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TITLE:

Monkeypox - Enhancing Public Health Preparedness for an Emerging Lethal Human Zoonotic Epidemic Threat in the Wake of the Smallpox Post-Eradication Era

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Highlights

- Human monkeypox is a zoonotic disease with epidemic potential with case fatality rates of between 1% and 10%.
- Nigeria is currently experiencing an unusually large and lethal outbreak mostly affecting young adults and children. The last confirmed case of human monkeypox in Nigeria prior to this outbreak was in 1978.
- Increasing numbers of human monkeypox cases reported from Central and West Africa during the past two decades may in part be due to cessation of smallpox vaccination in the early 1980s. However, major knowledge gaps remain on the epidemiology, host reservoir, and emergence, transmission, pathogenesis.
- The World Health Organisation considers monkeypox to be “a rare viral zoonotic disease that occurs primarily in remote parts of central and Africa, near tropical rainforests”. This WHO statement may no longer be valid and requires further discussion and debate.
- A ‘ONE-Human-Environmental-Animal Health’ approach across Africa to strengthen surveillance and response capacities to emerging and re-emerging pathogens and conduct priority research to fill major knowledge gaps.

ABSTRACT

The identification of monkeypox in 3 separate patients in the United Kingdom in September raised media and political attention on an emerging public health threat. Nigeria, whose last confirmed case of monkeypox was in 1978, is currently experiencing an unusually large and outbreak of human monkeypox cases, a ‘One Human-Environmental-Animal Health’ approach is being effectively used to

define and tackle the outbreak. As of 13th October 2018, there have been one hundred and sixteen confirmed cases the majority of whom are under 40 years. Over the past 20 years ten Central and West African countries have reported monkeypox cases which have risen exponentially. We review the history and evolution of monkeypox outbreaks in Africa and USA, the changing clinical presentations, and discuss possible factors underlying the increasing numbers being detected including the cessation of smallpox vaccination programs. Major knowledge gaps remain on the epidemiology, host reservoir, and emergence, transmission, pathogenesis and prevention of monkeypox.

INTRODUCTION

The repeated outbreaks of zoonotic infectious diseases with epidemic potential in Central and West Africa, such as Ebola, Rift valley fever, Chikungunya and Dengue, continue to pose major public health threats to regional, continental and global health security [WHO,2018]. Whilst lessons are being learnt from each outbreak [Zumla et al 2017], and the 'One Human-Environmental-Animal Health' approach is gaining momentum [Eteng et al, 2018], much more remains to be done to achieve a substantial change of the status quo [Zumla et al, 2016]. Critical to achieving this will be to effectively take forward and consolidate new African-led initiatives [Nkengasong et al 2017; Nkengasong & Onyebujoh, 2018] that will reinforce integration of contextual knowledge of drivers and risks, and better enable Africa's preparedness to tackle and prevent emerging and re-emerging infectious diseases threats.

MONKEYPOX IN THE UNITED KINGDOM

Monkeypox has recently focused global media, political and scientific attention after the identification in the United Kingdom (UK) in September 2018 of 3 separate patients diagnosed with monkeypox [PHE, 2018]. The first 2 had a recent travel history to Nigeria where there is an ongoing outbreak of the disease [Vaughan et al, 2018]. Both cases were symptomatic during their return flight to the UK. A third case of monkeypox in the United Kingdom occurred in a healthcare worker who cared for one of the two first cases. The healthcare worker was infected well before monkeypox was suspected and special infection control precautions were put in place. Secondary and tertiary human-to-human transmission of monkeypox has been well documented [Jezek et al,1986; Nolen et al 2016; Kalthan et al 2018]. Since these three cases of human monkeypox were the first ever reported from the European Union (EU) and the disease has similar clinical features with smallpox which had a devastating impact globally, media hype and enhanced political, and scientific attention ensued. Whilst the clinical manifestations of monkeypox are milder than smallpox, the disease can be fatal with case fatality rate between 1% and 10% being reported [Jezek et al, 1988; Hutin et al, 2001; Di Giulio & Eckburg, 2004; Jezek et al 1987].

