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EDITORIAL

Importance of epidemiological research of monkeypox: is incidence increasing?

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1. Introduction

Monkeypox research was mostly of academic interest until the 1980s when with the global waning of smallpox, monkeypox emerged as the most important *Orthopoxvirus* of public health importance [1,2]. As a result of the knowledge gap in monkeypox epidemiology and ecology, the Global Commission for the Certification of Smallpox Eradication recommended surveillance and research for monkeypox and other *Orthopoxvirus* infections [1]. Four decades after this report, there has been a global increase in reported cases of the disease, while the epidemiology and ecology of the disease are still yet to be fully understood. The recent resurgence of monkeypox in a number of African countries, the exportation of the disease to other continents and the possibility of the virus being a potential agent of bioterrorism has placed it on the global public health agenda [3–6]. We reviewed the current monkeypox situation across the African continent and discuss the critical need for more research in tackling this public health challenge.

2. Virology and natural history

Monkeypox is a zoonotic disease caused by monkeypox virus, a DNA virus, member of the genus *Orthopoxvirus*, which includes other pathogenic viruses such as the variola virus (the causative agent of smallpox) [7]. Monkeypox was first discovered in 1958 in an animal facility in Copenhagen, Denmark, among Asian monkeys weeks after their importation from Singapore [8]. Human monkeypox was initially described during smallpox surveillance as part of the eradication programme [1,9]. The first reported human monkeypox case was in a nine-month-old child from the then Zaire current day Democratic Republic of Congo (DRC)) in 1970 [10,11]. The natural reservoir of the monkeypox virus remains unknown, although rodents are believed to be the main source of its introduction into human populations [1,7,12,13]. This zoonotic infection is endemic to Central and West African countries, sporadically causing outbreaks in human populations [10–12]. Two clades of monkeypox virus are known; the Central African or Congo Basin clade (CB) found predominantly in the Central African Region and the West African clade (WA) found mainly in the West African Sub-region [14]. The CB clade is known to present with more severe disease than the WA clade [1]. However, the recent outbreaks caused by the WA clade in Nigeria has also been associated with more severe disease and death than previously reported with this clade with a case fatality rate of 6% [15].

3. Clinical presentation and management

Human monkeypox has a similar but milder clinical presentation to smallpox. The incubation period varies between5 and 21 days. It often presents with nonspecific features such as fever, chills, myalgia, headache, lethargy and lymphadenopathy followed by vesiculo-pustular rash [10]. With no approved anti–viral drug, clinical management of human monkeypox cases is largely symptomatic and supportive treatment [3]. Recently, the United States Food and Drug Administration has licensed the first drug, tecovirimat, with an indication for treatment of smallpox (under Animal Rule) [16,17,18]. However, the effectiveness of the drug for the treatment of smallpox disease has not been determined in the absence of human cases of smallpox. The clinical trial to evaluate tecovirimat was carried out in animals infected with monkeypox virus [17,18]. Similarly a modified vaccinia Ankara vaccine (MVA) vaccine has been developed and licensed for the prevention of monkeypox, based on the knowledge that a smallpox vaccine could also protect against other orthopoxviruses, including monkeypox [18]. Clinical trials to demonstrate the efficacy of the vaccine in humans is yet to be carried out, though a study of the effectiveness and safety of the vaccine is ongoing among healthcare workers in DRC [17,19].

4. Incidence and geographical distribution

Although human monkeypox was rare in the last century, sporadic cases were reported from parts of Africa. The frequency of reporting and the geographical distribution of cases has, however, expanded over the last two decades (with more cases reported than in the first 30 years of its discovery) in several African countries including the Central African Republic, DRC, Liberia, Cameroon, Republic of the Congo, Sudan, Gabon, Sierra Leone and Nigeria [3,20–24].

The DRC recorded a 20-fold and 4-fold increase in incidence between 1980s and 2006–07; and between 2001 and 2013 respectively [23,24]. The annual human monkeypox incidence of has been over 1000 cases since 2005 [3]. It is noteworthy that

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this dramatic increase in human monkeypox incidence in rural DRC occurred thirty years after the cessation of mass smallpox vaccination campaigns and could not be explained by improved surveillance system [23,24]. Apart from the DRC where the annual incidence of the disease has continuously risen, the other aforementioned countries have also recorded sporadic cases over the past decades amounting to a wider geographical distribution of the disease within the African continent [3]. Six countries reported cases in 2017 compared to less than three countries each year in the preceding decades [3] with a surge in the reported number of cases from less than 20 annually to about 188 cases (Figure 1), largely from Nigeria and the Republic of Congo (after excluding DRC). Even though there has been no reported human monkeypox case in Ghana, the 2003 USD human monkeypox outbreak was linked to non-human primates imported from the country, suggesting the existence of a potential zoonotic reservoir. The animals infected other animals in the US, and later infected humans [25,26].

