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International outbreaks of Monkeypox virus infection with no established travel: A public health concern with significant knowledge gap

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The recent international spread of human cases of Monkeypox virus infection among returning travelers are a cause for concern for the public health community. Between 13 and 21 May 2022, a total of 92 laboratory-confirmed cases of Monkeypox have been reported to the World Health Organization (WHO) mostly from the UK, Europe, Australia, Canada, and USA, with an additional 28 suspected cases [1] (Fig. 1). There was no established travel among those patients and had mainly occurred amongst men who have sex with men (MSM) [1].

The Monkeypox virus which is an enveloped DNA virus that is a member of the genus *Orthopoxvirus* also includes the Smallpox virus (variola major), which is the most feared of these viruses. Smallpox had killed over 300 million in the twentieth century alone but was eliminated in 1980 ten years earlier than set-out to by the WHO. Currently, and since the smallpox virus was officially eradicated in 1980, the only two countries that are storing the original virus are the US Center for Disease Control and Prevention, Atlanta, and the Research Institute for Viral Preparations in Moscow. Since its eradication by mass vaccination, most countries have abandoned routine smallpox vaccination which have led to the occurrence of Monkeypox virus (MOXV) infection with increasing frequency [2]. Monkeypox is a zoonotic disease with an unknown reservoirs. It has been named Monkeypox because it was first isolated in captive monkeys shipped to the Netherlands from Africa in 1958. The first human case was not reported till 1970. The disease has then spread extensively in central and western Africa, and over the last 20 years there has been a gradual increase of cases in Africa with occasional international spread through travel. In addition to the increasing contact between rodents and humans due to forest destruction that pushed the population to live around Monkeypox infected rodents in Central Africa, and the collapse of wild game and fisheries that led many to hunt for bushmeat infested with infected rodents [3].

MOXV is now considered an endemic virus in West and Central Africa, more so in the Congo Basin with each area having its own distinct variant [4]. In a study from the Democratic Republic of the Congo (DRC), the annual incidence of MOXV infection doubled in 2011–2015 compared to 1980–1985 due to waning human immunity to Smallpox [5]. In an earlier study between 2005 and 2007 Rimoin et al. tracked down Monkeypox cases in fifteen remote villages in the DRC and found that MOXV infection in humans had grown twentyfold compared to the period between 1981 and 1986 [6]. Several cases have also been reported outside these geographical locations with outbreaks in Nigeria in 2017–2018 and in the Cameroon in 2018 [7]. MOXV infection has an incubation period that ranges between 5 and 21 days and presents clinically with malaise, fever, rigors, headache, generalized lymphadenopathy and centrifugal pattern of skin rash which typically starts between one and three days of fever onset, and starts initially as maculopapular, and pruritic, then become vesicular then pustular and painful then umbilicate, ulcerate and finally crust and scabs, the rash typically lats between two to four weeks, and shows predominance on the face with palms and soles involvement in three-quarters of cases. In a study of 223 MOXV cases, about 67% had mild rash (5–100 lesions) and 33% had severe rash (>100 lesions) [8]. A systematic review showed that MOXV had a case fatality rate of 8.7%, with a fatality of 10.6% in those infected with clades-Central African and 3.6% among those

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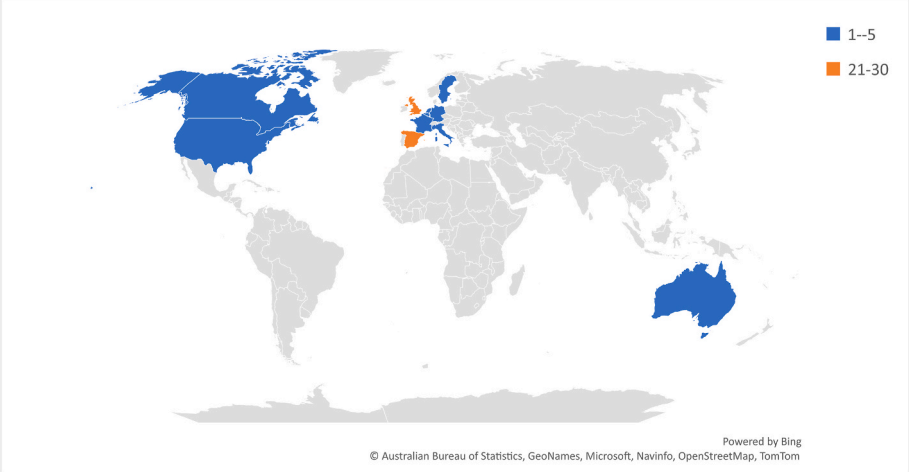