MONKEYPOX IN CENTRAL AND WEST AFRICA

Nigeria, whose last confirmed case of monkeypox was in 1978 [Gromyko et al 1979], is currently experiencing an unusually large and lethal outbreak [WHO 2017; CDC 2017; Yinka-Ogunleye et al 2018]. On September 22, 2017, the Nigeria Centre for Disease Control (NCDC) commenced an outbreak investigation following the identification of an 11-year old child with suspected monkeypox [Eteng et al, 2018]. Epidemic preparedness requires close collaboration between human and animal health sectors to define the outbreak and effectively respond in order to prevent regional and global spread. The Nigeria CDC was prepared, activating a multiagency interdisciplinary emergency operations center (EOC) on October 9th, 2017, which took forward a well implemented comprehensive incident action plan (NCDC, 2018). This included targeted epidemiological and research investigations at high-risk areas at the Human-Environmental-Animal interface, enhanced laboratory diagnostic and rapid sequencing capacities, assessment of risk factors and modes of transmission. [Yinka-Ogunkiye et al, 2018; Faye et al 2018]. Available data suggest that human cases are not epidemiologically linked in the current outbreak, and that it is either a multisource outbreak with limited human to human transmission or an outbreak that has arisen from increased human contact with previously undetected endemically infected humans [Nigeria CDC, 2018; Durski et al 2018; Faye et al, 2018]. The exact zoonotic origin and the specific role(s) of environmental and ecological factors in the Nigeria outbreak are not yet known.

New cases of monkeypox continue to be detected in Nigeria. As of 13th October 2018, there have been one hundred and sixteen confirmed cases (with 8 deaths = 6% mortality), and 280 additional suspected cases from across 16 Nigerian States [Nigeria CDC 2018] affecting children and adults of all ages (**Figures 1a and 1b**). The majority of confirmed monkeypox cases are under 40 years with a median age of 31 years. Notably, these people were born after global vaccination programs for smallpox were discontinued in 1978. Studies in monkeys have shown that immunization with smallpox vaccine induces cross-protection against monkeypox [McConnell et al 1968]. The question arises - did the mass smallpox vaccination program help prevent the spread of human monkeypox? There have been several suggestions [Durski et al 2018; Rimoin et al, 2010; Reynolds et al, 2012] that increasing number of monkeypox cases in Central and West Africa is probably a consequence of the cessation of smallpox vaccination in the early 1980s, following the eradication of smallpox. The apparent lack of cross-protection against monkeypox among the non-vaccinated younger age groups and the waning smallpox vaccine-induced population immunity in the vaccinated groups, may contribute to the increased susceptibility to monkeypox infection. This creates an ecological niche where the monkey pox virus can expand in humans outside its natural reservoir.

Of note is that the number of human monkeypox cases being reported have risen exponentially over the past 20 years, more than the total number of cases over the previous 45 years since its first discovery [WHO, 2018; Sklenovska & van Ranst, 2018; Durski et al 2018; Yinka-Ogun et al 2018;

Rimoin et al 2010]. To date human cases of monkeypox have been reported from ten African countries - Democratic Republic of the Congo, Republic of the Congo, Cameroon, Central African Republic, Nigeria, Ivory Coast, Liberia, Sierra Leone, Gabon and South Sudan [WHO 2018]. Whilst the cessation of smallpox vaccination might be an important risk factor, there may be other factors which could explain the increase [Nolen et al, 2015; Sklenovská & Van ranst,2017] such as: a) higher frequency of contact with animal host reservoirs by children and young adults, b) deforestation leading to increased exposure of humans with displaced animals, c) Wars, conflicts and poverty leading to population movement into forests, d) reliance on rodents for food, e) increased population density, and f) Improved surveillance and diagnostic capability, although the latter was probably not the case due to reduced resources. Further multidisciplinary, regional collaborative research, including carefully designed case-control and cohort studies are required to fill the major knowledge gaps in the epidemiology, host reservoir, transmission, pathogenesis surveillance and prevention, as well as to explore potential prevention, infection control and treatment interventions.

The World Health Organisation (WHO) [WHO,2018] currently considers monkeypox to be “a rare viral zoonotic disease that occurs primarily in remote parts of central and Africa, near tropical rainforests”. This WHO statement may no longer be valid, and requires further discussion, review of evidence and debate. There is thus an urgent need for the conduct of priority research and surveillance through a combined ‘ONE-Human-Environmental-Animal-Health’ effort across Central and West Africa to increase the evidence base [Zumla et al 2017; Doshi et al 2011; Bass et al, 2013]. The continuing spread of monkeypox across a wide geographic area of Central and West Africa, and the real potential for further spread regionally and internationally is of major concern and requires coordinated review [Durski et al 2018; Sklenovska & van Ranst, 2018]. The ecological, zoonotic, epidemiological, clinical and public health aspects of monkeypox remain inadequately characterized [WHO, 2018; Heymann et al, 1998; Sklenovska & van Ranst, 2018; Rimoin et al, 2007 & 2010; Hoff et al, 2017; Learned et al 2013; Durski et al 2018; Yinka-Ogun et al 2018]. Data from reports and case studies of sporadic outbreaks in West and Central Africa over the past 50 years provide basic understanding, although the available literature is limited in its scope and the outbreak reports are incomparable. It is an opportune time to reflect on the discovery and historical evolution of monkeypox in Central and West Africa and view this in light of the current global attention on emerging infections.

