Reports of Asymptomatic Monkeypox Suggest That, at the Very Least, Some Infections Go Unnoticed

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Two recent case reports from Europe have raised the possibility that some monkeypox virus infections may be asymptomatic. Whether or not these infections were truly symptom free, the studies suggest that clinicians and individuals at high risk should be aware that monkeypox can go unnoticed—possibly even when it’s transmissible.

As of August 26, almost 48,000 monkeypox cases had been confirmed globally this year, according to the US Centers for Disease Control and Prevention (CDC), by far the largest outbreak on record. The infections were distributed over 99 countries, only 7 of which, all in Africa, have historically reported monkeypox.

To date, the current outbreak mostly has affected communities of men who have sex with men (MSM). In the 2 studies, published days apart this August, separate teams of researchers in Belgium and France used polymerase chain reaction (PCR) testing to retrospectively analyze samples collected from MSM as part of routine chlamydia and gonorrhea screening at sexual health clinics.

In the Belgian study, which included 224 patient samples collected this May, 3 of 4 men with positive monkeypox virus test results reported that they were asymptomatic at the time of testing and that they were also symptom free in the 2 months leading up to the test and through their follow-up visits about 3 to 5 weeks later. The fourth patient had a perianal rash that had been misdiagnosed as a herpes flare-up. Clinical examinations during the return visits found no signs of monkeypox on the 3 patients’ skin, throats, or anogenital regions. In the French study, 13 asymptomatic men had positive test results and only 2 of them later presented to the clinic with symptoms. That analysis involved 200 samples collected over 5 weeks starting early this June.

"These studies suggest that in contrast to what was known about monkeypox in Africa, not all the patients present with symptoms," Marjan Van Esbroeck, MD, a clinical microbiologist at the Institute of Tropical Medicine in Antwerp and a senior author of the Belgian study, wrote in an email to JAMA.

Asymptomatic or Subtle?

Van Esbroeck said she now believes that monkeypox infections can occur without symptoms. Still, she acknowledged that subtle, unrecognized symptoms could not be ruled out completely in her study. She explained that the 3 asymptomatic individuals with positive test results were not physically examined the day their samples were taken because, according to clinic policy, only patients with health complaints are referred to a clinician.

"We cannot exclude that minor lesions have been overlooked or that general symptoms like mild fever or malaise were not recalled by the persons."

In an interview, Boghuma Kabisentanji, MD, MSc, DTM&H, PhD, an assistant professor of medicine in the Division of Infectious Disease at Emory University, said that a few factors make her think the latter scenario is more likely.

Titanji, who was not involved with either of the new studies, pointed to the “remarkable spectrum” of monkeypox presentations in the current outbreak, ranging from...
cold-like symptoms and single pustules mistaken for pimples to diffuse skin rashes and painful anogenital or oropharyngeal lesions.

A study of 528 monkeypox infections that occurred in 16 countries by late June of this year found that 95% of patients presented with a rash. Still, as Titanji said, “very subtle findings are possible, very florid findings are possible, and everything in between.”

Add to that, she said, there’s evidence that monkeypox has been circulating undetected for some time in nonendemic countries prior to when cases were first identified in England early this May. (In fact, a positive sample from 1 of the asymptomatic patients in Belgium was collected several days before the first case was identified in that country.) Meanwhile, it’s unknown how long the virus can continue to be detected on patient samples collected from different body parts, like the mouth, nose, anus, and genitals.

Titanji said that although the new studies are important, these factors taken together suggest to her that the reportedly asymptomatic patients may not have noticed subtle symptoms or recalled them later because they occurred before monkeypox was on their radar.

Sarah Anne J. Guagliardo, PhD, MPH, a lead health scientist in the CDC’s Division of Global Migration and Quarantine, wrote in an email that the reports “certainly suggest that asymptomatic monkeypox infections could be at play” but that “it’s really not clear what proportion of cases are truly asymptomatic or just present with very subtle symptoms and are therefore unrecognized by patients and clinicians alike.”

“The more important question is, if this is really happening, can those patients with asymptomatic or very mild disease infect others?” she said.

An Incredible Mimic

In time, large-cohort natural history studies should provide a more complete understanding of monkeypox, a long-neglected disease. Ideally, this work will reveal whether people can experience truly asymptomatic infections and, if so, whether they can transmit the virus to others.

Guagliardo investigated potential asymptomatic monkeypox in Cameroon in 2017 as an Epidemic Intelligence Service officer in the CDC’s Poxvirus and Rabies Branch and is now participating in the agency’s monkeypox outbreak response. She said it’s concerning that low cycle threshold values, which indicate high viral load, were reported in people with no symptoms in the recent European studies, but that this alone doesn’t answer the question of transmission.

