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Correspondence

Monkeypox vaccination: Does it cause neurologic and psychiatric manifestations? – Correspondence

Dear Editor,

While the world continues to struggle with the current ongoing coronavirus disease 2019 (COVID-19) pandemic, we are witnessing an emerging multicountry outbreak of a new virus, monkeypox (MPX). Due to the escalating MPX outbreak worldwide, World Health Organization (WHO) on July 23 declared it a public health emergency of international concern (PHEIC) [1]. Since early May 2022, appearance of MPX cases occur in several patients in Great Britain and Portugal. Until June 22, 2022, over 33273 confirmed cases and one death have been reported from 87 countries [2].

MPX, is a zoonotic disease caused by a double DNA virus, a member of the Orthopoxvirus genus in the Poxviridae family related to the virus which caused smallpox (eradicated in 1980). Monkeypox virus (MPXV) can be transmitted mainly through contact with infected animals or its secretions, and between humans through respiratory droplets and direct skin-to-skin contact with body fluids and contact with contaminated objects. The unique feature of the current MPX outbreak is its rapid spread through sexual contact (mainly among certain groups of homosexual, bisexual, and men who have sex with men (MSM)) [3,4]. Common viral signs and symptoms are seen in MPX after a 7–21 day-incubation period, including fever, headache, myalgia, cough, backache, lymphadenopathy, chills, and exhaustion. Vesiculopustular rash occurs on the face within 1–3 days after the fever and mouth and throat ulcers [3,5]. Subsequent complications include bacterial superinfection, corneal infection/permanent scarring, cellulitis, bronchopneumonia, sepsis, respiratory distress, encephalitis, and dehydration [3].

For neurological presentations of MPX, non-specific encephalopathy is the most common central nervous system manifestation [6]. Post-infectious and post-immunization acute disseminated encephalomyelitis (ADEM) make up of about three-quarters of cases [7]. Unlike the Ebola virus and rift valley fever virus which show neurotropism, direct neurotropism is not yet known for monkeypox virus (MPXV), SARS-CoV-2, MERS-CoV, and even smallpox virus. However, some features of neurological manifestation of MPXV have been spotted. A recent meta-analysis showed headache in 53.8% (95%CI 30.6–75.4%) of patients, fatigue 36.2% (2.0–94.0%), myalgia 55.5% (12.1–91.9%), seizure 2.7% (0.6–10.2%), confusion 2.4% (1.1–5.2%) and encephalitis 2.0% (0.5–8.2%) [8]. Other presentations include sensory-perceptual disturbance (alteration of vision, photophobia, and dizziness) and psychiatric symptoms (anxiety and depression) [8]. An earlier report showed dysphagia to roughly affect 12% of monkeypox patients as a neurological manifestation [9]. The preliminary evidence shows a range of neurological presentations of MPX, with a spectrum from common and nonspecific symptoms like myalgia, fatigue, and headache to rare but more specific severe manifestations like encephalitis and seizures [6].

Various Orthopoxviruses share comparable genetic and antigenic characteristics making the smallpox vaccine effective in preventing MPX disease (efficacy: 85%). When MPX was declared a PHIC, the WHO's released information to identify and respond to serious adverse events following immunization, and following use of smallpox vaccine which was available in countries stockpile including ACAM2000, LC16m8, NYCBH strain, Lister strain, and Modified Vaccinia Ankara (Imvanex, Imvamune) [10]. The Strategic Advisory Group of Experts (SAGE) recommend the licensed vaccines of ACAM2000 and LC16m8 to be adopted as the vaccines to control an outbreak [11]. Furthermore, any vaccines that meet the WHO standards of potency, purity, and stability can be used to prevent the anticipated outbreak. The WHO calls against mass vaccination for MPX, and advises the use of active surveillance, rapid case and contact identification and proper isolation to prevent the ongoing spread of MPX, to limit pre-exposure and post exposure vaccination to groups at increased risk of disease acquisition or complications.

The first-generation vaccines contained live vaccinia virus and were advised before and during the eradication phase [10]. This virus was produced by infecting abdominal skin or flanks of large animals like sheep or cows. After collection of inflammatory exudate about seven days after inoculation, it is subjected to purification, stabilization, and finally lyophilization [12].

The second-generation vaccines are similar to the first-generation vaccines in consisting of vaccinia virus. However, its production method has shifted to tissue culture comprising of using embryonated eggs or mammalian cell lines [10]. This provides an advantage of a higher purity i.e., free of bacteria and animal proteins, and product consistency. Some second-generation vaccines include Lister vaccine (RIVM), ACAM2000, Elstree-BN (Bavarian Nordic), VV Lister/CEP (Sanofi Pasteur) and CJ-50300 (CJ Cheil Jadang Corporation) [10]. Among these vaccines, ACAM2000 has entailed non-inferiority trials in contrast with the first-generation vaccine Wyeth's Dryvax [13]. Owing to its efficacy and safety profile, ACAM2000 has been licensed in the United States [14].

The third-generation vaccines are more attenuated vaccine strains produced by further passage in cell culture (chick embryo fibroblasts) or animals like horses [10,12]. This results in a live virus incapable of replication in human tissues, thus mimicking a killed virus vaccine. These vaccines are MVA (Imvanex, Imvamue, or MVA-BN (JYNNEOS)) and LC16m8 [10]. MVA has been included in the National Strategic Stockpile whereas LC16m8 has not yet been due to its deference for licensure in the United States. The Advisory Committee on Immunization Practices (ACIP) - CDC has recommended JYNNEOS as an alternative to ACAM2000 as pre-exposure prophylaxis [15,16], and in 2019, U.