FIRST DISCOVERY AND ANIMAL HOST RESERVOIR

The monkeypox virus was first discovered in 60 years ago [von Magnus et al 1959] and continues to remain on the radar of WHO since then [Heymann et al, 1998; Breman et al, 1980; WHO 1984; WHO 2018]. This zoonotic infection remains endemic to Central and West Africa in animal(s) reservoir(s), with increasing numbers of human cases and outbreaks being reported [Sklenovska & van Ranst, 2018; Rimoin et al, 2007 & 2010; Hoff et al, 2017; Learned et al 2013; Durski et al 2018; Yinka-Ogun et al

2018]. Monkeypox is caused by a double stranded DNA virus which belongs to the Orthopoxvirus genus of the family *Poxviridae* family [WHO 2018; CDC 2018; Shchelkunov et al, 2001]. The monkeypox virus was first detected in the 1958 in an outbreak of a vesicular diseases in captive monkeys brought to Copenhagen, Denmark from Africa for research purposes, hence the name monkeypox [von Magnus et al, 1959]. The term ‘monkeypox’ may be inappropriate since the virus has been found in rodents and squirrels and the specific host reservoir has not yet been identified [Doty et al, 2017]. The extent of the host animal reservoir, the natural history and pathogenesis of monkeypox in both animal and humans remains unknown and requires definition through case-control studies. In August 1970 the first human case of monkeypox was identified in a 9-year-old child with smallpox-like vesicular skin lesions in the village of Bukenda in the Equatorial region of Zaire (now Democratic Republic of Congo - DRC) [Marrenikora et al, 1972]. This patient was found during a period of intensified surveillance for smallpox cases, 9 months after the elimination of smallpox in DRC was certified by WHO. Retrospective studies indicated that similar cases had occurred between 1970-1971 in the Ivory Coast, Liberia, Nigeria, and Sierra Leone (Fine et al, 1988; Heymann et al 1998; Hepna et al 1998; Breman et al,1980; WHO 1980]. Subsequent increased surveillance led to a steady increase in the number of human monkeypox cases being identified, and each human case was investigated using standardized case investigation forms. Cases continued to be detected as isolated cases, in small clusters, or during large outbreaks in the community and in households [Nolen et al 2016]. An exponential rise in the number of cases were reported from the DRC [Hutin et al, 2007; Learned et al, 2013; Reynolds et al, 2013; Nolen et al 2016] and from across Central and West Africa has occurred over the past two decades [WHO 2018; Khodakevich et al, 1985; Sklenovska & van Ranst, 2018; Rimoin et al, 2007 & 2010; Learned et al 2013; Kantele et al, 2016; Hoff et al, 2017; Durski et al 2018; Yinka-Ogun et al 2018].

MONKEYPOX PREVALENCE, CHANGING CLINICAL PRESENTATIONS AND SMALLPOX VACCINATION

In 1980, the Global Commission for the Certification of Smallpox Eradication (GCCSE) continued to designate monkeypox as an important public health threat and recommended that the epidemiological, ecological and surveillance program on monkeypox be continued [WHO, 1980]. In response, the WHO supported an active surveillance program for human monkeypox from 1981 to 1986. Other countries of Central and West Africa continued to report cases of monkeypox in humans and in wildlife [Doty et al, 2017; Hutin et al 2001]. At the end of the smallpox eradication campaign, the GCCSE stated that continued smallpox vaccination to prevent monkeypox was not justified based on the evidence available at that time.

