current outbreak relates to the fact that disease clusters are known to include high risk groups like men who have sex with men (MSM). This is important from a disease dynamics standpoint for several reasons: 1. it could explain why despite the relatively inefficient transmission of monkeypox, so many cases are being reported in such a broad geographical extension. 2. Provides evidence on close contact as the potential source of transmission and 3. Argue in favour of a possible sexual link for all these seemingly unconnected outbreaks throughout MSM communities. Naturally, its differential diagnosis would be challenging, including other exanthematic febrile diseases, including Smallpox, Measles, Chickenpox, and Syphilis, depending on the local epidemiology (e.g. Peruvian warts in some Latin American countries, or Buruli ulcer in Africa) [33].

Predicting the ongoing spread of Monkeypox to other geographic settings is challenging. Monkeypox is a significant health concern for people living in endemic regions across Africa where virus circulation is confirmed. However, it is also a global health security issue, and appropriate and effective interventions

such as active surveillance and contact tracing are urgently needed to prevent delayed identification of cases and implementation of public health measures [16-18]. All efforts should be now focused towards containment of cases in order to prevent the virus entering other human networks (healthcare personal) which is still facing the challenges imposed by the current SARS-CoV-2 pandemic. As for monkeypox, vigilance most be doubled for other viruses circulating in wild animal populations, which can sporadically spillover to human populations, as it most likely occurred with SARS-CoV-2 [34]. Prevention and control of these emerging zoonoses depend upon a reduction of exposure to and conservation of both wildlife in their natural habitats.

The general recommendation for preventing Monkeypox virus transmission includes the use of the smallpox vaccine [35]. This vaccine which confers apparently 85% of cross-protection against monkeypox remains to face the challenge of these ongoing outbreaks. Although there are no specific treatments for monkeypox, the Centers for Disease Control (CDC) recommends smallpox vaccine as post-exposure prophylaxis for high-risk contacts within 4 days and up to 14 days of contact, but if given between 4–14 days after date of exposure, vaccination may reduce the symptoms of disease, but not prevent the disease [36]. In addition to smallpox vaccine, immune globulin is available and can be used as prophylaxis for severely immunocompromised patients, although the benefit still remains unclear [37]. Antiviral drugs approved to treat smallpox including tecovirimat and brincidofovir, can be potentially deployed for its use on treating monkeypox [38].

Currently, residents and travellers from endemic areas and where Monkeypox cases are currently being reported should maintain contact precautions and health personnel who care, especially for men who have sex with men which may indicate a potential risk of sexual transmission [39]. However, there may be other factors related to the predilection of cases among this specific at-risk population that require further epidemiologic assessments.

The SARS, Influenza, MERS, and SARS-CoV-2/COVID-19 pandemics of the 21st century demonstrate that there is a perennial risk of pandemics. While we cannot predict their occurrence, there is an urgent need to decrease vulnerability to become infected with any of these pathogens. Responding to the current outbreak of monkeypox involving many countries requires global collaboration and the institution of best practices learned during the current SARS-CoV-2 pandemic.

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Table 1. Key features of Smallpox and Monkeypox.

Orthopoxvirus	
Smallpox	**Monkeypox**
More infectious	Less infectious
Vaccines used until used up to four decades ago	No specific vaccine is available yet (cross-immunity with Smallpox vaccine)
Eradicated in 1980 (last known case in 1977 in Somalia)	Known circulation in Africa since 1958 (1970 first human case in DRC)
Similar transmission routes	
CFR: Variola minor: 1% Variola major: 30%	CFR West African clade: 1% Central African clade: 10%

Figure 1. Countries that have reported Monkeypox in 2022, up to May 23.