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Conference report

Human monkeypox – After 40 years, an unintended consequence of smallpox eradication

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ABSTRACT

Smallpox eradication, coordinated by the WHO and certified 40 years ago, led to the cessation of routine smallpox vaccination in most countries. It is estimated that over 70% of the world's population is no longer protected against smallpox, and through cross-immunity, to closely related orthopox viruses such as monkeypox. Monkeypox is now a re-emerging disease.

Monkeypox is endemic in as yet unconfirmed animal reservoirs in sub-Saharan Africa, while its human epidemiology appears to be changing. Monkeypox in small animals imported from Ghana as exotic pets was at the origin of an outbreak of human monkeypox in the USA in 2003. Travellers infected in Nigeria were at the origin of monkeypox cases in the UK in 2018 and 2019, Israel in 2018 and Singapore in2019. Together with sporadic reports of human infections with other orthopox viruses, these facts invite speculation that emergent or re-emergent human monkeypox might fill the epidemiological niche vacated by smallpox.

An *ad-hoc* and unofficial group of interested experts met to consider these issues at Chatham House, London in June 2019, in order to review available data and identify monkeypox-related research gaps.

Abbreviations: CDC, Centers for Disease Control, Atlanta USA; DRC, Democratic Republic of Congo (formerly Zaire); EMA, European Medicines Agency; FDA, United States Food & Drug Administration; HBV, hepatitis B virus; HIV, Human Immunodeficiency Virus; MVA-BN, Modified Vaccinia Ankara, proprietary Bavarian Nordic derivative; NCDC, Nigeria Centre for Disease Control; PCR, polymerase chain reaction; WHO, World Health Organization.

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Gaps identified by the experts included:

- understanding of zoonotic hosts, reservoirs and vectors.
- risks associated with transmission.
- full description of the clinical spectrum and the natural history of infection including an estimation of the prevalence of monkeypox specific antibodies in humans living in areas of emergence.

The experts further agreed on the need for a better understanding of the genomic evolution and changing epidemiology of orthopox viruses, the usefulness of in-field genomic diagnostics, and the best disease control strategies, including the possibility of vaccination with new generation non-replicating smallpox vaccines and treatment with recently developed antivirals.

1. Introduction

The vaccinia virus vaccine that eradicated smallpox also protected against other orthopox infections, and if given within four days of infection could modify or prevent onset of clinical disease [1]. With the eradication of smallpox and the subsequent cessation of routine smallpox vaccination [2,3], human monkeypox appeared with increasing frequency in unvaccinated populations. Second-generation smallpox vaccines have been demonstrated to protect against monkeypox [4,5]. However, better understanding of the epidemiology of monkeypox virus has gained importance.

Variola virus, the causative agent of smallpox, is thought to have adapted to the human host as early as 3 to 4 thousand years ago. Smallpox immunisation had existed in some form for at least one thousand years, according to Chinese records [6,7]. Rational vaccine design began with Jenner's 1796 cowpox vaccine [8], made from a virus that caused a usually mild disease, transmitted to humans by animal hosts. Vaccination laid the basis for the eradication of Variola in 1980 [9]. Several orthopox viruses, including the monkeypox virus, are thought to have caused similar mild and sporadic human illness prior to the innovation of smallpox vaccination [10], and remain in circulation in animal hosts with periodic emergence in human populations. Variola minor (sometimes called alastrim) was a less common and genetically distinct form of the variola virus [11]. In contrast to the 30–50% fatality rate of smallpox, the Variola minor fatality rate was reportedly less than 1%. Many Variola minor patients felt quite well, were mobile and were able to infect their contacts, providing protection to Variola major [12]. Vaccination and protective Variola minor exposure contributed to smallpox eradication and likely reduced the number of other human orthopox infections.

Just as smallpox virus appears to have evolved into two distinct clades, so Monkeypox displays two distinct clades, Congo Basin and West African [13]. With monkeypox, the Congo Basin clade has reported mortality at about 10% [14], whereas the West African clade usually displays fatal outcomes in less than 1% of cases, although, this was observed to be much higher in HIV patients [15].

As originally noted by Jenner, infection with one orthopox virus, cowpox (and subsequently, vaccinia-derived vaccines), offered smallpox protection. However, the proportion of smallpox vaccinated individuals has fallen from over 80% in1980, to less than 30% today [16]. In some developing nations, young non-vaccinated individuals exceed 75% of the population [17]. Such individuals are almost certainly susceptible to monkeypox virus infection.