There were, however, additional hints in the Belgian study that asymptomatic transmission may be possible. When Van Esbroeck’s team analyzed positive samples from the patients who remained asymptomatic, they found replication-competent virus in 2 out of the 3 men’s anogenital swabs. According to the researchers, these 2 individuals may have been able to transmit the virus before they learned they were infected.

All 3 asymptomatic patients reported having sexual encounters around the time they were tested but the researchers could not confirm whether onward transmission occurred. In the French study, the investigators did not attempt to isolate replication-competent virus in the samples and thus could not comment on the potential for transmission.

In Van Esbroeck’s view, the difference between completely asymptomatic patients and patients with unrecognized minor symptoms is theoretical. “Both will have the consequence that persons do not isolate themselves and potentially continue to have high-risk behavior,” she wrote in her email.

She and Titanji emphasized that clinicians and people at high risk need to be aware of the range of clinical manifestations so that patients with even subtle symptoms present to their physicians for timely testing, diagnosis, and information on how to reduce their chances of transmitting the virus to other people and even pets.

At the HIV clinic where Titanji provides primary care, about 50% of monkeypox tests are coming back positive. “That just tells you we’re not testing enough,” she said. She has now treated several patients whose only symptoms were intractable pain with swallowing, which easily could be misdiagnosed. In some cases, lesions are not visible externally but are found by specialists in the larynx or rectum. Titanji wants clinicians to know that infection with the monkeypox virus “can look and sound like a lot of things that we see in clinical practice.”

“Monkeypox is an incredible mimic,” she said.

Titanji can’t proactively test every patient with high-risk behaviors. The test costs around $200 without insurance, she said, and commercial laboratories are backed up. She has to reserve resources for patients with symptoms.

It’s urgent that testing be decentralized, says Abraar Karan, MD, MPH, DTM&H, an infectious disease physician and post-doctoral researcher at Stanford University. Using lateral flow tests, for instance, could shorten the interval between contagiousness and detection. “With asymptomatic transmission, this is especially key,” he wrote in an email.

A Surprising Roadblock

According to Karan, the unprecedented extent of transmission in the current outbreak suggests that infectious virus shedding by individuals who are asymptomatic or mildly symptomatic is very likely underappreciated.

“[I]f only those who had clinically significant disease were shedding virus, we would probably not have seen an outbreak this large, as few sexual partners would be willing to engage in high-risk sex with someone if they were visibly sick or had visible lesions,” he noted.

He pointed out that asymptomatic or paucisymptomatic cases are present even for more severe viral diseases, such as Ebola, which makes it not entirely surprising that this is true for monkeypox as well.

“Moving forward, to get a better sense of asymptomatic infections and their potential to transmit, we’ll need data from prospective studies that include frequent, repeated physical exams and testing in exposed to persons to see how infection evolves clinically, if present,” Guagliardo wrote.

Karan raised another type of study. Serological testing at a population level could eventually help reveal the extent of undetected transmission, he said.

Surprisingly, such an undertaking isn’t yet possible. Despite the thousands of annual monkeypox cases in Africa, antibody tests have not been developed specifically for the virus, Daniel Douek, MD, PhD, an immunologist at the National Institute of Allergy and Infectious Diseases (NIAID), explained in an interview. For now, serology can only identify exposure...
to general orthopoxviruses, the family to which the monkeypox, smallpox, and vaccinia viruses all belong. People who have been vaccinated against smallpox with vaccinia virus will test positive on a generic orthopoxvirus antibody test, muddying the results.

Douek, who is chief of the Human Immunology Section at the NIAID’s Vaccine Research Center, studies HIV. When monkeypox infections started making headlines earlier this year, people he knew in the MSM community all had the same question for him: how long had it been spreading? He decided then to develop an assay that could distinguish between monkeypox and vaccinia reactivity. He’s now producing the test in collaboration with poxvirus experts at the CDC. If it works, which should be known as soon as mid-September, it could be deployed as early as this fall in cohort studies involving groups such as MSM, sex workers, and people in nations where monkeypox is historically endemic. Although monkeypox can affect anyone, including children, who come into close contact with the virus, these groups currently are at greatest risk of contracting it.

“These are the vulnerable people who most need our attention,” Douek said. “Presumably, we will be catching any instances of asymptomatic monkeypox infection because there will be people potentially who have antibodies against monkeypox but no recorded symptomatic history of actual known infection.”

For now, new global monkeypox cases are trending down, which the World Health Organization said may reflect early signs of a decline in cases in Europe. The news has given Titanji hope that the outbreak could still be contained: “It would take vaccines and it would take engaging the highest-risk communities without stigma to provide them with the information that they need in order to better protect themselves and their communities at large.”

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Note: Source references are available through embedded hyperlinks in the article text online.