The clinical presentation of monkeypox includes symptoms with skin and mucosal lesions which are difficult to distinguish from smallpox [Jezek et al 1987; Jezek et al, 1988; Hutin et al, 2001; Di Giulio & Eckburg, 2004;]. As with smallpox, the prodromal period of monkeypox infection starts with fever,

headache, back pain, myalgia and asthenia followed by eruption of skin and mucosal lesions starting with the face (within 1-3 days after development of fever). The lesions evolve from maculo-papular to fluid filled vesicles to pustules followed by crusting within 10 days and complete disappearance of the crusts within 3 weeks [Nigeria CDC, 2018; Osadebe et al, 2017]. Whilst immunosuppression may be a risk factor for severe disease, the effects of HIV co-infection remain to be determined. Lymphadenopathy is common and may be a clinical distinguishing feature from smallpox. Laboratory tests available for confirming a diagnosis of monkeypox include Polymerase chain reaction (PCR), antigen detection tests, Enzyme-linked immunosorbent assay (ELISA) and viral cell culture [PHE, 2018; CDC, 2018]

Based on clinical and epidemiological features, and linking genotypic studies of monkeypox virus isolates two distinct clades of virus have been characterized [Likos et al, 2005; Nakazawa et al, 2015]: Congo Basin (CB) and West African (WA). The CB clade is associated with higher (approximately 10%) mortality and seems to transmit more frequently between humans with several human-to-human transmission cycles. The WA clade causes milder disease with lower mortality rates [Breman et al, 1980].

There are differences in skin and mucosal lesions in patients with previous smallpox vaccination as defined by presence of vaccination scar, compared to those patients who were not vaccinated [Jezek et al 1987; Huhn et al 2005; Damon IK 2011; Di Giulio & Eckburg, 2004; McCollum & Damien, 2004]. In vaccinated individuals the skin rashes and vesicles appear less intense, milder and more pleomorphic, and fewer in comparison with those unvaccinated individuals. Smallpox vaccination appeared to provide 85% protection against monkeypox infection [Fine et al, 1988]. The average annual primary attack rate was estimated at 1.7 per 10,000 in those unvaccinated, compared to a rate of 0.04 per 10,000 among those who were vaccinated [Rimoin et al, 2010]. Whilst new vaccines are being developed for monkeypox, there is a need to conduct controlled clinical trials to evaluate the efficacy and impact of smallpox vaccines for prevention of monkeypox or modification of disease severity. Studies should focus on the cost benefit of population level vaccination and investigation of alternative vaccination strategies such as targeting vaccination to affected areas, contacts and healthcare workers, and wider geographical areas. Currently, the CDC recommends pre-exposure smallpox vaccination for field investigators, veterinarians, animal-control personnel, contacts of monkeypox patients, researchers and health-care workers caring for patients and their contacts [CDC 2018].

Several reviews have summarised human monkeypox outbreaks over the past 38 years [Rimoin et al 2010; Sklenovská and Van Ranst, 2018; Durski et al 2017; Kara et al 2018]. Population-based surveillance studies conducted in nine health zones in DRC identified 760 laboratory-confirmed human monkeypox cases with an annual cumulative incidence of 5.53 per 10,000 (2.18-14.42) [Rimoin et al 2010]. Factors associated with increased risk of infection included: living in forested areas, male

gender, age less than 15years, and absence of prior smallpox vaccination. A 5.2-fold lower risk of monkeypox was seen in those who had received smallpox vaccination than unvaccinated persons (0.78 vs. 4.05 per 10,000). A 20-fold increase in human monkeypox incidence was observed compared to surveillance data from the same region from the 1980s. Between January 2001 and December 2004, the DRC Ministry of Health surveillance program [Rimoin et al 2007] reported that 2,734 cases of suspected human monkeypox from 11 provinces which showed annual upward trends: 380 cases in 2001, 545 in 2002, 783 in 2003, and 1026 in 2004. The majority of cases (94%) occurred in children and young adults less than 25 years of age who had not received smallpox vaccination. Surveillance activities after 2005 were then interrupted by the civil war over 20 years. In the conflict zone of the Kivu region refugee displacements into forested areas increased in 2012 when the war accelerated. Monkeypox cases continue to be reported from the DRC [Hoff et al 2017] including areas of conflict [McCullum et al,2015], with human to human transmission occurring during outbreaks [Nolen et al 2016].

