

# Monkeypox virus mutates at a higher rate

The mutation pattern does not conclusively prove sustained human-to-human transmission

R. PRASAD

As of June 1, 2022 over 550 lab-confirmed monkeypox cases have been reported from 30 countries, the World Health Organization (WHO) said at a press briefing.

These countries are predominantly in Europe and North America, which are not endemic for monkeypox virus.

With 190 cases as on May 30, the outbreak in the U.K. is the largest so far, with Spain (132 cases) and Portugal (132 cases) being the other countries with a large number of monkeypox cases.

The WHO once again stressed that the large number of cases detected in more than two dozen countries within a short time interval suggests that there “may have been undetected transmission for some time”.

The cases have predominantly been reported among men who have sex with men presenting with symptoms at sexual health clinics.

The two rave parties in Belgium and Portugal have turned out to be super-spreader events. In a statement released on May 31, 2022 the European Union underlined the link between these parties and cases.

It said, “Multiple countries have reported cases which appear to be linked to events taking place in Spain (Madrid and the Canary Islands) and Belgium (Antwerp).”

However, cases have been reported in people with no

epidemiological link to the rave parties, travel history to countries in Africa or even contact with other people with infection, the statement noted.

## Highly speculative

Though the first case that was detected on May 7, 2022 in the U.K. was in a person who had just returned from Nigeria, samples of at least two people, one in Canada and another in Portugal, that were collected prior to the return of the U.K. person had tested positive for monkeypox virus.

The notion that virus may have been imported from Nigeria is “highly speculative”, Christian Happi from Nigeria’s African Centre of Excellence for Genomics of Infectious Diseases told *Science*.

Epidemiologist Ifedayo Adetifa, head of the Nigeria Centre for Disease Control also told *Science* that “there’s too much emphasis for whatever reasons in Western capitals and news media about trying to hold somebody responsible for a particular outbreak. We don’t think those narratives are helpful”.

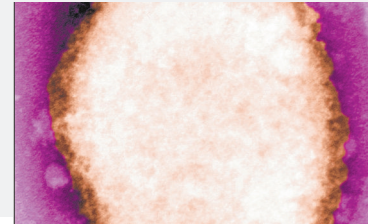
So far in 2022, seven African countries have reported 1,392 suspected and 44 confirmed monkeypox cases to the WHO, which are slightly fewer than half of cases reported last year.

## 47 mutations

Meanwhile, Dr. Andrew Rambaut from the University of Edinburgh found 47 mutations in the virus genome based on an analysis of the

## Sustained transmission of the virus in the last four-five years

There are 47 new mutations seen in the monkeypox virus compared with the 2017-2019 sequences



**Lack of proof:** There is no evidence that monkeypox virus collected all the 47 mutations in humans. ■ SPECIAL ARRANGEMENT

■ As of June 1, over 550 lab-confirmed monkeypox cases have been reported from 30 countries

■ The notion that the virus may have been imported from Nigeria is “highly speculative”

■ The 47 mutations seen in the genome sequence does indicate that the virus has collected these mutations in a short period of time

■ The mutation rate of two per year for monkeypox virus comes from limited data from other poxviruses that have been studied

■ Many of the mutations now seen are due to the action of a particular enzyme that is present in the host (animals and humans) to prevent the

virus from multiplying

■ The large collection of mutations clearly suggests that monkeypox virus mutates at a higher rate than what was assumed

■ There has been sustained transmission, but cannot be certain if the sustained transmission has been in humans

■ The significance of these mutations is not known yet. But most of the mutations are likely to be inconsequential

sequences from the current outbreak outside Africa and comparing it with the earlier genomes from samples from patients in 2017-19 in Singapore, Israel, Nigeria and the U.K.

“Forty-seven substitutions in the space of three-four years is an unexpectedly large number. As MPXV [monkeypox virus] is considered a zoonotic virus with limited human-to-human transmission, this long branch may be evidence of adaptation to humans allowing for the sustained transmission that is now observed,” he said in [virological.org](http://virological.org).

But Dr. Vinod Scaria, a senior scientist at Delhi’s Institute of Genomics and Integrative Biology (CSIR-IGIB), says the mutation rate of monkeypox virus has not been well established.

“The number (about two per year) comes from the limited data from other poxviruses which have been studied,” he explains. “The inaccuracies also stem from the fact that monkeypox virus is primarily a zoonotic disease and genomes have not previously come from sustained human-human transmission in the past.”

About the 47 mutations that appear in the genomes now being sequenced, he says, “While the number of mutations look significantly large from what is expected, this could mean many things – the mutation rate estimates for monkeypox could be different for different hosts (animals vs humans), and many intermediate paths of evolution and their representatives have not been sequenced to accurately ascertain the evolutionary

path of these specific isolates.”

## Sustained transmission?

According to Dr. Rambaut, many of the mutations arise due to the action of a particular enzyme that is present in the host to prevent the virus from multiplying. Based on the mutation pattern seen in the genome of the virus isolated from people since 2017 is “indicative of replication in humans”, says Dr. Rambaut. And the “inheritance of the specific changes that occurred between 2017 and 2018, and then in the viruses from 2022 means that there has been sustained human-to-human transmission since at least 2017”.

However, Dr. Scaria is not convinced that the presence of the mutation pattern is indicative of sustained human-to-human transmission.

He says, “The evidence suggests many of the mutations match the profile of a unique set of enzymes. Whether this was in the primary host, an unknown intermediate host or in humans is still unknown and something difficult to conclusively prove with the data at hand, as we do not have genomes which span the period between the last major outbreak to present.”

While the presence of 47 mutations does indicate that the monkeypox virus mutates at a much higher rate than the previously believed rate of two-three mutations per year, the mutations do not necessarily suggest that the monkeypox virus has become more transmissible, says Dr. Scaria.

“The mutations we see do not change the amino acids in protein. All adaptations to evolutionary pressure typically happen due to changes in the amino acid, which we don’t see here. This suggests that the mutations we see are relics of the enzyme action and not necessarily an evolutionary process or adaptations of the virus,” Dr. Scaria explains.

“Also, unlike the SARS-CoV-2 virus, which relies on a particular receptor to gain entry into cells, the monkeypox viruses don’t rely on receptors for cell entry. So a few mutations are unlikely to significantly increase infectivity,” he added.

But the presence of 47 mutations in the virus does point to sustained transmission in the last four-five years.

“But we do not know for sure if the virus collected these mutations in humans or in animals. We do not have genomes of the virus sequenced at intermediate time periods between 2017 and 2022, and so cannot say for sure if the sustained transmission has been in humans,” he says.

## Higher rate

But the large collection of mutations does clearly suggest that the earlier notion of a mutation rate of two-three per year for monkeypox virus is a gross underestimation. The monkeypox virus indeed mutates at a higher rate than what was earlier assumed.

The 47 mutations seen in the genome sequence does indicate that the virus could have collected these mutations in a short period of time.

“This change in mutation pattern likely marks the jump from the original host to humans or an intermediate host where a host enzyme (maybe APOBEC3) might mutate the genome. The rate of change increased 10-20 fold and is now around one change per month,” Dr. Richard Neher from the University of Basel tweeted. “We don’t know what these mutations do. The great majority of them are likely inconsequential or deleterious to the virus and we have no evidence of viral adaptation. But they will help us tell apart different clusters of the outbreak of monkeypox and understand how the virus spreads.”