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S. Food and Drug Administration (FDA) approved JYNNEOS for preventing both smallpox and monkeypox [17]. The advantages over the first and second-generation vaccines are their better safety profile with less adverse effects and applicability in immunocompromised patients and patients with atopic dermatitis. On the other hand, its optimal levels of immunity require two doses [10,12]. Hence, close-contact with cases may not be protected after the first inoculation. In such conditions, the second-generation vaccines are warranted.

Many adverse events are associated with smallpox vaccination mainly with the second and third-generation vaccines. These range in severity from mild to moderate, including local reactions such as pain, erythema, and inflammation at the site of vaccination, and systemic reactions such as fever, malaise, headache, chills, nausea, and lymphadenopathy. Severe adverse events include inadvertent inoculation, eczema vaccinatum, vaccinia keratitis, erythema multiforme, generalized vaccinia, progressive vaccinia, and congenital vaccinia post vaccinial encephalitis (PVE)/meningoencephalitis (PVEM) and cardiological problems including myocarditis, pericarditis, and dilated cardiomyopathy [10,18,19]. In general, neurological complications following vaccination are rare, and in most cases, despite monophasic neurological events, clinical recovery is expected [19,20]. Nevertheless, serious and fatal neurological complications have also been reported. One of the most serious complication is PVE/PVEM with a mortality rate which ranges from 10% to 50% [18]. There are no markers to predict who will develop these complications, but it is more commonly seen in children less than two years of age [18]. In older children and adult populations, PVEM presents with stupor, seizure, coma, paraparesis, and other neurological abnormalities, and in 16% of cases, there are permanent neurologic sequelae [21]. The rates of PVEM vary from 1 in 4000 to 1 in 80,000 after the first vaccination and from 1 in 50,000 to 1 in 450,000 after the second vaccination [22]. These figures point toward a very rare possibility to contract neurological complication following vaccination. The type of neurological complication depends on the type of vaccine used (Table 1). The widespread news of alleged vaccination adverse outcomes has created the “urban myth” regarding serious neurological outcomes and endorsed by anti-vaccination associations [23].

These vaccines are associated with drawbacks. Caution is required due to potential post-vaccination local and systemic reactions [24]. ACAM2000 is known to potentially cause several neurological adverse events such as headache, pain, vertigo, dizziness, and non-serious limb paresthesia (17 cases) [25]. More neurological severe adverse events have been reported, such as encephalitis, meningitis, seizures, Bell palsy, and Guillain- Barre syndrome [25].

Use of ACAM2000 is contraindicated in immunocompromised individuals, during pregnancy, and in persons with cardiac diseases [24]. Improving safety and efficacy of vaccinia vaccines was a focus of research till the eradication of variola [24]. However, the MPX outbreak raised concern on importance of modernizing vaccinia vaccines [24]. In contrast, LC16m8, an attenuated, replicating smallpox vaccine, has proved to possess lower neurotoxicity and less pathogenicity versus unattenuated vaccines in nonclinical studies [26].

Table 1
Each type of neurological manifestation based on the type of vaccine used.

Vaccine	Neurological (mild-moderate)	Neurological manifestation (severe)
ACAM2000	Headache, fatigue, myalgia,	post-vaccinial encephalitis (PVE), encephalomyelitis (PVEM), encephalopathy, and permanent neurological sequelae.
Lister strain/ NYCBH	Headache, fatigue, myalgia	PVE, PVEM, encephalopathy, PV, GV, and EV, which may result in severe disability, permanent neurological sequelae
IMVANEX, MVA	Headache, dizziness, Paresthesia	Peripheral sensory neuropathy
JYNNEOS	Headache, Fatigue, myalgia	Extraocular muscle paresis

IMVANEX is also known to potentially cause several neurological adverse events, such as headache – paresthesia, dizziness, peripheral sensory neuropathy, migraine, and somnolence [27]. The only known psychiatric adverse event is sleep disorder [27]. Therefore, patients should be informed about these potential neurological adverse events, especially severe ones. Individuals with an acute illness with a fever should not receive the vaccine till after recovery [28]. In addition, individuals should be aware of the importance of informing the medical practitioner in case of any allergies (especially to chicken protein, gentamicin, or ciprofloxacin) [28].

ACAM2000 is administered percutaneously using several punctures [16]. ACAM2000 involves one dose of vaccine, and peak vaccine protection is conferred within 28 days. ACAM2000 is therefore considered to be acceptable as a booster dose in previously vaccinated individuals. However, individuals at high risks of smallpox should not receive ACAM2000 due to its potential severe adverse events. It is contraindicated in severely immunocompromised individuals [29].

On the other hand, JYNNEOS has fewer contraindications as it involves a replication-deficient virus [16]. Besides, healthcare workers are more experienced in the subcutaneous route of administration of JYNNEOS [16]. However, JYNNEOS involves two doses at 28 days apart, and vaccine protection is delayed until two weeks after receipt of the second dose [16].

Recommendations to Healthcare providers and policymakers:

Significant neurological adverse events of MPX are considered rare [30]. However, epidemiological surveillance is essential to avoid further outbreaks [30]. Suspected MPX cases should receive adequate neurological investigations [30]. Even after recovery, a long-term follow-up is beneficial [30]. The available vaccines are associated with neurological adverse events. Therefore, the benefits and risks of vaccination should be weighed with caution [28]. Any decision about vaccination should be a shared decision between health professionals and patients so that informed decisions can be made.

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Author contribution

RAF: designed the study. RAF, ABS and ME: made the first draft. RAF and ZAM: updated the manuscript. RAF and ZAM: reviewed the final draft and edited final. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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