ANIMAL EXPORTS AND OUTBREAKS IN THE USA

Monkeypox remained an ignored global public health threat and only became the center of global attention when the first human monkeypox cases outside Africa were detected in the United States of America in 2003 [CDC, 2003a; CDC 2003b; CDC 2003c]. Several people in the mid-west United States developed fever, rash, respiratory symptoms, and lymphadenopathy and outbreak investigations linked the monkeypox cases following exposure to pet prairie dogs (*Cynomys species*) [CDC 2003a]. Cases of monkeypox were reported from six states—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin - during the 2003 U.S. outbreak [CDC update 2003b]. Molecular and epidemiological investigations found that a west African genetic group (clade) of monkeypox was imported from Ghana into the state of Texas, USA on April 9, 2003, through a shipment of nine different species of small mammals, including six genera of African rodents [CDC 2003c]. Evidence of monkeypox virus was cultured from 22 animals and monkeypox DNA was found in at least 33 [Hutson et al, 2007]. These included rope squirrels (*Funisciurus sp.*), tree squirrels (*Heliosciurus sp.*), brush-tailed porcupines (*Atherurus sp.*), African giant pouched rats (*Cricetomys sp.*), dormice (*Graphiurus sp.*), and striped mice (*Lemniscomys sp.*). Some of the infected animals were housed near North American prairie dogs (*Cynomys sp*) which were sold as pets. The prairie dogs harbored large amounts of monkeypox virus which was detected in lesions in the, tongue, skin, lung, and eyelid samples [Hutson et al 2007]. Genomic studies of monkeypox viruses isolated from a human, a prairie dog, a rope squirrel, a dormouse, and a giant pouched rat showed identical viral isolates.

ANIMAL RESERVOIRS

Indirect or direct contact with live or dead animals is assumed to be the driver of human monkeypox infections in humans [Durski et al, 2018; Sklenovská & Van Ranst, 2018]. Monkeypox primarily occurs

in animals in the equatorial rain forests in West Africa and Central Africa [WHO, 2018; CDC, 2018; Nigeria CDC, 2018; Khodakevich et al 1986; Hutin et al 2001). In 1985, the virus was isolated from a moribund rope squirrel (*Funisciurus anerythrus*) in Zaire (DRC) during an outbreak investigation [Khodakevich et al, 1986]. Evidence of monkeypox infection has been found in a range of animal species: squirrels (rope and tree), rats, striped mice, dormice and monkeys (Khodakevich et al, 1986; Reynolds et al 2010; Radonic et al, 2012; Radonic et al 2014; Doty et al, 2017]. The specific animal host reservoir of monkeypox, the natural history of animal and human monkeypox infections remains unknown. Further studies are needed to understand the extent of animal host reservoir, how the virus maintained in nature, the natural history, the pathogen-host associations and the effect of climatic and ecological factors which affect shifts of monkeypox between geographical areas and to causing disease in humans (Thomassen et al, 2016].

MODES OF TRANSMISSION

The exact mode of transmission of the monkeypox virus to humans remains unknown. Primary animal to human infection is assumed to occur through direct or indirect contact with monkeypox infected animal bodily fluids through handling, bites or scratches, although the specific mechanism(s) remains to be defined. The virus is thought to enter the body through broken skin, the respiratory tract, or the mucous membranes (eyes, nose, or mouth). Secondary human-to-human, transmission is well documented [Jezek et al, 1988; Jezek 1986; Hutin et al 2001] and is thought to occur through large respiratory droplets or direct or indirect contact with body fluids, lesion material, and contaminated surfaces or other material such as clothing or linens. Prolonged contact places hospital staff and family members at greater risk of infection. Nosocomial transmission has been recorded (Learned et al 2003). There is no evidence, to date, that person-to-person transmission alone can sustain monkeypox infections in the human population.

There have been few genomic studies on the origins of monkeypox outbreaks. Human-to-human transmission has been reported from primary human cases, secondary cases [Jezek et al 1985;1986] and serial transmission across four cases has been observed [Nolan et al 2016]. In the current monkeypox outbreak in Nigeria, genomic studies on monkeypox virus isolates from human cases [Faye et al 2018] suggest that the index case was not imported into Nigeria. Current evidence suggests that the outbreak is caused by multiple source emergence into the human population, and not sustained by human to human transmission. The zoonotic source(s) of the outbreak are currently under investigation, and it is unclear what, if any, environmental or ecologic changes might have facilitated its sudden reemergence in Nigeria. Clustering of cases has been identified within states, although no epidemiological linkages across states have yet been identified. Three family clusters have been identified and this suggests human-to-human transmission (NIGERIA CDC, 2018; Faye et al 2018]. In one family the secondary attack rate was 71%. However, since most cases have no obvious epidemiologic linkage suggestive of person-to-person contact, the hypothesis of a multiple-source

outbreak is reinforced, but this does not exclude emergence from contact with humans that are a part of previously unrecognized human endemic disease.