Fig. 1. The World Map Showing Countries with Reported Monkeypox in the recent outbreak (Data are from WHO [1]).

infected with West African clade [9]. The severity of the skin lesions seems to correlates with Smallpox vaccination with a resulted protection of approximately by 85% against monkeypox infection [10].

Since 2003, import- and travel-related spread outside of Africa has occasionally resulted in outbreaks [9]. In September 2019, there were three MOXV cases in the United Kingdom with one case being a healthcare associated infection [11,12]. A follow up of 134 potential contacts, 4 contacts developed symptoms [13]. Additional travel related MOXV cases has also been reported in relation to travel to Nigeria [14].

Human to human transmission of the MOXV has been increasingly reported as clusters and outbreaks [15–17]. In one such outbreak in Sudan, up to 5 generations of human-to-human transmissions have been reported in 2005 [15]. The origin of the outbreak was not found but the virus was a novel type belonging to the Congo Basin clade [15]. In addition, MOXV infection was documented in mid-west United States in 2003 which began when the virus was imported from Ghana along with Gambian giant rats for the exotic pet market, the virus transferred to prairie dogs housed in the same pet shop as the rats and jumped from there to their owners, infecting 71 people in total with 19 hospitalization [16]. More recently a case was reported in a returning traveler from Nigeria to Maryland, USA in 2021 and another case in Texas [18,19]. The 194 monitored contacts including 144 (74%) flight contacts did not show evidence of secondary infection [19]. One of the possible contribution to this finding is the use of the face mask during the COVID-19 pandemic [19]. Additional travel related cases were also identified in the United Sates and related to those coming from Nigeria [19]. The reason for the current outbreak and the full epidemiological characteristics are still unknown, this places further strains on developing effective control measures. For travelers, it is recommended that they avoid contacts with rodents and infected persons. The use of vaccine is not routinely recommended. A pos-texposure ACAM2000 *orthopoxvirus* vaccine is a possible recommendation for intermediate and high-risk exposure [19]. The ACAM2000 vaccine and JYNNEOS since this is a trade name which in other countries is also called Imvanex, Imvamune, suggest elaboration between brackets: (a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus) vaccine can be given to healthcare workers involved in the investigation of monkeypox outbreaks [18]. The increased occurrence of MOXV infection with secondary transmissions are of particular concern as people born after 1980 have no vaccine-induced immunity to the virus. The treatment of MXOV is usually supportive with home isolation for up to 21 days. Two oral antiviral medications which received approval for use in smallpox and demonstrated efficacy against MXOV in animals (brincidofovir and tecovirimat).

The recent occurrence of multiple zoonotic diseases such as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the continued transmissions of MXOV are leading examples for the world to adopt a global strategy and one-health strategy to deal with emerging and re-emerging infectious diseases.

Huge research gaps exist for this disease despite its known existence since 1970. From the reservoir, to modes of transmission from animal to human, human-to-human, viral dynamics inside the host, best infection control practices and therapeutic and preventative strategies. In addition, many healthcare workers and public health practitioners might not be familiar with the disease; however, recent events should prompt high index of suspicion. Fortunately, there is evidence that basic infection control principles with rapid identification, isolation, use of personal protective equipment, contact tracing and monitoring are important in limiting the spread of the disease [18].

With a world still weary of a two-year long pandemic due to COVID-19, the relaxation of mitigation measures and re-opening of international commercial flights, the re-emergence of MOXV and the increased number of cases with possible human-to-human transmission are concerning and call for immediate long-term public and travel health planning. In addition, extensive genomic surveillance is needed [20].

CRediT authorship contribution statement

Jaffar A. Al-Tawfiq: Conceptualization, Methodology, Writing – original draft. **Mazin Barry:** Additional literature, Writing – review & editing, Writing – original draft. **Ziad A. Memish:** Writing – original draft, Preparation, Conceptualization, All authors finalized the manuscript and edited it for clarity.

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