In September 2017, human monkeypox was reported from Nigeria, 39 years after the last known case [6]. This evolved to become the largest known outbreak of the West African clade of monkeypox in history. As a result of intensified monkeypox surveillance in Nigeria, 165 confirmed cases have been reported from 17 of the 36 states and Federal Capital Territory in Nigeria by June 2019 [26]. Over 90% of the cases reported in Nigeria had no known history of contact with animals contrary to the situation in Central Africa where hunting and bushmeat preparation were associated with monkeypox [15,20,23]. Most cases in Nigeria were reported from urban and peri-urban parts of the southern regions of the country unlike in DRC where most cases were from forested villages. In 2019, most cases of monkeypox in Nigeria have been reported within the cosmopolitan city of Lagos [27]. The transmission of monkeypox virus in urban locations increases the risk for international spread of the disease to non-endemic areas further raising concern for the global health community [4,5,27]. Human monkeypox cases outside of Africa in countries such as the United Kingdom, Israel and Singapore in the past year all had a history of recent travel from Nigeria [4,5,28].

Unlike most other African countries, DRC has a routine surveillance system for monkeypox and had continued to record an increasing number of cases annually since the post smallpox eradication era. Although a monkeypox surveillance system was instituted in Nigeria, the increase in cases reported in Nigeria compared to the previous four decades may not be fully explained by improved disease surveillance. The continued detection and reporting of human monkeypox in Nigeria in the last two years suggests an enzootic and/or endemic disease [27] (Figure 2).

5. Available evidence and role of research

Although there has been an increase in knowledge on clinical and epidemiological characteristics of monkeypox, this is largely based on outbreak reports, case reports and passive intermittent surveillance. The true prevalence and burden of this (re-)emerging zoonosis is yet unknown, as there is no systematic routine monkeypox surveillance in many African countries. This situation is further worsened by the poor awareness of the disease among health care workers and the community in many African countries.

Experience from the Nigeria outbreak has raised the need for critical evaluation of monkeypox epidemiology. Has there been continuous undetected and unreported monkeypox transmission in Nigeria over the last 39 years? Is the waning immunity from the smallpox vaccination since the cessation of smallpox vaccination in the 1980s contributing to the current monkeypox resurgence? What is the role of human to human transmission of monkeypox? The factors driving the continued transmission of human monkeypox remain unclear. Does the endemic trend demonstrate a previously unreported, missed or misdiagnosed disease that has been endemic in the region over the past decades? Cases of human monkeypox have often been misdiagnosed as chickenpox while co-infection with monkeypox and chickenpox has also been documented [29].

In the DRC, monkeypox outbreaks occur in small remote villages close to the tropical rainforest contrary to outbreaks in Nigeria that are occurring mainly in urban and peri-urban areas [15]. This may provide insight into the sources of infection in

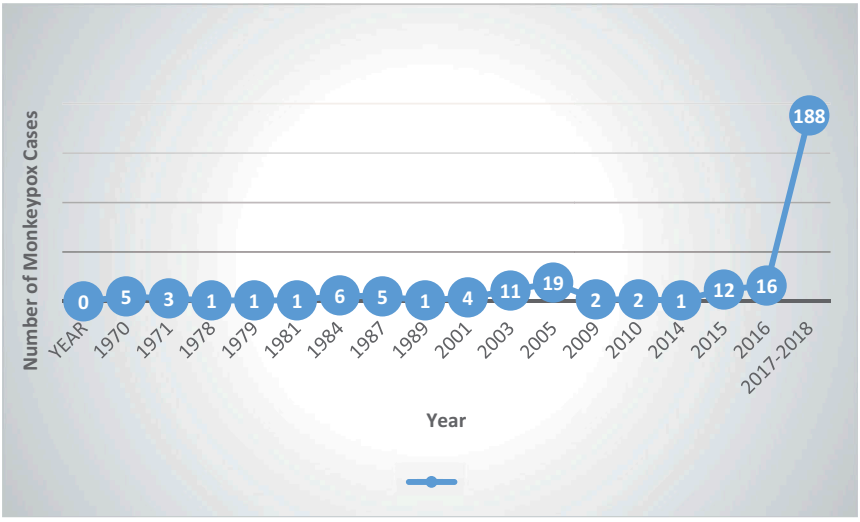

Figure 1. Trend in incidence of monkeypox across African continent reported to the WHO excludingcases in DRC (Data source: Durski et al. 2018).