Monkeypox was first identified in Denmark in 1958, following an outbreak of pustular disease in a macaque colony [18]. The macaques had been imported from Singapore. The first human monkeypox case was identified in the Democratic Republic of Congo (DRC, then Zaire) in 1970 as the incidence of smallpox was decreasing [19,20]. The true burden of monkeypox disease is unknown, and many countries, which may harbour the disease, have not included monkeypox screening into routine surveillance systems. The prevalence of asymptomatic infection is not understood, should it occur in human populations.

Despite-re-emergent human monkeypox disease, the animal reservoirs of monkeypox viruses and the human behaviours that facilitate initial animal to human transmission are unconfirmed. It has been shown that in intermediate hosts the virus can be transmitted from one animal to another, and subsequently to humans. This occurred in the US Midwest outbreak, when 47 confirmed and probable cases, including many children, were infected by prairie dogs thought to have contracted monkeypox from rodents shipped to the United States from Ghana [21].

In June 2019 an informal seminar brought together a group of experts to review the status of human monkeypox disease, highlighting facts and deficient understanding. Included in the group were: epidemiologists based in the UK and the US; field epidemiologists based in Nigeria and DRC where current outbreaks are occurring; experts in DNA virus genomics and evolution; and observers from a pharmaceutical company that has developed and is marketing a non-replicating vaccine for both smallpox and monkeypox indications.

2. Re-emergent monkeypox in Africa

Hypothesised factors in the emergence or re-emergence of monkeypox disease include [22,23]:

- *Climate change*
- *Rain Forest exploitation*
- *Geopolitical and armed conflicts in disease areas*
- *Highly mobile populations*
- *Waning herd immunity, following cessation of smallpox vaccination.*

After the eradication of smallpox, there was concern that the monkeypox virus might fill the epidemiological niche left by smallpox [24]. Smallpox had no known zoonotic host and was transmitted only on a human-to-human basis, whereas monkeypox may be transmitted to man by animal hosts. WHO-sponsored serological surveys were conducted in rural communities in West and Central Africa where human monkeypox was sporadically occurring. Prior to 1986, population-based surveys suggested that orthopox virus antibodies were present in 12–15% of children. The mean age of patients was just 4·4 years. Cases of monkeypox were linked to animal sources in 245 of 338 cases [25]. A major outbreak of human monkeypox occurred in Katako-Combe, Zaire in 1996, From February 1996 to February 1997, 89 persons in this outbreak were diagnosed with human monkeypox [19,26]. 73% of cases reported contact with another human case while 27% had known contact

with a wild animal. Prior to 1996, chains of transmission were short and infrequent, variously reported as involving up to 3–5 non-vaccinated persons. Several longer chains of transmission occurred during the 1996–1997 Katako-Combe outbreak, with up to 7 non-vaccinated persons infected from the same index case. From 1998, numbers of infections increased, with an increase in mean age [25]. A 2007 study showed orthopox antibodies in unvaccinated residents of the Likouala region (Republic of Congo, ROC, not DRC) [27]. By 2006–7 a very significant 20–fold increase in human monkeypox was reported in DRC [28]. Only24·5% of the population appeared to have been vaccinated. Was this emerging infection out of control [29]?

In 2017, outbreaks of human monkeypox in Nigeria were preceded by very heavy rainfall and flooding that is hypothesised to have brought animal hosts and human populations into close proximity, as both sought higher ground and dry environments [30]. The outbreak was first reported to the Nigerian Centre for Disease Control (NCDC) in September 2017, following an unknown rash illness in southern Nigeria, and regular reports followed [31]. Active surveillance confirmed human monkeypox, and as of September 2019, a total of 176 human monkeypox cases had been confirmed from 18 states [32,33].