ADDRESSING GAPS IN KNOWLEDGE AND STRENGTHENING PUBLIC HEALTH PREPAREDNESS

Most of the currently available data on monkeypox comes from individual case or outbreak reports, and from passive intermittent surveillance, all of which do not portray an accurate overall picture. The rapid response by the Nigerian CDC [Nigeria CDC, 2018] to the ongoing monkeypox outbreak is an example of how a locally led integrated Human-Animal Disease Surveillance and Response system can be used effectively to define the outbreak, and points the way forward for other African countries. Nigeria's experience is important for regional training and help build networks to improve surveillance capacity, laboratory diagnostics, best public health and clinical practice, and regional capacities to launch locally led efficient responses. This would contribute to the need to build public health and surveillance capacities across Africa to guide appropriate surveillance, data collection, prevention, preparedness and response activities to monkeypox and other emerging and re-emerging infections with epidemic potential. Advancing public health preparedness and aligning proactive surveillance activities to priority research will require a coordinated, locally-led, multidisciplinary effort aligned closely with capacity development and training.

CONCLUSIONS

An approximately 20-fold increase in monkeypox incidence compared to the historic data up to 1986 has occurred in and West Africa [WHO, 2018; Sklenovska & van Ranst, 2018; Durski et al 2018; Yinka-Ogun et al 2018; Rimoin et al 2010]. Novel lethal zoonotic pathogens of humans with epidemic potential and high mortality rates have threatened global health security for centuries and continue to do so [Zumla et al 2017]. The ecological gap of the increasing number of humans with no immunity to poxvirus after the end of the smallpox vaccination program resulted in a susceptible population where secondary epidemiological cycles can occur. Whilst there is no evidence to date, that person-to-person transmission alone can sustain these zoonotic infections in the humans, the continuing outbreaks caused by lethal zoonotic pathogens such as Ebola Virus, the Middle East respiratory Syndrome coronavirus and monkeypox virus highlights the interconnectedness between Humans, Animals and the Environment. This emphasizes that a 'One-Human-Environmental-Animal Health' approach is required to reduce the risk of outbreaks and this challenge warrants priority political and funder attention [Zumla et al, 2016]. Whilst the 'One Human-Environmental-Animal Health' approach is gaining traction, much more remains to be done to achieve a substantial change to the status quo [Zumla et al 2017].

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CONFLICTS OF INTEREST

All authors have an interest in global public health and emerging and re-emerging infections. All authors have no other conflict of interest to declare.

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Figure 1a (Source: 'Situation Report- Nigeria CDC. www.ncdc.gov.ng)

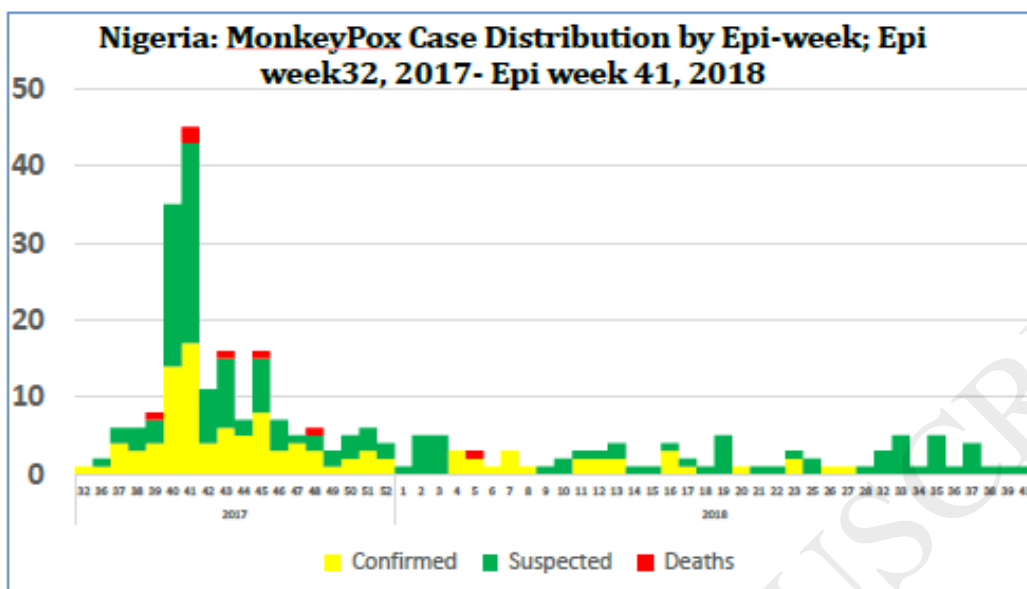


Figure 1b (Source: 'Situation Report- Nigeria CDC. www.ncdc.gov.ng)

