Urging caution but not panic on monkeypox

June 2 2022, by Katherine Unger Baillie

Credit: Pixabay/CC0 Public Domain

Endemic to Central and West Africa, monkeypox has been making headlines in Europe and the United States. An initially small outbreak of the poxvirus—a relative of the much deadlier smallpox—has been rippling through countries including Spain, Belgium, the United Kingdom, Germany, and Canada. A case in Massachusetts was

confirmed by the Centers for Disease Control and Prevention last week and, at the time of this writing, additional cases have been identified elsewhere in the United States.

The first human case of monkeypox, so named because it was first discovered in a colony of research monkeys, was diagnosed in 1970 in the Democratic Republic of Congo. Since then, limited cases have been seen outside Africa, typically owing to global travel from places in Africa where monkeypox is endemic.

The disease is known for its characteristic lesions, but generally starts with flu-like symptoms like fever, fatigue, and body aches. A rash can emerge a few days after the onset of fever, with lesions progressing through various stages before scabbing over and resolving in roughly two weeks. It's transmitted by close contact with infected people or their clothing or bedding, entering through broken skin, mucous membranes, or the respiratory tract. Most people recover, though the disease is considered to have a fatality rate between 3 and 10%.

Penn Today spoke with researchers Gary Cohen and Robert Ricciardi of the School of Dental Medicine and Stuart Isaacs of the Perelman School of Medicine, who have collaborated for decades on research related to developing vaccines and therapeutics for poxviruses. They weigh in on what to look out for in the latest outbreak, how governments and clinicians are preparing, and why monkeypox is nothing like COVID-19.

Can you share some basic information about monkeypox and how it compares with its relative, smallpox?

Isaacs: Poxviruses are very big DNA viruses; they have about a 200,000 base pair genome. Compared to HIV, an RNA virus with a 10,000 base

pair genome, or coronaviruses, which have about 20,000 base pairs of RNA, poxviruses are 10 to 20 times bigger. They carry a lot of genes that interact with the host immune system.

Members of the poxvirus family, like cowpox, smallpox, and monkeypox, are distinct, but there are enough protein similarities that immunity to one gives cross-immunity to others. Thus, the vaccine used to eradicate smallpox is protective against these other poxviruses.

Both smallpox and monkeypox create these similar rash lesions that are very characteristic and very observable. But smallpox is only found in humans, which was one of the reasons it was able to be eradicated; there was no animal reservoir. Once you stopped human-to-human transmission, you could stamp it out.

Monkeypox has an animal reservoir, and it keeps jumping into humans. There's also some human-to-human transmission, like we've been seeing recently. Smallpox is much more deadly in a nonimmune person—the fatality rate is 30%—whereas monkeypox is considered milder with a lower fatality rate.

Ricciardi: If you're under 50 years old, you've probably never had the smallpox vaccine. The more senior members of society who received the smallpox vaccine years ago have about 85% protection against monkeypox due to the commonality of many genes in both viruses.

Unlike RNA viruses, such as SARS-CoV-2, which rapidly accumulate mutations, monkeypox is a DNA virus, which tends to mutate far less often. So, while we have all these new variants of SARS-CoV-2 that continue to emerge, a frequent occurrence of new monkeypox strains is less likely. Consequently, the vaccines and therapeutics that were produced years ago against smallpox are expected to remain effective against monkeypox virus.

Are any groups particularly vulnerable to monkeypox?

Isaacs: Even 30, 40, 50, 70 years after a childhood smallpox vaccination, people are probably protected from severe disease or death. You could still get monkeypox and show some lesions and some symptoms. Those who are unvaccinated will be susceptible and could have serious outcomes. Monkeypox is likely to be more severe in the very young and people who are immunocompromised and pregnant. Those were groups who had problems in smallpox times as well.

How is your research connected to monkeypox?

Cohen: I came to Penn in the 1960s and started working on poxvirus. I learned a great deal. Penn at that time was a hotbed of biochemical virology. I did my postdoc, got a job at the dental school, and went into herpes virology as smallpox receded as a threat. And I didn't come back to it for a few decades.