Previously, there had been one reported outbreak of human monkeypox in Nigeria in the 1970s, and after that, three sporadic cases were reported before the onset of the 2017 epidemic [34]. The chains of transmission investigated in the current outbreak suggest a primary infection contracted from an animal, with subsequent human-to-human transmission. Human-to-human transmission has been demonstrated among family contacts, and in prison populations, but human-to-human chain lengths appear to be short at 1–3 individuals in each link, although this requires more analysis [32,35]. Monkeypox laboratory diagnosis by PCR has been established by NCDC [36] and suggests that young male adults are most affected. A case fatality rate of 5·6% has been recorded, with most deaths among HIV infected patients [37]. The case fatality rate, excluding those with HIV infection is reported as <2%. Persons vaccinated prior to 1980 had a five–fold lower risk of monkeypox compared to those who had not been vaccinated [24]. Human-to-human transmission of monkeypox is now regularly observed and the disease has become more common.

Risk factors for infection are unclear, with confirmed animal contact in approximately 10% of cases, while the prevalence of asymptomatic infection, should it occur, remains unknown. Sexual transmission has been hypothesised for some cases with genital and groin lesions [37]. The current research focus in Nigeria is on epidemiological risk factors, animal reservoirs and HIV co-infection. Control and prevention measures include education and personal hygiene, drawing on known epidemiology and risk factors. Vaccination has been considered for healthcare workers in treatment centres but was not initiated. Human monkeypox is being added to routine disease surveillance protocols, with genomic studies and serological surveys being planned. Additional questions that could be examined include, transmission routes from human-to-human, and the natural history of dual monkeypox/HIV infection.

Social issues have emerged, including the stigma of being diagnosed with monkeypox. One suicide was reported [37]. Many patients with monkeypox feel relatively well and containment is complicated by a desire to return to a normal life – often expressed quite strongly. The same sentiment was expressed by a person secondarily infected in the 2018 UK cases [38].

3. International spread of human monkeypox

In 2003 an outbreak of human monkeypox occurred in the USA [21]. It was initiated by rodents imported from Ghana to be sold as exotic pets. It is thought that these rodents infected co-housed prairie dogs, also sold as pets, through some type of animal to animal contact. 47 confirmed and probable cases were reported, but there were no deaths. The outbreak consisted mainly of isolated skin lesions. Smallpox vaccine (DryVax, Wyeth) was offered to those who had direct physical contact with human cases and rodents that were sold. Two cases in the 2003 outbreak in the USA may have involved human-to-human transmission, but contact with infected rodents could not be excluded.

In September 2018, there were two unrelated importations of monkeypox to the UK, by two persons travelling from Nigeria [39]. One was a Nigerian naval officer who came to the UK for a training course. The other a Nigerian businessman. Both were well before travelling, and developed skin lesions after arrival in the UK. Soiled bedsheets probably led to infection of a hospital cleaner [40], the first confirmed case of human-to-human transmission outside Africa. In 2018, all UK patients were rapidly diagnosed and isolated with over 200 contacts identified and offered smallpox vaccination (Imvanex, Bavarian Nordic) [41,42]. In December 2019 a further case of human monkeypox was confirmed in the UK, again imported from Nigeria [43]. Contact tracing was initiated and smallpox vaccine (Imvanex) was procured.

In 2018 human monkeypox was imported to Israel by an Israeli resident who lived and worked in Nigeria [44]. He became ill after his return to Israel, and PCR and Electron Microscopy confirmed infection with the monkeypox virus. Following diagnosis, the patient was isolated, and 16 contacts were identified and offered smallpox vaccination (ACAM2000, Emergent Biosolutions). No secondary transmission is known to have occurred [45].

In 2019, a Nigerian travelling to Singapore for a training course developed skin lesions shortly after arrival and was diagnosed with human monkeypox. 23 close contacts were identified, were offered smallpox vaccination (ACAM2000) and were placed under quarantine at home or in a government facility for 21 days monitoring [46,47].

The smallpox vaccines offered in all these instances were used off license.

4. New genomic tools aid diagnosis, epidemiology and evolutionary studies

The monkeypox viruses isolated recently from patients in Nigeria, the UK, Israel and Singapore were quickly diagnosed and identified as West African monkeypox virus using PCR and genetic sequencing. Recent studies of the monkeypox virus in the DRC and Nigeria examined isolates from humans [48,49], and potential animal hosts [50]. Complementing PCR, newer technologies such as (Minion nucleotide sequencing (Oxford Nanopore) [51], might allow field sequencing of the monkeypox virus in animals commonly killed as bushmeat. This technology can be used with little infrastructure and ensures rapid data generation, as was demonstrated in the West African Ebola outbreak of 2013–2016 [52]. Detailed animal data will require the establishment of protocols for sample collection and preparation. To date, only anecdotal data link bushmeat hunting and preparation with monkeypox infection.

