EDITORIAL

Enigma of the Monkeypox Outbreak

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The pandemic of Covid-19 has raised awareness of infectious diseases like never before in the history of mankind. After millions of deaths from the SARS COV-2 virus globally, the appearance of yet another zoonotic disease has caught world attention. In year 2022 Monkeypox took the world off guard and is fueling the fear of yet another disease spate. A new and Emerging Infectious Disease is spreading, although it is too early to grasp the trajectory. On July 23 the WHO declared Monkeypox a "global emergency" with 16,000 reported cases from 75 countries and territories, and five deaths. 2933/3413 (86%) were reported from the WHO European Region. Other regions reporting cases include: the African Region (73/3413, 2%), Region of the Americas (381/3413, 11%), Eastern Mediterranean Region (15/3413, <1%) and Western Pacific Region (11/3413, <1%). One death was reported in Nigeria in the second quarter of 2022. The case count is expected to change as more information becomes available daily and data are verified under the International Health Regulations (2005) (IHR 2005).[1] No human case has yet been identified or reported from any Asian country.

The monkeypox virus (MPV) was first detected in captive Asiatic monkeys; however, the virus has been found naturally only in Africa, and rodents have been found to be an important reservoir host. The disease was first described in 1959 as a primate infection and subsequently led to eight additional laboratory outbreaks between 1958 and 1968. In August 1970, the first human case was identified in a village in Equateur province in the Democratic Republic of the Congo. Between 1970 and 1995, more than 400 human cases of monkeypox were detected sporadically in Zaire and it became evident that human-to-human transmission was occurring.[2] In 2003, an outbreak of human monkeypox in the United States resulted in 47 confirmed or probable cases. The outbreak was linked to prairie dogs that had been housed with exotic animals shipped from Ghana.[2,3]

MPV belongs to the genus Orthopoxvirus family of Poxviridae, a group of large, complex, double-stranded DNA viruses that replicate in the cytoplasm of the host cell and are defined by their genomic, structural, and antigenic similarities. Orthopoxvirus infections are mostly zoonotic, affecting ground squirrels and possibly other rodents, while man and monkeys serve as accidental hosts, the exception being variola (smallpox) which has no human host. Orthopoxviruses that are known to infect humans are variola, monkeypox, vaccinia (cowpox) and buffalopox.[2] Variola and monkeypox are often disseminated infections, whereas vaccinia and cowpox generally are associated with local lesions.[4,5]

Since the variola virus and MPV have genotypic similarities, it is essential to review variola in its historical context. Variola, also called smallpox, was known from ancient times as a devastating disease of humankind, and in all corners of the world was feared as a death knell. The disease was known 10,000 years ago from three Egyptian mummies from the 18th to 20th dynasties (1570–1100 BC), all showing the characteristic pustules of acute smallpox. From India, smallpox spread across China (about 250 BC) and to other parts of Asia. In the eighth century, smallpox became firmly established throughout Europe. By the seventeenth century, the virus continued to kill more than 400,000 people in Europe every year. The saga of smallpox in the Americas represents one of the most sordid chapters in the history of mankind's cruelty to deliberately destroy the native populace of a continent. In 1507 the Spaniards brought smallpox to the islands of the West Indies and decimated 80-90% of the island's population. North American Indians fared no better. Stories abound about the invaders wrapping virus-loaded scabs in blankets and offering them to native Indians as a peace-making gesture. The disease spread to annihilate wide swathes of the population.[6,7]

In 1798 Edward Jenner utilized a form of inoculation in his now famous experiment in which he took pustular material from a cowpox (vaccinia) lesion on the hand of a dairymaid and inserted it into the arm of a young boy, James Phipps [Bennet][3]. In reproducible experiments, he proved that there was cross protectivity of cowpox vaccine with variola. Jenner's discovery was acclaimed at the time and is recognized even now as one of the most important and innovative of all medical discoveries. The vaccine methodology was improved upon and was later produced in the laboratory on Vero cell. Vaccine inoculation was intensified globally, and the last naturally occurring smallpox case was reported from Somalia in

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October 1977, after which routine smallpox vaccination ceased worldwide in 1980. This is the only infectious disease to have been eradicated, and it remains among the most notable and profound public health successes in the history of medicine.[6-8]