Isaacs: After medical school and residency I had gone to the NIH to do a postdoc and fellowship and worked with one of the most prominent pox virologists in the world. When I got a job here at Penn I continued to study poxviruses in my own lab.

Shortly after 9/11 and the anthrax attacks in 2001, the National Institutes of Health funded centers to address bioterrorism, and Penn played a big role in what was called the Middle-Atlantic Regional Center of Excellence for Biodefense and Emerging Infectious Diseases, or MARCE. We had a poxvirus project where we were developing new therapeutics and next-generation vaccines. The government was looking to develop a next-generation vaccine because the historical smallpox vaccine, which helped eradicate smallpox and also prevents monkeypox,

has lots of mild side effects but also some serious and concerning adverse effects.

Gary's group was heavily involved in developing therapeutics using monoclonal antibodies. That was almost 20 years ago, and at that time the MARCE advisory panel for our group told us that monoclonal antibodies were too expensive and too hard to pursue. So we kind of put that on the backburner and put all of our energies into a subunit protein-based smallpox vaccine. Gary's group made recombinant proteins that could be purified, and my group worked with the proteins mixed with adjuvants and vaccinated mice and challenged them. This protein-based vaccine looked promising, but the NIH was also looking at other next-generation vaccines and ended up going with a vaccine called modified vaccinia virus (MVA) vaccine, a further attenuated, nonreplicating smallpox virus.

Ricciardi: I was also asked by NIH to join MARCE to develop a smallpox drug based on a novel viral target we were working on. Even though we made substantial progress in a short time, by twist of fate MARCE funding ended due to the U.S. government accepting a completely different smallpox drug ST-246, now called Tecovirimat. Importantly, Tecovirimat is also approved for monkeypox.

As an aside, my former Penn graduate student Alfred Del Vecchio was involved in discovering ST-246 in a small startup company under the medicinal chemist inventor Thomas R. Bailey, who is currently one of my collaborators.

Fortuitously, however, our work on developing a smallpox drug has led our lab to produce the very first drug candidate for a different poxvirus called Molluscum Contagiosum, which is a skin disease of children and immune compromised individuals.

What are you keeping an eye on in terms of what's happening with this latest outbreak?

Cohen: Monkeypox has a two-to-three week incubation period, which could mean that the cases we're seeing now were all exposed around the same time, and then those individuals traveled elsewhere. If this outbreak continues to expand and we understood which people were exposed, then we could do ring vaccination, vaccinating their close contacts.

One other important element of this latest outbreak is that many of those affected seem to be gay men. Having had a close-up view of what happened in 1982 with HIV, I think we need to be very careful about not stigmatizing this disease or people who get it. It can be passed by any kind of close contact. In 1982 various social conventions stood in the way of us getting control of HIV, and it turned into a pandemic.

COVID-19 and monkeypox are very different diseases, but are there any lessons from the pandemic that we might apply to thinking about this outbreak?

Isaacs: It's hard not to compare the current widespread monkeypox outbreak to COVID: here's this zoonotic infection that started and then spread worldwide.

The good news is that monkeypox isn't a new virus, and we have a better toolkit to battle it than we had for SARS-CoV-2 back in 2020. We have vaccines that should be protective, and we have therapeutics that should work in patients who are becoming seriously ill. The other good news is that the monkeypox virus doesn't spread efficiently from person to person unless there's close contact. By isolating infected people and avoiding close contact, this current outbreak could burn, but whether we

can do that is still unknown.

Ricciardi: At this point, while there's no cause for panic, we still need to be cautious by being fully prepared with vaccines and therapeutics. We need to remain aware of the number and location sites of the monkeypox infections. For each infected person, the CDC and health officials need to immediately employ contact tracing. The public should be reminded periodically as to how the virus is spread and its symptoms. On the scientific side, stockpiling of the new smallpox vaccine and the Tecovirimat drug are in place as first lines of defense. However, as a precautionary measure, additional therapeutic drugs against monkeypox should be developed in the event of resistance to Tecovirimat as well as any adverse reactions that may be experienced by some individuals. For these reasons, it is always wise to have an assortment of drugs available for treatment.

Provided by University of Pennsylvania