Two major monkeypox clades–West African and Congo Basin–have been identified [13], and all reported human monkeypox outside Africa has been caused by the West African clade [50]. West African monkeypox is associated with lower mortality, less severe illness, and less human-to-human transmission than Congo Basin monkeypox. However, these observations were based on a small number of infections (<100) observed since the 1970s. The larger number of infections identified from Nigeria has shown that mortality, severe illness, and human-to-human transmission can occur [37]. More work is needed in order to fully describe the epidemiology and impact of West African monkeypox.

The evolutionary history of monkeypox virus is unclear. Orthopox viruses differ in gene content, in particular genes affecting virulence and host range. Viruses with narrow host ranges contain fewer genes, for example; variola virus has about 165 genes, whereas those with broad host ranges have more. Cowpox viruses contain about 214 genes. The smallpox virus encodes virulence factors that modulate the human immune system [53,54], and similar virulence factors exist in monkeypox virus [55]. Understanding of the genetic basis for these differences is incomplete. The availability of additional full monkeypox virus genomes (currently there are 59 complete genomes in the NCBI nucleotide database [56], may allow researchers to observe future adaptations associated with changes in virus properties.

The study of orthopox DNA isolated from historical samples may provide information on the evolution, pathogenicity and stability of the monkeypox virus. The isolation of DNA from Hepatitis B virus (HBV) and identification of HBV genotypes from human remains up to 5000 years old illustrates this potential [57]. DNA can be isolated from ancient biological material such as found in burial sites and mummified remains [58]. DNA from monkeypox virus has been isolated from skin samples of five species of African rope squirrel (Funisciurus sp) up to 120 years old [59]. Appropriate historical specimens could provide clues about reservoirs and intermediate hosts, as well as past changes of the virus.

5. The future

Human monkeypox epidemiology has changed. With the cessation of widespread smallpox vaccination, increased study of the monkeypox virus, the human disease it causes, and its epidemiology are important. Monkeypox has been viewed as "just another neglected disease". Global travel and easy access to remote and potentially monkeypox-endemic regions are a cause for increasing global vigilance.

Investigation of human monkeypox outbreaks using modern tools is increasing understanding of the epidemiology of human monkeypox, including measures to prevent and respond to outbreaks. It must be continued, and as further information becomes available it should be used to parameterise epidemiological models in order to suggest the comparative effectiveness of interventions such as isolation, safe burial, contact tracing, antivirals and vaccines.

Funding for monkeypox research must be increased, and newly emerged orthopox viruses that cause disease in humans such as Akhmeta virus, identified in the Georgia Caucusus [60] or Alaskapox virus discovered in 2015 [61], add urgency to this need.

A recent systematic review of monkeypox epidemiology highlights both progress and deficits in our understanding [62]. Emphasis is placed on high-risk patient groups, nosocomial transmission and genetic strains. As monkeypox is no longer a rare disease, there is need for more rigorous epidemiological studies, with particular reference to zoonotic hosts [63], transmission potential [64–66] and human case severity. Enhanced fieldwork should address these issues with particular reference to:

- *Identification of wild species which harbour these viruses in different areas of Africa*
- *Better definition of the clinical spectrum and severity of disease, including asymptomatic carriage and risk factors for acquisition*
- *Improved description of outbreak patterns by size and duration*
- *Measurement of risk of transmission associated with different sorts of contact with clinical cases*

Authors contributions

Simpson organised the seminar that led to this publication. He wrote the article, reviewed and edited authors' contributions

Heymann Chaired the seminar and co-wrote the article, reviewed and edited authors' contributions

All co-authors contributed equally to the seminar with presentations and discussion. All made valued contributions to the final manuscript.

All authors have reviewed this work and have given their permission to be named as authors in this publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Authors Elsgaard, Hochrein, Maclennan and Powell are employees of Bavarian Nordic, manufacturer of a vaccine registered as **Jynneos** for smallpox and monkeypox indications in the USA (**Imvanex** for smallpox only in Europe and **Imvamune** for smallpox only in Canada. Simpson works as a consultant for Bavarian Nordic.

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