The relationship between monkeypox and smallpox has raised anxieties and misperceptions among the public, patients, and healthcare providers. Monkeypox was recognized as a cause of human illness in 1970. Genomic analysis has confirmed the existence of two monkeypox clades: Congo Basin and West Africa. The Congo Basin clade causes higher morbidity, mortality, and transmissibility rates. Studies with the West African clade revealed that those vaccinated against smallpox administered 3 to 19 years prior had 85% protection.[9] A case-fatality rate of approximately 10% was observed in unvaccinated persons, and the majority of fatalities and the most severe disease manifestations were observed in children younger than 5 years. Most cases were presumably from animal exposure, while 28% of cases were ascribed to human-to-human transmission. Subclinical infections may occur and remain undiagnosed.[4]

Orthopoxvirus infections can cause a spectrum of febrile rash illnesses in humans, ranging from fairly benign, localized skin infections to severe systemic infections. Other diseases confused with vesicular rashes are smallpox, generalized vaccinia (vaccinia is the virus used in smallpox vaccination), disseminated herpes zoster, disseminated herpes simplex, drug eruptions, erythema multiforme, buffalopox, scabies, enteroviral infections, insect bites, impetigo, molluscum contagiosum, meningococcemia, and idiopathic thrombocytopenic purpura.[10,11] The most striking feature that distinguishes monkeypox from others is the presence of cervical lymphadenopathy, while in all other orthopoxviral infections this feature is absent.[2,3,5]

Since few in this generation have witnessed a live case of variola, the commonly encountered varicella and disseminated herpes zoster must be differentiated clinically from variola and monkeypox. Variola presents with a more severe prodrome of fever, headache, vomiting and prostration, followed by the appearance of a rash characteristically centrifugally distributed i.e., lesions starting in greater numbers on the oral mucosa, face, followed by extremities including on the palms and soles, then on the trunk. The rash evolves from appearing macular, then papular, enlarging and progressing to a vesicle, a pustule by day 7, becomes encrusted and scabbed by day 14, and sloughs off, leaving disfiguring pits. Skin lesions are deep-seated and in the same stage of development in any one area of the body. The most severe and invariably fatal of all is hemorrhagic smallpox.[6,7]

The prodrome of chickenpox begins with mild fever and systemic symptoms, followed by a centripetally distributed rash (i.e. starting on the trunk), and rarely appears on the palms and soles; the lesions are superficial and in different developmental stages in the same area of the body. Barring complications, the infection is self-limiting, and recovery is complete with scabs that do not leave sequelae. Disseminated herpes zoster occurs in immunocompromised persons. The vesicles resemble varicella but begin in a dermatome and spread beyond the midline.[2,7]

The typical presentation of monkeypox consists of a short febrile prodromal period followed by progressive development of a classic rash with indurated and umbilicated lesions, starting on the head or face and progressing to the limbs and trunk from macules, to papules, to vesicles, to pustules and eventually, crusts which shed. There are often ulcers in the mouth eyes and/or genital area. The most obvious difference from other exanthems is the pronounced lymphadenopathy, which involves the submandibular, cervical, and sublingual regions. Transmission is primarily through droplet respiratory particles or direct contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects.[3,5] The US Public Health System is reporting concentrated infections among men who have sex with men, and is setting up warning signages for such practitioners.

Access to timely and accurate laboratory testing of samples from cases under investigation is an essential part of the diagnosis and surveillance. All countries should have access to reliable testing either nationally or through referral to laboratories through the Regional Offices of WHO. The recommended specimen type for laboratory confirmation of monkeypox is skin lesion material, including swabs of lesion surface and/or exudate, roofs from more than one lesion, or lesion crusts. Confirmation of MPV infection is based on nucleic acid amplification testing (NAAT), using real-time or conventional PCR, for the detection of unique sequences of viral DNA.[12-14] Testing for the presence of MPV should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures.

Monkeypox has so far shown to be a self-limiting disease; however, in the case of severe disease (e.g., haemorrhagic

disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization) treatment after consultation should be considered with vaccinia immunoglobulin intravenous (VIGIV), and antivirals brincidofovir or tecovirimat which are approved for variola. Cidofovir has been shown to be effective against orthopoxviruses, and cytomegalovirus in AIDS.

Monkeypox is unlikely to affect as many people as did Covid-19 or AIDS. However, learning from past epidemics, it is important to follow the transmission trends to learn that unchecked spread may not stay limited to any one continent or a subset of population. Vigilance around the globe must continue.

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