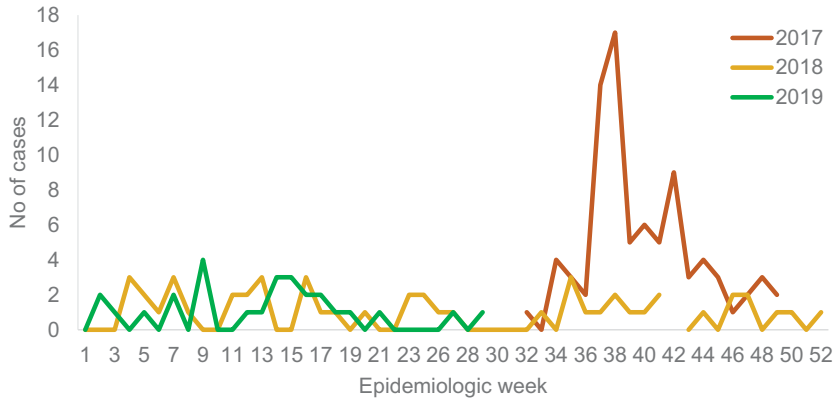

Figure 2. Weekly trends of confirmed monkeypox cases, Nigeria, 2017–2019.

these settings. Experimental research suggests that monkeypox may have a broad range of animal hosts/reservoirs facilitating the adaptation of the virus to new hosts in various regions and may explain the varied epidemiological patterns [7]. The possibility of human infection through indirect contact with animals through environmental contamination should be investigated.

There are still limitations in our understanding of the transmissibility of human monkeypox and the natural reservoirs. Studies have shown a prevalence of orthopox antibodies in wild animals of 2% in DRC and 2% and 33% in non-human primates and rodents respectively in Zambia. It is of interest that Zambia with a higher serological evidence of *Orthopoxvirus* infection has no record of human monkeypox infection while a bordering country, DRC, records thousands of human monkeypox annually [12,13]. Outstanding questions include: What are the sources of monkeypox virus infection? What is the mode of transmission of the monkeypox virus? Are there differences in the reservoirs for the West and Central African clades of monkeypox? While monkeypox is believed to be enzootic in Central and West Africa, no animal study has demonstrated the presence of an animal reservoir for the virus in Nigeria.

Monkeypox resurgence in Nigeria occurred concurrently with the resurgence or large outbreaks of other viral diseases such as yellow fever and Lassa fever. This could suggest the need to examine the impact of increased human-to animal interface in emerging and reemerging diseases brought about by the encroachment on the habitat of the reservoir of these zoonoses through urbanization, human search for food and the possible role of climate change. The rising incidence of monkeypox may also provide the opportunity for clinical trials to measure the impact of available *Orthopoxvirus* vaccines and medications. There is also a great need to determine the role of improved surveillance system in disease outbreak detection.

6. Challenges to monkeypox research

Operational research to understand the transmission dynamics and control of monkeypox is currently faced with challenges such as inadequate resources for detailed case investigations and contact follow-up in affected communities. There is a lack of adequate laboratory diagnostic facilities. This limited capacity and access to laboratory diagnosis and the complexity of the diagnosis of monkeypox hampers the ability to investigate its etiology. Sero-prevalence studies would help in understanding exposure and subclinical infection among contacts in communities [30]. However, currently available serological assays are generic orthopox assays which are nonspecific for monkeypox virus. This is due to cross-reactivity with vaccinia virus and variola virus and therefore unable to distinguish monkeypox virus exposure from previous smallpox vaccination or other *Orthopoxvirus* infections. Furthermore, these assays are not commercially available. Data from Nigeria shows the presence of orthopox antibodies in about 20% of 70 monkeypox negative patients with similar rash illness who had the serological test done. Further research, including using molecular and genomic approaches, to identify other *Orthopoxviruses* being transmitted in human and animal population is needed.

7. Conclusion

Epidemiological and basic research to unravel the source and mode of transmission of the monkeypox virus and the true incidence of this disease demands greater attention. Enhanced surveillance system with effective case and contact investigation, laboratory diagnostics including serological assays and genomics would be necessary to ensure that data from outbreaks and routine surveillance contribute adequately to our understanding of this reemerging public health threat. Effective preventive and control strategies are dependent on a good knowledge of disease burden, transmission and management.

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Declaration of Interest

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