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## Investigating the monkeypox outbreak

*Here's what we know, and what we need to know*

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Between 4 and 25 May, 221 confirmed (by reverse transcriptase PCR) and 86 suspected cases of monkeypox have been reported from 23 countries in Europe plus Argentina, Australia, Canada, United Arab Emirates and the United States.<sup>1</sup> Such a large number of cases has never previously been reported from so many countries outside Africa [Q to A OK? Morocco is in Africa] in just a few weeks. New cases are being reported daily; more can be expected and in more locations. Why the extraordinary surge now? What do we need to know to stop it?

Almost all patients so far are male (3 are female) and presented with symptoms typical of monkeypox, including fever, vesicular rash, skin lesions and ulcers, and swollen lymph nodes.<sup>2</sup> The first case in this outbreak was a man who visited Nigeria from the UK.<sup>3</sup> He developed a rash on 29 April before leaving Nigeria, arriving back in the UK on 4 May. He was immediately isolated at a London hospital on the same day [correct?]. His contacts on the flight to the UK, together with others in the community plus healthcare staff, are being followed for 21 days, considered the upper limit of the incubation period for monkeypox.<sup>4</sup> By 24 May, none of these contacts had reported symptoms.

Another 70 confirmed cases have been reported in the UK (all in England except one in Scotland), in several different groups. There is evidently person-to-person transmission within groups but no known links between groups or with the first case in England. One group is a household of three; another is four men who identify as gay or bisexual and seem to have been infected in London.<sup>5</sup> Other than the first case, none have recently visited, or are known to have contacts that visited, endemic areas of Africa.

## Informed response

Against this background, at least six lines of investigation will help to develop national and global responses in the coming days and weeks. The first is to find out whether the exceptionally large number of exported infections is linked to the increased frequency of travel to and from endemic areas of Africa now that covid restrictions have been lifted. If it is, published travel schedules between countries will help to specify and then mitigate risk around the world.

The second is to investigate whether and how the spread of monkeypox is being driven by a rise in case numbers at source in west and central Africa. The number of monkeypox cases increased in Africa between 1970-79 and 2010-19 following the demise of smallpox and the decline in smallpox vaccination, especially in the Democratic Republic of the Congo (DRC).<sup>6 7</sup> This rise has included major outbreaks, the largest of which affected 17 states of Nigeria in 2017-18.<sup>8 9</sup>

Thirdly, the main routes of transmission need to be re-examined. The 2017-18 Nigerian epidemic was caused by multiple introductions from animals (most likely rodents) to humans, plus limited and perhaps non-sustaining chains of transmission between people.<sup>8 10 11</sup> Now, however, waning immunity to smallpox and smallpox (vaccinia) vaccine could have magnified the risk of sustained transmission between people, within and beyond Africa.<sup>12 13</sup> The relative importance of different transmission routes could also have changed. Close contact is normally needed to acquire infection from skin lesions, body fluids, exhaled droplets, or contaminated clothing and bedding. The discovery of cases among gay and bisexual men, notably in Canada, Spain, and the UK, points to sex as one among other forms of close contact, although monkeypox is not primarily a sexually transmitted disease.

Fourthly, we need to reassess what proportion of infections cause severe or fatal disease. Historically, two different genomic clades of monkeypox virus have been described in west and central Africa.<sup>7</sup> All cases so far genotyped in Europe during the current outbreak are more closely related to the west African clade [Q to A correct? ] and to viruses exported from Nigeria to Israel, Singapore, and the UK in 2018 and 2019.<sup>14 15</sup> The west African clade has been associated with milder illness and a lower case fatality ratio (roughly 4%) than the central African clade (roughly 10%).<sup>7</sup> If some infections are asymptomatic, as previously described,<sup>11</sup> these estimates of case fatality could be too high. Asymptomatic cases might also be missing links in transmission chains. Case fatality, and the risk of severe disease, can be reduced with

some antivirals effective against poxviruses, but there is undoubtedly more to be learnt about supportive and therapeutic clinical care.

The fifth line of investigation is to determine whether monkeypox could evolve, or has recently evolved, to become more pathogenic or more transmissible, or transmissible in a different way. Monkeypox virus is genetically variable and adaptable. The two main African clades consist of multiple lineages and many variants within each lineage. One genetic deletion identified in samples from DRC has been associated with human-to-human transmission.<sup>16</sup> Clinical, epidemiological, and genomic surveillance is vital to detect possible changes in mode of transmission, human susceptibility, infectiousness, and pathogenicity.<sup>15 17</sup>

Lastly in this short list, the effectiveness of vaccination in protecting individuals and populations should be further evaluated. Because smallpox is caused by an orthopoxvirus closely related to monkeypox, pre-exposure inoculation with vaccinia vaccine is efficacious (about 85%) against monkeypox disease and probably also reduces onward transmission.<sup>18</sup> Post-exposure inoculation gives less protection, so vaccine effectiveness in practice—assessed, for example, while tracing and vaccinating contacts of cases<sup>19</sup>—will depend on what proportion of people at risk can be immunised before rather than after acquiring infection.

On present evidence, monkeypox is unlikely to become a global health emergency. Nevertheless, vigilance and open minded investigation are needed worldwide because until these and other questions are answered, we will not know how best to contain the unprecedented spread of this disease. [correct?]

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